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In Utero Efavirenz Exposure and Neurodevelopmental Outcomes in HIV-Exposed Uninfected Children in Botswana

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Abstract

Background: Minimal data exist related to neurodevelopment after *in utero* exposure to Efavirenz (EFV). We sought to compare neurodevelopmental outcomes in HIV-exposed/uninfected (HEU) children with *in utero* exposure to EFV-based triple antiretroviral treatment (ART) versus non-EFV-based ART, and to examine whether timing of initial EFV exposure is associated with neurodevelopment deficits.

Methods: Women living with HIV who had received EFV-based ART during pregnancy and whose HEU newborn participated in a prior study were re-consented for their HEU toddler to undergo neurodevelopmental testing at 24 months old. We administered the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), Developmental Milestones Checklist (DMC), and Profile of Social Emotional Development (PSED). We compared outcomes to previously-collected data from a cohort of 24-month-old HEU children with *in utero* exposure to non-EFV-based ART. Adjusted general linear models were used to compare mean outcomes.

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Results: Our analysis included 493 HEU children (126 EFV-exposed, 367 EFV-unexposed). Adjusted mean scores for the EFV-exposed group were worse than the EFV-unexposed group on BSID-III Receptive Language, (adjusted means=21.5 vs 22.5, p=0.05), DMC Locomotor (30.7 vs 32.0, p<0.01), and Fine Motor scales (17.8 vs 19.2, p<0.01); and PSED (11.7 vs 9.9, p=0.02); but better on the DMC Language scale (17.6 vs 16.5, p=0.01). Earlier (vs later) EFV exposure was associated with worse scores on the BSID-III Receptive Language scale (20.7 vs 22.2, p=0.02).

Conclusion: HEU children exposed *in utero* to EFV-based ART may be at higher risk for neurodevelopmental and social-emotional deficits than HEU children exposed to non-EFV-based ART.

Keywords

child; neurodevelopment; HIV-exposed/uninfected; efavirenz

INTRODUCTION

With 80% of women who live with HIV (WLHIV) having access to 3-drug combination antiretroviral treatment (ART) during pregnancy and breastfeeding, rates of new pediatric HIV infections have dropped by 35% since 2010[1]. At the same time, the population of HIV-uninfected children born following *in utero* exposure to HIV has grown to nearly 15 million worldwide[1] and is particularly high in low- and middle-income countries (LMICs)[2,3] where a host of other medical and sociodemographic risk factors threaten healthy development[4]. With the scale-up of ART and the introduction of universal treatment, the proportion of HIV-infected pregnant women who conceive on ART (vs. start ART in pregnancy) is increasing rapidly[1].

HEU children constitute a vulnerable population with higher rates of early-life mortality[5,6] and higher risk for a range of morbidities compared with HIV-unexposed children, including hematologic dysfunction[7–11], mitochondrial abnormalities[12], infection[13–16], and growth delay[17–20]. Relative to HIV-unexposed children, neurodevelopmental deficits in cognitive, language, and/or motor abilities have also been reported among young HEU children in some studies[21–26], although findings have been mixed[27–31] and differences in maternal ART regimens in pregnancy and length of *in utero* exposure to ART regimens across studies limit the generalizability of findings.

Of particular concern is the lack of data on neurodevelopmental and social-emotional/self-regulatory outcomes among young HEU children exposed *in utero* to efavirenz-based ART. Efavirenz (EFV) is a widely-used non-nucleoside reverse transcriptase inhibitor that was commonly included as a component of first-line 3-drug combination ART regimens in most resource-limited settings worldwide since ~2013, including among WLHIV who are pregnant or who may become pregnant[32]. Although highly effective at suppressing HIV-1 RNA, treatment with EFV has also been associated with several adverse neuropsychiatric side effects including insomnia, anxiety, depression, and suicidality[33–36]. In one study, *in utero* EFV exposure has been linked to increased risk of neurologic abnormalities such as microcephaly and seizure disorders in infancy and childhood[37]. Minimal data exist related to neurodevelopment after *in utero* exposure to EFV[25]; and, despite increased vulnerability of

first trimester neurogenesis and gliogenesis to disruption by teratogenic exposures[38], we are not aware of any data regarding the impact of timing of *in utero* EFV exposure on child neurodevelopmental outcomes.

We aimed to evaluate 24-month neurodevelopmental and social-emotional outcomes among HEU children in Botswana following *in utero* exposure to EFV-based vs. non-EFV-based 3-drug ART. We hypothesized that (a) HEU children who had been exposed to EFV-based ART would exhibit worse neurodevelopmental and social-emotional outcomes than HEU children exposed to non-EFV-based ART and (b) among children with *in utero* EFV exposure, initial exposure beginning earlier in gestation would be associated with worse neurodevelopmental and social-emotional outcomes than exposure beginning later in gestation.

METHODS

Participants and Procedure

Participants in our study, entitled "*Tshipidi Plus*", were 24–28-month-old HEU children with prior *in utero* exposure to EFV-based 3-drug ART and whose mothers participated in the previously-completed *Mpepu Study* (a randomized trial that examined the effects of 15 months of prophylactic co-trimoxazole on infant mortality among HEU children in Botswana[39]). EFV was nearly always taken in combination with tenofovir/emtricitabine. Children in *Mpepu* received either a single dose of nevirapine at birth and 4 weeks of prophylactic zidovudine, or 4 weeks of nevirapine prophylaxis. We enrolled children in the new Tshipidi Plus neurodevelopmental study May 2016-May 2017 in Gaborone, Botswana. Enrollment was stratified by timing of initial EFV exposure (conception/first trimester vs. second/third trimester). Participants took part in a single session of child neurodevelopmental testing (between 24–28 months of age) and maternal interview, both conducted by an experienced trained nurse.

Comparator data were drawn from two prior studies of neurodevelopmental outcomes in Botswana, in which HEU children who had been exposed to non-EFV-based ART regimens underwent neurodevelopmental testing at 24–30 months of age (between 2009 and 2015). Study design, procedures, and findings have already been reported[27,28,40]. A subset of our comparator group had been exposed *in utero* to abacavir/zidovidine/lamivudine or to ritonavir boosted lopinavir/zidovudine/lamivudine, and breastfed through 6 months of age (after previously participating in the *Mma Bana Trial*[41]). The remaining children in our comparator group were exposed *in utero* to other ART regimens (detailed in Results) or to zidovudine, after their mothers enrolled in the observational *Tshipidi Study* (in which mothers chose to breastfeed or formula-feed). All HEU children received a single dose of nevirapine prophylaxis at birth followed by one month of zidovidine.

Neurodevelopmental testing protocols were identical in the prior (*Tshipidi* and *Mma Bana*) and current (*Tshipidi Plus)* studies. The research nurse who conducted neurodevelopmental assessments in the *Tshipidi Plus* EFV-exposed group also conducted many of the assessments in the earlier *Tshipidi Study* participants.

Studies were approved by the Botswana Health Research Development Committee and the institutional review boards of Boston Children's Hospital (*Tshipidi Plus*) and the Harvard T. H. Chan School of Public Health (*Tshipidi and Mma Bana*). Caregivers provided written consent for their and their childrens' participation.

Measures

Measures included: the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)[42], a measure developed for the United States population which had undergone adaptation (including consulting with focus groups, modifying items, piloting, and re-piloting) to more appropriately match the cultural experiences of children in Botswana,[27,43]; and two parent/caregiver questionnaires developed in sub-Saharan Africa, the Developmental Milestones Checklist (DMC)[44], measuring language, motor, and personal/social skills, and the Profile of Social Emotional Development (PSED)[45], measuring a child's emotional/behavioral self-regulatory capacities.

Statistical Analysis

The two primary exposure groups were HEU children whose mothers received EFV-based ART during pregnancy ("EFV-exposed") and HEU children whose mothers received ART during pregnancy that did not include EFV ("EFV-unexposed"). In a secondary analysis, neurodevelopmental outcomes were compared among only children with *in utero* EFV exposure, by timing of first EFV exposure – either early exposure (at conception/in the first trimester) or later exposure (beginning in the second/third trimester). Demographic characteristics were compared across EFV-exposure groups using Wilcoxon rank-sum tests for continuous variables and Chi-Square tests for categorical variables. Unadjusted general linear models were tested to compare neurodevelopmental and social-emotional outcomes by EFV-exposure group, and were followed by adjusted models controlling for child age, sex, infant feeding method, and *in utero* ART initial exposure timing, as well as other medical/sociodemographic factors found to be associated with outcomes at $p \leq 0.20$ in univariate analyses (Table 2). An identical approach was undertaken in comparing outcomes according to timing of initial *in utero* EFV exposure. Sensitivity analyses were then conducted to explore the impact of study enrollment site and feeding method on outcomes. Interaction effects of ART exposure group * feeding method were tested using two-way ANCOVAs. Primary analyses did not include preterm birth, low birthweight (LBW), or child growth parameters as confounders, as all are potentially on the causal pathway; however, these variables were included in sensitivity analyses to evaluate their impact on adjusted analyses. With the exception of height-for-age, weight-for-age, and weight-for-height z-scores, for which World Health Organization standards were used, raw scores were included in all analyses due to the lack of applicable norms for Botswana. Mean differences were also expressed as effect sizes (Hedges' g[46]) to allow for improved interpretation of differences. Statistical analyses were conducted using IBM SPSS Statistics Version 25.

RESULTS

Participant Characteristics

Our study population included 493 HEU children (126 EFV-exposed, 367 EFV-unexposed). Of the EFV-exposed children, 53 (42%) were exposed to EFV from the time of conception or during the first trimester and 73 (58%) were first exposed to EFV in the second or third trimesters. Demographic and socioeconomic characteristics are shown in Table 1.

EFV-exposed children were older at the time of assessment (mean age= 26.1 vs 24.4 months), more often born preterm (16% vs 8%), and less often breastfed (29% vs 73%) than EFV-unexposed children. The mothers of EFV-exposed children were also older on average at the time of assessment, had a higher baseline CD4 count, and tended to have higher socioeconomic indices than the mothers of EFV-unexposed children (in most but not all regards). Almost all EFV-exposed children (99%) were recruited from Gaborone (a city), while the EFV-unexposed group was divided between those recruited in Gaborone (48%) versus in more rural settings (52%). Exposure to EFV-based ART tended to occur earlier than exposure to non-EFV-based ART regimens. Prophylactic co-trimoxazole was not associated with neurodevelopmental outcomes (data not shown).

Mothers of children whose initial EFV exposure began at conception or during the first trimester were older than the mothers of children whose initial EFV exposure began later in gestation, but early- versus later-exposure groups were otherwise comparable.

EFV Exposure and Outcomes

Unadjusted analyses.—In unadjusted analyses, mean scores for the EFV-exposed group were significantly lower (worse) than the EFV-unexposed group on the BSID-III Receptive Language scale and the DMC Locomotor and Personal-Social scales, and higher (worse) on the PSED (Table 3). In contrast, mean scores for the EFV-exposed group were significantly higher (better) on the BSID-III Gross Motor scale and the DMC Language scale. BSID-III Cognitive scale scores did not differ between exposure groups.

A number of sociodemographic and clinical variables were associated significantly and in expected directions with neurodevelopmental outcomes, including child age and sex, LBW, history of breastfeeding, initial ART exposure timing, maternal age and income, and having indoor faucet/toilet facilities at home.

Adjusted analyses.—In analyses adjusting for child age and sex, infant feeding method, and the timing of *in utero* ART exposure, as well as other sociodemographic and clinical factors found to be associated with outcomes at $p \leq 0.20$ in univariate analyses, mean scores for the EFV-exposed group remained significantly worse than the EFV-unexposed group on the BSID-III Receptive Language scale, DMC Locomotor, Fine Motor scales and PSED; and better on the DMC Language scale. Differences in BSID-III Gross Motor scale and on the DMC Personal-Social scale scores were no longer significant (Table 3).

Sensitivity analyses.—Sensitivity analyses were conducted to further explore neurodevelopmental and social-emotional outcomes (a) adjusting for preterm birth and/or

LBW; (b) adjusting for growth parameters; (c) restricting to urban enrollment sites; and (d) accounting for feeding method. The patterns of results and inferences were unchanged when preterm birth and/or LBW were included in the models, and also when height-for-age was included as a covariate (data not shown).

Adjusting for weight-for-height, group differences on the BSID-III Receptive Language scale were no longer significant although qualitatively in the same direction. All other results were unchanged (data not shown).

Analyses restricted to the 301 children recruited from a city yielded similar results to analyses that included all children (with the exception that group differences on the BSID-III Receptive Language scale were no longer significant although qualitatively in the same direction).

Among formula-fed children ($N = 188$: EFV-exposed $n = 90$ [48%], EFV-unexposed $n = 98$ [52%]), mean scores for the EFV-exposed group remained worse than the EFV-unexposed group on the DMC Locomotor, and Fine Motor scales, and better on the DMC Language scale. However, scores on the PSED were no longer significantly different. Two-way ANCOVAs revealed significant interaction effects of ART-exposure group and feeding method on BSID-III Cognitive, Fine Motor, and Gross Motor scales, the DMC Personal-Social scale, and the PSED (interactions $p < 0.05$). Among EFV-unexposed children, breastfeeding was associated with significantly better BSID-III Cognitive, BSID-III Fine Motor, DMC Personal-Social, and PSED scores. Among EFV-exposed children, formula feeding was associated with better BSID-III Fine Motor scores but was otherwise unrelated to outcomes.

Timing of Initial *in utero* EFV-Exposure and Outcomes

Unadjusted analyses.—In unadjusted analyses comparing EFV-exposed children whose initial *in utero* exposure to EFV began early (i.e., from conception or the first trimester) vs. later (i.e., during the second or third trimester), mean scores for the early-exposure group were significantly worse than the later-exposure group for the BSID-III Receptive Language and Expressive Language scales, but were otherwise comparable (Table 4).

Adjusted analyses.—In adjusted analyses, mean scores for the early-exposure group remained worse than the later-exposure group for the BSID-III Receptive Language scale, but were no longer significantly different for the BSID-III Expressive Language scale. There were no other significant differences between groups (Table 4). In additional adjusted analyses that included preterm birth and/or LBW (when either or both was associated with outcomes at $p < 0.20$ in univariate analysis) as well as other significant covariates, mean BSID-III Expressive Language scores for the early-exposure group were worse than the later-exposure group; the patterns of results and inferences were otherwise unchanged compared with adjusted analyses that excluded preterm birth and LBW (data not shown).

DISCUSSION

Among young HEU children in Botswana, we found that performance-based receptive language scores were lower among children with *in utero* EFV exposure, particularly those exposed from conception or during the first trimester, even after adjusting for child age and sex, infant feeding method, and other relevant sociodemographic and clinical factors (despite being rated by their caregivers on the DMC as having more well-developed expressive language capacities). In addition, EFV-exposed children were rated by their caregivers as having less well-developed motor and social-emotional/self-regulatory skills than their non-EFV-exposed peers. In contrast, *in utero* exposure to EFV-based ART was not associated with worse performance on cognitive or motor tasks than *in utero* exposure to non-EFV-based ART.

While it is reassuring that, compared to non-EFV-based ART, *in utero* exposure to EFV does not appear to confer increased independent risk for global cognitive impairment (on the BSID-III Cognitive scale), relative deficits in early receptive language and social-emotional/self-regulatory skills were identified in our cohort of EFV-exposed HEU children. Given their potential impact on subsequent development, these findings should be assessed in future studies, in particular in older HEU children with *in utero* EFV exposure. Early language and self-regulatory skills support the successful transition to school[47] and serve as the foundation upon which later literacy[48] and executive function[49] capacities are built. Thus, even subtle deficits in these critical domains warrant identification and intervention.

To our knowledge, our findings are the first to document an association between early *in utero* exposure to EFV-based ART, either from conception or in the first trimester, and neurodevelopmental outcomes. Specifically, in our sample, earlier timing of initial exposure to EFV was associated with worse language outcomes at 24-months of age, despite controlling for a range of potential confounding factors including child age, sex, and feeding history. These findings may suggest differential sensitivity of the developing fetal brain to EFV exposure, with particular concern for those children whose initial EFV exposure began earlier in gestation (which will occur with increasing frequency globally as the proportion of WLHIV conceiving on ART rises).

Until very recently, the number of women conceiving on EFV had been expected to decrease worldwide following the rollout of more effective and better-tolerated dolutegravir-based ART regimens. This has been called into question, however, by a recent report from an ongoing observational study in Botswana showing an early possible signal of a higher prevalence of neural tube defects with dolutegravir exposure from conception[50]. If this risk signal is borne out, it is possible that the number of WLHIV conceiving on EFV will continue to rise, further increasing the number of children exposed from very early in gestation, when risk for adverse language outcomes may be greatest.

As expected, breastfeeding among EFV-unexposed children was associated with better cognitive, motor, and social-emotional/self-regulatory outcomes; however, we were unable to detect similar effects among EFV-exposed children who were breastfed. With only 29% of EFV-exposed children being breastfed, power to detect a significant effect was limited.

This study has several strengths. Stratification of the sample according to timing of initial *in utero* exposure allowed us to look at relative risk within our EFV-exposed group. We also collected data on a range of relevant sociodemographic factors related to both child and maternal status, and our neurodevelopmental testing protocol included both direct child assessment and parent questionnaire measures that had previously been used in sub-Saharan Africa.

Our study also had several limitations, most notably a relatively small sample size and lack of a contemporaneous comparator group. The lack of population-standardized neurodevelopmental measures for Botswana also limits our ability to comment on the clinical significance of the small- to moderate-size group differences we found between exposure groups; although, given the potential for misinterpretation, use of raw scores (rather than applying US norms) was preferable. In addition, our study nurse conducted both recruitment/enrollment and child testing, and therefore was not blinded to timing of initial EFV exposure status. We did not examine EFV-related neuropsychiatric effects as potential mediators of outcomes.

We also acknowledge some differences between our performance-based tests and caregiver ratings, particularly in language, wherein EFV-exposed children performed worse on receptive language testing yet were rated by caregivers as having better language abilities. Of note, the DMC Language scale focuses predominantly on expressive language abilities (e.g., repeats single sounds; says more than 10 words), which were comparable between EFV-exposed and EFV-unexposed children on testing. Thus, differences may be a function of what specific domains are being assessed.

In conclusion, we identified an association between *in utero* exposure to EFV and lower receptive language BSID-III scores, and poorer emotional/behavioral self-regulatory capacities and gross and fine motor skills by caregiver ratings among HEU children at 24 months of age as compared to HEU children with *in utero* exposure to non-EFV containing ART regimens. Our findings highlight the need for routine neurodevelopmental and psychosocial assessment of HIV and ART exposed children and their caregivers, with provision of efficacious interventions to support HEU children with developmental deficits.

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Table 1

Child and maternal demographic and health characteristics by in utero efavirenz exposure

	EFV-unexposed (*n* = 367)	EFV-exposed (*n* = 126)	EFV-early (*n* = 53)	EFV-later (*n* = 73)	*p*-value comparing EFV-exposed vs. EFV-unexposed	*p*-value comparing EFV-early vs. EFV-later
CHILD						
Gestational age at delivery (wks)	39.2 ± 2.1	38.6 ± 2.4	38.5 ± 2.4	38.8 ± 2.5	0.036	0.46
Preterm birth (<37 wks)	28 (8%)	21 (17%)	9 (17%)	12 (16%)	0.003	0.96
Birth weight (kg)	3.0 ± 0.5	3.0 ± 0.5	3.1 ± 0.4	3.0 ± 0.5	0.20	0.20
Low birth weight (<2.5 kg)	49 (13%)	15 (12%)	3 (6%)	12 (16%)	0.68	0.065
Sex (female)	190 (52%)	67 (53%)	25 (47%)	42 (58%)	0.79	0.25
Ever breastfed	269 (73%)	36 (29%)	13 (25%)	23 (32%)	<0.001	0.39
Age at assessment (mos)	24.4 ± 0.9	26.1 ± 1.3	26.1 ± 1.3	26.1 ± 1.4	<0.001	0.96
Height for age (z-score)	−0.7 ± 1.1	−0.2 ± 1.1	−0.3 ± 1.1	−0.1 ± 1.1	<0.001	0.29
Weight for age (z-score)	−0.6 ± 0.9	−0.5 ± 1.1	−0.6 ± 1.0	−0.4 ± 1.2	0.22	0.27
Weight for height (z-score)	−0.4 ± 1.0	−0.6 ± 1.1	−0.7 ± 1.0	−0.6 ± 1.2	0.02	0.62
MOTHER/HOUSEHOLD						
Age at assessment (yrs)	29.1 ± 5.9	30.4 ± 6.2	32.8 ± 6.0	28.6 ± 5.7	0.048	<0.001
Baseline CD4 count	384.6 ± 185.6	531.5 ± 281.2	512.1 ± 232.7	544.8 ± 311.0	<0.001	0.82
ART regimen taken during pregnancy					-	-
EFV+2NRTI	0 (0%)	126 (100%)	53 (100%)	73 (100%)	-	-
NVP+2NRTI	155 (42%)	0 (0%)	0 (0%)	0 (0%)	-	-
LPV/r+2NRTI	111 (30%)	0 (0%)	0 (0%)	0 (0%)	-	-
3-NRTI (Trizivir)	101 (28%)	0 (0%)	0 (0%)	0 (0%)	-	-
ART start time during pregnancy					<.001	-
Prior to conception/first trimester	60 (16%)	53 (42%)	53 (100%)	0 (0%)	-	-
Second trimester	38 (10%)	40 (32%)	0 (0%)	40 (55%)	-	-
Third trimester	269 (73%)	33 (26%)	0 (0%)	33 (45%)	-	-
ART duration during pregnancy (wks)[a]	12.9 (0.6–45.0)	23.9 (1.3–42.0)	38 (25.9–42.0)	15.6 (1.3–27.4)	<0.001	<0.001
Site of enrollment:					<0.001	0.24
City (Gaborone)	176 (48%)	125 (99%)	52 (98%)	73 (100%)	-	-
Town/Village (Mochudi, Molepolole, Lobatse)	191 (52%)	1 (1%)	1 (2%)	0 (0%)	-	-

	EFV-unexposed (*n* = 367)	EFV-exposed (*n* = 126)	EFV-early (*n* = 53)	EFV-later (*n* = 73)	*p*-value comparing EFV-exposed vs. EFV-unexposed	*p*-value comparing EFV-early vs. EFV-later
No/primary education	76 (21%)	16 (13%)	8 (15%)	8 (11%)	0.046	0.49
Employed	125 (34%)	49 (39%)	21 (40%)	28 (38%)	0.35	0.89
No personal income	185 (50%)	77 (61%)	33 (62%)	44 (60%)	0.038	0.82
Married/cohabitating	90 (25%)	29 (23%)	13 (21%)	16 (22%)	0.69	0.73
Home electricity	162 (44%)	87 (69%)	39 (74%)	48 (66%)	<0.001	0.35
Indoor faucet	22 (6%)	40 (32%)	20 (38%)	20 (27%)	<0.001	0.22
Indoor toilet	69 (19%)	47 (37%)	24 (45%)	23 (32%)	<0.001	0.11

Note. EFV = efavirenz; ART = antiretroviral treatment; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; LPV/r = lopinavir/ritonavir; EFV-early = Efavirenz started prior to conception or during the first trimester of pregnancy; EFV-later = Efavirenz started during the second or third trimester of pregnancy; NA = not available. Data presented as *n* (%) or Mean ± SD. Growth parameter z-scores were calculated using World Health Organization growth standards; extreme values of ±3 were considered likely erroneous and set to missing. The vast majority of mothers who took EFV did so in combination with TDF/FTC; while the vast majority of mothers who took NVP did so in combination with ZDV/3TC; most of the mothers who took LPV/r did so with ZDV/3TC (although there was more variability in NRTI backbone with LPV/r).

[a] mdn (min-max)

Table 2

Covariates included in adjusted models comparing neurodevelopmental and social-emotional outcomes by EFV exposure and timing of initial EFV exposure

Outcome Measure	Covariates[a]	
	EFV-exposed vs. EFV-unexposed	EFV-early vs. EFV-later
BSID-III		
Cognitive	Maternal age, employment status, income, marital status, indoor faucet, (LBW)	Maternal age, baseline CD4 count, employment status, income, marital status, (LBW)
Receptive Language	Maternal age, income, marital status, home electricity, indoor faucet, indoor toilet, (preterm birth, LBW)	Maternal employment status, income, marital status, home electricity, indoor faucet, indoor toilet, (preterm birth)
Expressive Language	Maternal education, employment status, income, marital status, indoor faucet, (preterm birth, LBW)	Maternal marital status, (preterm birth, LBW)
Fine Motor	Maternal age, education, income, marital status, (preterm birth, LBW)	Maternal education, marital status
Gross Motor	Home electricity, (LBW)	Maternal age
DMC		
Locomotor	Maternal age, marital status, home electricity, indoor toilet	--
Fine Motor	Maternal age, home electricity, indoor toilet, (preterm birth)	Maternal age, income, (preterm birth)
Language	Maternal baseline CD4 count, home electricity, indoor faucet, indoor toilet, (preterm birth, LBW)	Indoor faucet, (preterm birth, LBW)
Personal-Social	Maternal age, indoor faucet, (preterm birth, LBW)	(Preterm birth)
PSED	Maternal baseline CD4 count, education, employment status, marital status, home electricity, (preterm birth, LBW)	Maternal marital status, indoor faucet

Note. EFV = efavirenz. BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DMC = Developmental Milestones Checklist; PSED = Profile of Social Emotional Development; LBW = low birth weight. Preterm birth and LBW were not included as covariates in the primary adjusted models but were included, if significant, in sensitivity analyses. Growth parameters (height-for-age, weight-for-height) were included separately as covariates in sensitivity analyses.

[a]All models included child age, sex, feeding history, and timing of initial ART exposure.

Table 3

Neurodevelopmental and social-emotional outcomes by EFV-exposure group

	Unadjusted Analyses				Adjusted Analyses			
	Means (*SD*s)		*p*-value comparing EFV-exposed vs. EFV-unexposed	Estimated Effect Size Hedges' *g* (95%CI)	Means (*SE*s)		*p*-value comparing EFV-exposed vs. EFV-unexposed	Estimated Effect Size Hedges' *g* (95%CI)
	EFV-exposed	EFV-unexposed			EFV-exposed	EFV-unexposed		
BSID-III								
Cognitive	56.2 (3.9)	56.4 (4.4)	0.65	−0.05 (−0.26, 0.16)	56.3 (0.5)	56.4 (0.2)	0.86	−0.02 (−0.24, 0.19)
Receptive Language	21.5 (3.5)	22.5 (3.1)	0.006	−0.31 (−0.52, −0.09)	21.5 (0.4)	22.5 (0.2)	0.050	−0.27 (0.49, −0.05)
Expressive Language	26.7 (4.8)	27.0 (4.7)	0.62	−0.06 (−0.27, 0.16)	27.0 (0.6)	26.8 (0.3)	0.86	0.04 (−0.18, 0.25)
Fine Motor	38.1 (3.7)	38.5 (3.3)	0.24	−0.13 (−0.34, 0.08)	37.9 (0.4)	38.6 (0.2)	0.19	−0.18 (−0.40, 0.03)
Gross Motor	55.4 (6.1)	53.7 (3.9)	0.002	0.36 (0.14, 0.58)	54.9 (0.6)	53.9 (0.3)	0.17	0.18 (−0.04, 0.40)
DMC								
Locomotor	31.2 (3.4)	31.9 (2.4)	0.015	−0.25 (−0.46, −0.05)	30.7 (0.3)	32.0 (0.2)	0.001	−0.35 (−0.56 −0.15)
Fine Motor	18.5 (2.7)	18.9 (2.3)	0.056	−0.20 (−0.40, 0.00)	17.8 (0.3)	19.2 (0.1)	<0.001	−0.59 (−0.80, −0.39)
Language	17.8 (2.7)	16.4 (2.9)	<0.001	0.49 (0.29, 0.70)	17.6 (0.3)	16.5 (0.2)	0.010	0.30 (0.09, 0.51)
Personal-Social	45.6 (3.5)	46.7 (4.7)	0.016	−0.25 (−0.46, −0.04)	45.7 (0.5)	46.6 (0.3)	0.13	−0.16 (−0.36, 0.04)
PSED	12.1 (5.5)	9.8 (5.2)	<0.001	0.43 (0.21, 0.66)	11.7 (0.6)	9.9 (0.3)	0.019	0.31 (0.10, 0.52)

Note. EFV = efavirenz. BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DMC = Developmental Milestones Checklist; PSED = Profile of Social Emotional Development.

Table 4

Neurodevelopmental and social-emotional outcomes by timing of initial in utero EFV exposure

	Unadjusted Analyses				Adjusted Analyses			
	Means (*SD*s)		*p*-value comparing EFV-early vs. EFV-later	Estimated Effect Size Hedges' *g* (95%CI)	Means (*SE*s)		*p*-value comparing EFV-early vs. EFV-later	Estimated Effect Size Hedges' *g* (95%CI)
	EFV-early	EFV-later			EFV-early	EFV-later		
BSID-III								
Cognitive	56.0 (3.9)	56.4 (3.8)	0.56	−0.11 (−0.48, 0.26)	56.0 (0.5)	56.3 (0.5)	0.71	−0.08 (−0.46, 0.30)
Receptive Language	20.5 (3.5)	22.3 (3.3)	0.004	−0.55 (−0.93, −0.18)	20.7 (0.5)	22.2 (0.4)	0.02	−0.45 (−0.82, −0.07)
Expressive Language	25.7 (5.0)	27.5 (4.4)	0.04	−0.39 (−0.77, −0.01)	25.9 (0.6)	27.4 (0.6)	0.09	−0.33 (−0.71, 0.04)
Fine Motor	38.0 (4.9)	38.1 (2.4)	0.82	−0.04 (−0.40, 0.32)	37.9 (0.5)	38.2 (0.4)	0.73	−0.09 (−0.45, 0.27)
Gross Motor	55.5 (6.3)	55.3 (6.0)	0.87	0.03 (−0.35, 0.41)	55.0 (0.9)	55.7 (0.8)	0.57	−0.11 (−0.49, 0.26)
DMC								
Locomotor	30.9 (3.7)	31.4 (3.3)	0.50	−0.12 (−0.48, 0.23)	30.9 (0.5)	31.4 (0.4)	0.41	−0.14 (−0.50, 0.21)
Fine Motor	18.5 (2.6)	18.4 (2.8)	0.90	0.02 (−0.33, 0.38)	18.4 (0.4)	18.5 (0.3)	0.78	−0.04 (−0.39, 0.32)
Language	17.6 (3.0)	18.0 (2.5)	0.45	−0.14 (−0.49, 0.22)	17.6 (0.4)	18.0 (0.3)	0.49	−0.15 (−0.50, 0.21)
Personal-Social	45.5 (3.7)	45.6 (3.4)	0.81	−0.04 (−0.40, 0.31)	45.5 (0.5)	45.6 (0.4)	0.95	−0.03 (−0.38, 0.33)
PSED	12.7 (5.4)	11.8 (5.6)	0.38	0.16 (−0.20, 0.52)	12.8 (0.8)	11.7 (0.7)	0.28	0.19 (−0.17, 0.55)

Note. EFV = efavirenz. BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; DMC = Developmental Milestones Checklist; PSED = Profile of Social Emotional Development.