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Pediatric Neurodevelopmental Functioning Following *in utero* Exposure to Triple-NRTI vs. Dual-NRTI + PI ART in a Randomized Trial, Botswana

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Abstract

BACKGROUND: *In utero* exposure to nucleoside reverse transcriptase inhibitor (NRTI)-containing antiretroviral treatment (ART) regimens may be associated with poor neurodevelopmental functioning in children of HIV-infected mothers. We investigated neurodevelopmental outcomes of HIV-exposed uninfected (HEU) children of HIV-infected women enrolled in a randomized trial of abacavir/zidovudine/lamivudine (Triple-NRTI regimen) vs. lopinavir/ritonavir/zidovudine/lamivudine (Dual NRTI+PI regimen).

SETTING: The Mma Bana randomized trial was conducted in urban and rural sites in Botswana.

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Conflicts of Interest: The authors have no conflicts of interest to report.

METHODS: The Mma Bana study randomized HIV-infected pregnant women with CD4 ≥ 200 cells/mm^3 to a triple-NRTI vs. dual-NRTI+PI regimen from 26–34 weeks gestation through planned weaning at 6 months postpartum. Partway through the study, neurodevelopmental assessments were added at 24 months of age, including the Developmental Milestones Checklist, the Bayley Scales of Infant and Toddler Development 3rd edition, Ten Questions Questionnaire, and Profile of Social Emotional Development. We evaluated differences in mean scores between the two arms using unadjusted and adjusted linear regression.

RESULTS: A total of 197 HEU infants (48% male) completed a neurodevelopmental assessment (101 in triple-NRTI arm; 96 in dual-NRTI+PI-exposed arm). Means for all neurodevelopmental outcomes were similar for children of mothers randomized to either ART regimen, with no significant differences in either unadjusted or adjusted models (estimated effect sizes ranging from −0.12 to 0.14).

CONCLUSION: Neurodevelopmental outcomes in 24-month-old HEU children of HIV-infected mothers with baseline CD4≥200 were similar in those randomized to a dual-NRTI+PI-based versus a triple-NRTI-based ART regimen, suggestive of lack of short term toxicity. Monitoring of long term toxicity and newer regimens is warranted.

Keywords

Antiretroviral agents; Human Immunodeficiency Virus; neurodevelopment; HIV-exposed Uninfected Children

BACKGROUND:

Mother-to-child-transmission (MTCT) of HIV has substantially decreased with the expansion of programs promoting the use of antiretroviral treatment (ART) during pregnancy and to neonates during the first weeks of life.[1,2] From 2010 to 2016, the proportion of pregnant women living with HIV who received ART for prevention of mother to child transmission rose from an estimated 47% to 76% worldwide.[3] As a result, the number of HIV- and ART-exposed, HIV-uninfected children born each year has steadily increased. In Africa, a continent with growing numbers of perinatally HIV-exposed uninfected (HEU) children, elevated rates of morbidity and mortality among HEU children have been observed,[4–6] making an understanding of the contribution of antiretroviral exposure to their health particularly important. Antenatal or perinatal ARV or HIV exposure may be associated with worse child neurodevelopmental functioning through multiple potential mechanisms.[7] Many antiretrovirals have been shown to cross the placental barrier, and may induce changes to the central nervous system structure in the fetus and the developing brain. *In utero* or perinatal exposure to nucleoside reverse transcriptase inhibitor (NRTI)-containing regimens has been associated with depletion of mitochondrial DNA, a marker of mitochondrial toxicity in animal[8] and human[9] studies; NRTI exposure has been associated with neurologic anomalies in newborns,[10] and mitochondrial dysfunction in the form of a wide spectrum of clinical abnormalities including CNS disorders[11] which has heightened concern regarding possible links between exposure to these regimens and lower than expected neurodevelopmental functioning.

Studies have yielded mixed results regarding the potential effect of perinatal ART exposure on children's neurodevelopment. Most studies of very young as well as school aged children have not shown associations after adjustment for confounders.[12–15] The few studies to date comparing child neurodevelopmental outcomes by type, timing, and duration of exposure to maternal ART regimens in very young children have been primarily conducted in the US[12,15,16] and are complicated by the substantial heterogeneity in maternal socio-demographic characteristics, substance use and ART regimen use during pregnancy in that country. Previous studies have been observational[12–14,16–20] which has posed several methodological challenges. One key challenge is controlling for the many other factors in mothers' and children's lives (e.g., maternal HIV disease severity, substance use, socioeconomic status) which can influence developmental outcomes, and may also be associated with ART exposure. Additionally, differences in study population characteristics, age when neurodevelopmental functioning is assessed, and measurement of neurodevelopmental functioning limit comparability of results across studies.

The purpose of this study was to investigate neurodevelopmental outcomes at two years of age in perinatally HIV-exposed uninfected children whose mothers had been randomized to receive a triple-NRTI regimen (abacavir/zidovudine/lamivudine) vs a dual-NRTI and protease inhibitor (PI)-based regimen (lopinavar/ritonavir/zidovudine/lamivudine) during pregnancy and breastfeeding. We hypothesized that triple-NRTI exposed children would have worse neurodevelopmental functioning relative to children exposed to a regimen containing two NRTIs and a PI. This study addresses some of the major limitations of previous studies by nesting a study of infant neurodevelopmental outcomes in a randomized controlled trial of MTCT HIV prevention regimens (the Mma Bana study), making it possible to control for potential confounders when comparing neurodevelopmental outcomes by maternal ART regimen.

METHODS

Study Population and Procedures:

The methods of the Mma Bana study in southern Botswana have been described in detail previously.[21] Briefly, from July 2006-May 2008, the study randomized HIV-infected pregnant women with CD4 ≥ 200 cells/mm^3 to receive either abacavir/zidovudine/lamivudine (triple-NRTI ART regimen) or lopinavir/ritonavir/combivir (dual-NRTI+PI ART regimen) beginning at 26–34 weeks (median = 27) gestation and continuing throughout pregnancy. Infants received single-dose nevirapine (6 mg) at birth and received zidovudine (4 mg per kilogram of body weight twice daily) from birth through 4 weeks. Women were counseled to breastfeed exclusively and to complete weaning by 3 days before the 6-month study visit. Infants received free formula and took complementary food from the time of weaning through 12 months of age. Infants received monthly physical examinations from birth to 7 months of age, then every 3 months starting at 9 months of age through 2 years of age.

Partway through the Mma Bana study, starting in September 2009, child neurodevelopmental assessments were administered to children who were 22 to 28 months of age. Children whose mothers/guardians provided written informed consent were eligible

to take part. The Botswana Health Research Development Committee and the Harvard T. H. Chan School of Public Health Institutional Review Board (Office of Human Research Administration) approved the study protocol and related materials.

Outcome Measures: Neurodevelopmental Functioning at Age 24 months

Neurodevelopment was assessed using a battery of instruments. A modified version of the Bayley Scales of Infant and Toddler Development (3rd edition) (Bayley-III)[22] was used to evaluate the performance of children in five domains of development: Fine Motor (FM), Gross Motor (GM), Cognitive (Cog.), Receptive Language (RL), and Expressive Language (EL). The Ten Questions Questionnaire[23] was used to screen for the potential presence of impairments/disability. Because the Social Emotional and Adaptive scales of the Bayley-III were not culturally appropriate in the Botswana context, we did not include them and instead added two tests that were developed in Kenya; these tests were both completed by parent interview and therefore did not require child cooperation. Parental assessment of the children's development was measured using the Developmental Milestones Checklist (DMC),[24–25] and the Profile of Social Emotional Development (PSED)[26] was used to measure emotional, behavioral and regulatory problems.

All tests were initially adapted after local review. Prior to making adaptations to the instruments, we conducted focus groups with local professionals in the child development field and with a group of caregivers from one village where we planned to enroll participants in the study. We made minor but important changes to the items which were of concern in this group, e.g., changing "apples" to "bananas." Given that the Bayley-III was developed in the US, it required additional piloting, with further adaptations after the initial pilot, and re-piloting. The final instruments were translated into Setswana and back translated into English. Training in testing administration was completed by three of the study psychologists (BK, PH, VT). Consistency of administration was achieved through ongoing observation by the study coordinator (GM), and monitoring via weekly discussion and periodic video monitoring (BK). All assessments were conducted in Setswana, by interviewers fluent in spoken Setswana. The majority of assessments were done at one visit, but 32 (16%) participants had assessments done over 2 or more visits. For all neurodevelopmental functioning measures, raw summary scores were created and were utilized in analyses due to a lack of applicable norms for Botswana. Assessments were considered invalid when the child was unable to complete the neurodevelopmental assessment or received a score that did not appear to be an accurate reflection of the child's skills due to illness or behavioral problems suggestive of potential clinical impairment. Invalid scores were noted by clinical assessors and confirmed by the lead psychologist. If needed, children were referred for neurological evaluation, hearing testing, and physical or occupational therapy after assessments took place.

Exposure: ARV Regimen

The primary exposure of interest was the intra-partum ART regimen that women were randomized to receive. The two maternal randomization groups compared were maternal use of triple-NRTI vs. dual-NRTI+PI ART regimen during pregnancy and breastfeeding.

Statistical Analysis:

Our analyses included HEU children who completed at least one component of the assessment of neurodevelopmental functioning at two years of age, and whose mothers had been randomized to receive one of the two ART regimens in the Mma Bana study during pregnancy. In addition, we collected maternal demographic characteristics at enrollment into the Mma Bana study during pregnancy (site of enrollment, maternal age, marital status, education, type and amount of monthly income, electricity in home, gestational age at enrollment), maternal health characteristics at enrollment (median CD4 cell count and viral load), and maternal health characteristics at follow up, including occurrence of at least one grade 3 ("severe") or 4 ("life threatening") clinical diagnosis during pregnancy, or up to the child neurodevelopmental assessment, maternal grade 3 or 4 anemia based on hemoglobin laboratory evaluations at each follow up visit, maternal low body mass index (BMI, <18.5), at one or more clinic visits after delivery and up to the child neurodevelopment assessment, preterm birth (<37 weeks gestation), and infant characteristics at birth (low birth weight (<2500 kg), and infant sex) as well as age at time of neurodevelopmental assessment. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, National Institutes of Health, Version 1.0[27] was used for grading clinical diagnoses and anemia. We compared these maternal and child characteristics between children who were available for neurodevelopmental assessment vs. children who were eligible but did not participate or who had already completed the study and who were therefore not eligible for neurodevelopmental testing, to evaluate whether characteristics of those not assessed for neurodevelopmental outcomes differed systematically from those who were assessed. We also compared these characteristics by treatment arm (among children who underwent neurodevelopmental testing), using Chi-Square tests or Fisher's Exact test as appropriate to test for differences in proportions, and t-tests or Wilcoxon rank sum tests as appropriate for continuous measures. We then formally compared mean raw scores for each of the neurodevelopmental outcomes between the two randomized arms and tested for differences between the two arms using unadjusted and adjusted linear regression models. The adjusted linear regression models included potential confounders, which were defined as maternal and infant characteristics associated with both the ART regimen and neurodevelopmental outcome at $p<0.1$. We evaluated the maternal demographic and health characteristics described above as potential confounders; those meeting the criteria were included in multivariable models. These included electricity in the home, gestational age at enrollment/start of ART, and any occurrence of maternal BMI<18.5 after delivery up to the infant neurodevelopmental assessment. Adjusted linear regression models also included adjustment for child age in months at time of neurodevelopmental assessment. An intention-to-treat approach was used. Cohen's *d* effect sizes were estimated.[28] Sensitivity analyses excluding any observation corresponding to a neurodevelopmental score that was an extreme outlier were also conducted. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS:

Among 553 live-born infants enrolled in the two randomized arms of the Mma Bana study, 547 were HEU, of whom 261 were less than 30 months old and had not yet completed the

study at the time neurodevelopmental assessments were added and therefore eligible for the neurodevelopmental study. Within this group, 62 were not offered enrollment due to limited capacity at the site to enroll and test all of the children before they exited the age window. A total of 199 (103 in the triple NRTI arm and 96 in the dual-NRTI+PI-based regimen arm) were offered enrollment in the neurodevelopmental study, all of whom agreed to participate. Of these, 197 (101 in the triple-NRTI arm and 96 in the dual-NRTI+PI-exposed arm) completed at least one neurodevelopmental assessment. Demographic and clinical characteristics of neurodevelopmental study participants were similar to those of the 256 non-participants. However, mothers of neurodevelopmental study participants had more often enrolled at the Gaborone site (44% vs. 30%, $p<0.01$), and had started ART earlier in pregnancy (26–28 weeks gestational age) (73% vs. 64%, $p=0.02$) compared to non-participants. Neurodevelopmental study participants were less often born preterm than non-participants (5% vs. 22%, $p<0.001$) (data not shown in tables).

The proportion of children completing each component of the neurodevelopmental assessment ranged from 80% to 98%. Completion rates were higher for the PSED and DMC, and lower for the Bayley-III and Ten Questions Questionnaire, but similar across treatment arms. The lower rates for the Bayley-III completion were related to problems with child cooperation, fatigue, and illness. Specifically, 81% of participants completed all five Bayley-III scales, 4% completed some, and 14% completed no Bayley-III assessments. Among the 197 completing at least one neurodevelopmental assessment, 10% had at least one assessment that was considered invalid. Participants with invalid scores for particular neurodevelopmental measures were excluded from analyses of that neurodevelopmental outcome, but not from analyses of other neurodevelopmental outcomes for which they had valid scores.

Sample Characteristics by Randomized ART Regimen Group

Maternal sociodemographic, study, and clinical and infant birth characteristics of the 197 neurodevelopmental study participants are summarized in Table 1 by randomized treatment arm. The median age of mothers was 27 years, most mothers were unmarried, and the majority had finished secondary school. Thirty-nine percent of infants lived in households with electricity in the home. Most mothers (73%) initiated their ART regimen at 26–28 weeks gestation. However, children of mothers randomized to the dual-NRTI+PI arm more often had mothers enrolled in the study at 29–31 weeks gestation ($p=0.03$), and had mothers with BMI<18.5 during follow-up (26% vs. 14%, $p=0.03$) compared to triple-NRTI-exposed children (Table 1). Children of mothers randomized to the dual-NRTI+PI arm more often resided in households with electricity (45% vs. 33%, $p=0.11$) (Table 1). Other infant characteristics were similar by treatment arm (Table 2). Children's mean age at time of neurodevelopmental assessment was 24.4 months.

Neurodevelopment Scores by Maternal ART Regimen and Other Characteristics

Figure 1 summarizes unadjusted mean neurodevelopmental scores by maternal ART regimen. Mean scores for children were similar in both antiretroviral regimen exposure groups for all neurodevelopmental measures, with no significant differences by exposure group. Estimated effect sizes ranged from −0.12 to 0.14, indicating minimal differences.

Mean neurodevelopmental scores were also generally similar by gestational age category at ART initiation and by maternal BMI<18.5 (data not shown). Mean neurodevelopmental scores were lower among children from households with no electricity in the home for the DMC Locomotor and DMC Language assessments, compared to children living in households with electricity (Supplemental Table 1).

Results from multivariable linear regression models of associations of antiretroviral exposure arm with each neurodevelopmental outcome, adjusting for maternal BMI<18.5 and electricity in the home similarly showed no statistically significant differences between the two antiretroviral regimen exposure groups (Table 3). We noted one extreme outlier that had not been classified as invalid, and conducted sensitivity analyses excluding this individual. Results from sensitivity analyses were similar to those including that individual, with one exception: Mean DMC Language scores were higher among children in the dual-NRTI+PI-exposed arm vs. the triple-NRTI-exposed arm (13.2 and 12.6, respectively, p=0.06), although this difference was not statistically significant, and was attenuated and not significant in adjusted analyses (p=0.09).

DISCUSSION:

We observed similar neurodevelopmental functioning in 24 month-old HEU children whose mothers were randomized to receive a dual-NRTI + PI-based versus a three–NRTI based regimen during pregnancy and breastfeeding. These results are consistent with studies showing no neurodevelopmental deficits associated with in utero exposure to specific ART regimens.[13,16]

Although previous studies have raised concern about links between NRTI exposure and mitochondrial toxicity, the current study did not observe worse neurodevelopmental functioning in HEU children exposed to three NRTIs versus two NRTIs plus a PI. There are several possible explanations for the results we observed, in addition to lack of a biological effect of the different exposures. It could be that exposure to particular ART regimens contribute to subtle neurologic changes that may not have manifested by two years of age, but could exert an effect later in life. Although exposure to any NRTI could potentially be associated with mitochondrial toxicity relative to a non-NRTI regimen, we observed no incremental effect of exposure to 3 rather than 2 NRTIs within the same regimen on early neurodevelopmental functioning. In addition, we observed lower scores on many measures of neurodevelopmental functioning among children in families without electricity in the home, which underscores the salience of other social, family and environmental stressors that may exert a stronger influence on neurodevelopmental functioning than the effect of any one particular ART regimen.

The results of this study should be interpreted in light of some limitations. Without a comparison group of HIV-unexposed or HIV-exposed but ART-unexposed children, we are not able to disentangle the contribution of HIV exposure (vs. no HIV exposure) or of ART-exposure (vs. no ART exposure) to neurodevelopmental outcomes. Since HIV exposure may be associated with negative outcomes in children even in the absence of HIV transmission, study designs that include HIV-unexposed comparison groups, including cohorts

subsequently enrolled in the Tshipidi study in Botswana, are needed to disentangle the relative contributions of ART, maternal HIV status and environmental and family characteristics to child neurodevelopmental outcomes.

In addition, because the neurodevelopmental test scores were raw scores not normed for Botswana, we are not able to assess how children's overall scores compared to the general population in Botswana. However, this did not limit our ability to compare outcomes in the two ART exposure groups. Inclusion of age-adjusted scores enhanced our ability to compare outcomes between the two groups. The modified versions of the neurodevelopmental assessments were not tested for reliability and validity. The few differences we observed between participants and non-participants in the neurodevelopment study could limit generalizability to the Mma Bana study population. However we do not anticipate that the differences would introduce bias since these characteristics did not differ by treatment arm; when they did differ, we controlled for them in multivariable models. Finally, both study arms contained the same zidovudine/lamivudine NRTI backbone, eliminating our ability to evaluate these specific agents, and limiting our comparisons to regimens including an NRTI (abacavir) versus a PI (lopinavir/ritonavir) added to this zidovudine/lamivudine backbone.

The current study has several strengths. A unique feature of this study design is the randomized comparison of two ART regimens with similar duration of exposure in the two groups which overcomes the limitations of previous studies in which there was considerable heterogeneity in ART exposure, and no randomization. The randomized study design, as well as the high participation rate, are key strengths. In addition, this study, set in Botswana, addresses an important gap in the literature on effects of ART exposure on children's neurodevelopmental functioning in resource-limited settings. HEU children had lower cognitive functioning scores compared to HIV-unexposed uninfected children in studies conducted in Congo[29] and Thailand[20] but neither study examined the role of type of ART exposure. Chaudhury et al (2017) found that neurodevelopmental outcomes of perinatally HIV and ART-exposed uninfected children in the Tshipidi study in Botswana did not differ from those of HIV-unexposed children at age 24 months.[30] Additionally, neurodevelopmental outcomes of HEU children perinatally exposed to 3-drug ART were similar to those exposed to zidovudine monotherapy.[31]

While we did not find significant differences in neurodevelopmental outcomes at 24 months of age in HEU children with exposure to this particular triple-NRTI regimen versus a dual-NRTI+PI ART regimen, continued evaluation of developmental outcomes in HIV-exposed uninfected children is warranted to evaluate the short and long-term effects of antiretroviral agents that are commonly prescribed in pregnancy to women with HIV infection. For example, recent US studies have shown small decrements in neurodevelopmental functioning among one year-old infants with perinatal exposure to atazanavir compared to those exposed to other antiretrovirals.[16,17,32] Continued monitoring of ART-associated toxicities in HEU children and their mothers worldwide is critically important to protect their health and development and to inform clinical guidelines aiming to optimize ART treatment choices for the growing numbers of pregnant women with HIV infection receiving ART globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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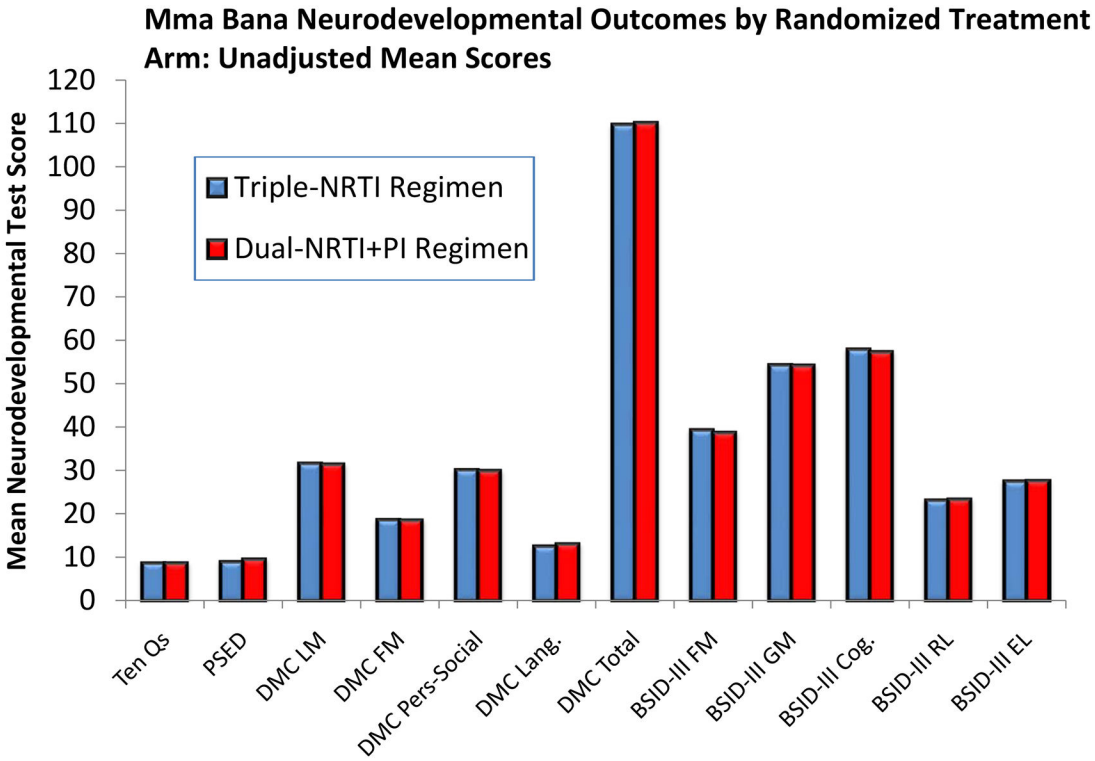

Triple-NRTI Regimen	mean	8.7	9.0	31.7	18.7	47.2	12.6	109.7	39.4	54.3	57.9	23.2	27.6
	SD	0.7	5.2	2.6	2.4	5.4	2.1	10.4	2.6	4.2	4.3	3.1	5.4
Dual-NRTI +PI Regimen	mean	8.7	9.6	31.5	18.6	47.3	13.1	110.1	38.8	54.2	57.3	23.4	27.7
	SD	1.0	4.3	3.3	2.6	4.7	2.7	12.2	5.0	5.2	7.4	2.6	5.2

Figure 1:
Mma Bana Neurodevelopmental Outcomes by Randomized Treatment Arm: Unadjusted Mean Scores

Table 1:

Baseline * Maternal Characteristics of HIV-Exposed Uninfected Infants in the Neurodevelopment Study and their Mothers, by Maternal Randomized Treatment Regimen

Characteristic	Triple-NRTI ART Regimen (ABC/ZDV/3TC) (N=101)	Dual-NRTI+PI ART Regimen (LPV/RTV/ZDV/ 3TC) (N=96)	Total (N=197)	P-Value **
Maternal age (years), median (IQR)	27.4 (23.1, 32.6)	26.3 (23.3, 31.1)	27.0 (23.2, 32.0)	0.69
Enrollment Site				
Molepolole (village)	25 (25%)	21 (22%)	46 (23%)	0.90
Mochudi (village)	15 (15%)	14 (15%)	29 (15%)	
Lobatse (town)	16 (16%)	19 (20%)	35 (18%)	
Gaborone (city)	45 (45%)	42 (44%)	87 (44%)	
Marital status				
Single	78 (77%)	76 (79%)	154 (78%)	0.41
Married/cohabiting	20 (20%)	19 (20%)	39 (20%)	
Widowed	2 (2%)	0 (0%)	2 (1%)	
Divorced	1 (1%)	0 (0%)	1 (1%)	
Education				
None or primary	21 (21%)	23 (24%)	44 (22%)	0.79
Secondary	75 (74%)	67 (70%)	142 (72%)	
University	5 (5%)	6 (6%)	11 (6%)	
Personal Monthly Income (Pula)				
None	49 (49%)	47 (49%)	96 (49%)	0.48
<P500	28 (28%)	20 (21%)	48 (24%)	
P501-P1000	12 (12%)	18 (19%)	30 (15%)	
>P1000	12 (12%)	11 (11%)	23 (12%)	
Employment				
Housewife	5 (5%)	3 (3%)	8 (4%)	0.51
Salaried (government)	3 (3%)	1 (1%)	4 (2%)	
Salaried (private)	13 (13%)	11 (11%)	24 (12%)	
Domestic work (paid)	11 (11%)	13 (14%)	24 (12%)	
Self-employed	8 (8%)	3 (3%)	11 (6%)	
Student	3 (3%)	1 (1%)	4 (2%)	
Unemployed	58 (57%)	64 (67%)	122 (62%)	
Electricity in home	34 (34%)	43 (45%)	77 (39%)	0.11
Gestational age at enrollment				
26–28 weeks	76 (75%)	67 (70%)	143 (73%)	0.03
29–31 weeks	14 (14%)	25 (26%)	39 (20%)	
32–34 weeks	11 (11%)	4 (4%)	15 (8%)	
CD4 cell count (cells/mm^3)				
200–349	36 (36%)	34 (35%)	70 (36%)	0.95
350–499	36 (36%)	32 (33%)	68 (35%)	
>=500	29 (29%)	29 (30%)	58 (29%)	

Characteristic	Triple-NRTI ART Regimen (ABC/ZDV/3TC) (N=101)	Dual-NRTI+PI ART Regimen (LPV/RTV/ZDV/ 3TC) (N=96)	Total (N=197)	P-Value**
HIV-1 RNA (copies/mL)				
<=400	10 (10%)	13 (14%)	23 (12%)	0.76
>400–999	6 (6%)	8 (8%)	14 (7%)	
1000–9999	32 (32%)	29 (30%)	61 (31%)	
>=10000	53 (52%)	46 (48%)	99 (50%)	
Grade 3 or 4 clinical diagnoses***				
During pregnancy	0 (0%)	3 (3%)	3 (2%)	0.11
During follow-up	4 (4%)	5 (5%)	9 (5%)	0.68
Grade 3 or 4 anemia during follow-up***	4 (4%)	7 (7%)	11 (6%)	0.31
BMI<18.5 during follow-up	14 (14%)	25 (26%)	39 (20%)	0.03

*All characteristics were assessed at maternal enrollment (“baseline”) unless otherwise indicated

**P-value by Wilcoxon ranksum test for continuous measures, Fisher’s exact test for binary outcomes, and chi-square test for categorical characteristics

PI=Protease Inhibitor, NRTI=Nucleoside reverse transcriptase inhibitor, BMI=body mass index, ABC=Abacavir, ZDV=Zidovudine, 3TC=Lamivudine, LPV=Lopinavir, RTV=Ritonavir.

***Grading by DAIDS adverse events grading, grade 3=moderate, grade 4=severe or life-threatening

Table 2:

Characteristics of HIV-Exposed Uninfected Study Participants by Maternal Randomized Treatment Regimen

Characteristic	Randomized Treatment Arm: Triple-NRTI ART Regimen (ABC/ZDV/3TC) (N=101)	Randomized Treatment Arm: Dual-NRTI+PI ART Regimen (LPV/RTV/ZDV/3TC) (N=96)	Total (N=197)	P-Value*
Gestational age at delivery				
Median (IQR)	39 (38, 40)	39 (38, 40)	39 (38, 40)	0.58
>=37 weeks	97 (96%)	90 (94%)	187 (95%)	0.46
<37 weeks	4 (4%)	6 (6%)	10 (5%)	
Low birthweight (<2500g)	8 (8%)	14 (15%)	22 (11%)	0.14
Female Infant sex	56 (55%)	45 (47%)	101 (51%)	0.23
Infant a twin	4 (4%)	0 (0%)	4 (2%)	0.12
Age (months) at neurodevelopmental assessment, Median (IQR)	24.05 (24.01, 24.41)	24.08 (24.01, 24.35)	24.08 (24.01, 24.37)	0.57

IQR- interquartile range, PI=Protease Inhibitor, NRTI=Nucleoside reverse transcriptase inhibitor, BMI=body mass index, ABC=Abacavir, ZDV=Zidovudine, 3TC=Lamivudine, LPV=Lopinavir, RTV=Ritonavir.

*P-value by Wilcoxon ranksum test for continuous variables, and chi-square test or Fisher's exact test as appropriate for categorical variables.

Table 3:

Adjusted Differences in Mean Neurodevelopmental Test Scores at Age 24 Months for HIV-Exposed Uninfected Children Exposed to Triple-NRTI vs. Dual-NRTI+PI ART Regimens

	Adjusted mean scores (95% CI)		Adjusted difference[2]		Effect Size
Neurodevelopmental Test	**Triple-NRTI ART regimen (ABC/ZDV/3TC)**	**Dual-NRTI+PI ART regimen (LPV/RTV/ZDV/3TC)**	**Mean Difference[1] (SE)**	**P value**	**Cohen's d (95% CI)**
Ten Questions Questionnaire	8.7 (8.6, 8.9)	8.7 (8.5, 8.9)	−0.02 (0.15)	0.88	−0.02 (−0.33, 0.29)
Profile of Social Emotional Development	9.0 (8.0, 9.9)	9.5 (8.5, 10.6)	0.58 (0.73)	0.43	0.11 (−0.17, 0.41)
Developmental Milestones Checklist					
Locomotor Score	31.7 (31.1, 32.3)	31.5 (30.8, 32.1)	−0.21 (0.45)	0.64	−0.07 (−0.36, 0.22)
Fine Motor Score	18.7 (18.2, 19.2)	18.4 (17.9, 18.9)	−0.29 (0.38)	0.45	−0.11 (−0.40, 0.18)
Personal-Social Score	47.4 (46.4, 48.4)	47.2 (46.2, 48.2)	−0.17 (0.73)	0.81	−0.04 (−0.32, 0.25)
Language Score	12.6 (12.1, 13.1)	13.1 (12.5, 13.6)	0.44 (0.37)	0.23	0.12 (−0.17, 0.40)
Total Caregiver Score	109.6 (107.3, 111.9)	110.1 (107.7, 112.6)	0.55 (1.73)	0.75	0.05 (−0.24, 0.33)
Bayley Scales of Infant Development III					
Fine Motor Score	39.3 (38.5, 40.2)	38.9 (37.9, 39.8)	−0.46 (0.64)	0.47	−0.12 (−0.42, 0.19)
Gross Motor Score	54.2 (53.1, 55.3)	54.3 (53.2, 55.5)	0.15 (0.80)	0.85	0.03 (−0.29, 0.35)
Cognitive Score	57.8 (57.0, 58.6)	58.1 (57.2, 59.0)	0.28 (0.63)	0.66	0.07 (−0.24, 0.39)
Receptive Language Score	23.2 (22.5, 23.8)	23.5 (22.9, 24.2)	0.34 (0.47)	0.48	0.11 (−0.20, 0.43)
Expressive Language Score	27.5 (26.4, 28.6)	28.2 (27.0, 29.3)	0.69 (0.81)	0.40	0.14 (−0.18, 0.45)

[1] Mean difference refers to difference in mean scores between children exposed to dual-NRTI+PI vs. triple-NRTI ART regimens

[2] Adjusted for child age at time of assessment, electricity in the home, gestational age at enrollment, and low maternal BMI at followup.

PI: Protease Inhibitor, NRTI: Nucleoside reverse transcriptase inhibitor, SE: Standard Error, BMI: Body Mass Index

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