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Neurologic Outcomes in HIV-Exposed/Uninfected Infants Exposed to Antiretroviral Drugs During Pregnancy in Latin America and the Caribbean

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Abstract

To evaluate antiretroviral (ARV) drug exposure and other factors during pregnancy that may increase the risk of neurologic conditions (NCs) in HIV-exposed/uninfected (HEU) infants. A prospective cohort study was conducted at 24 clinical sites in Latin America and the Caribbean. Data on maternal demographics, health, HIV disease status, and ARV use during pregnancy were collected. Infant data included measurement of head circumference after birth and reported medical diagnoses at birth, 6–12 weeks, and 6 months. Only infants with maternal exposure to combination ARV therapy (cART) (≥3 drugs from ≥2 drug classes) during pregnancy were included. Microcephaly, defined as head circumference for age *z*-score less than −2, and NC were evaluated for their association with covariates, including individual ARVs, using bivariable and logistic regression analyses. From 2002 to 2009, 1,400 HEU infants met study inclusion criteria. At least one NC was reported in 134 (9.6%; 95% confidence interval [CI]: 8.1–11.2), microcephaly in 105 (7.5%; 95% CI: 6.2–9.0), and specific neurologic diagnoses in 33 (2.4%; 95% CI: 1.6–3.3) HEU infants. Microcephaly and NC were not significantly associated with any specific ARV analyzed ($p > 0.05$). Covariates associated with increased odds of NC included male sex (odds ratio [OR] = 1.9; 95% CI: 1.3–2.8), birth weight <2.5 kg (OR = 3.1; 95% CI: 2.1–4.8), 1-min Apgar score <7 (OR = 2.5; 95% CI: 1.4–4.4), and infant infections (OR = 2.5; 95% CI: 1.5–4.1). No ARV investigated was associated with adverse neurologic outcomes. Continued investigation of such associations may be warranted as new ARVs are used during pregnancy and cART exposure during the first trimester becomes increasingly common.

Introduction

The long-term safety of *in utero* and neonatal exposure to antiretroviral (ARV) drugs in HIV-exposed/uninfected (HEU) infants, children, and youths is still not fully determined. Of particular interest is the impact of ARV exposure on neurologic outcomes in HEU infants. Concerns about toxicity related to zidovudine (ZDV) from *in vitro* animal[1,2] and adult human studies predated the landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 trial.[3] These concerns became more prominent with the results from the French Perinatal Cohort Study (FPCS) that reported eight (0.3%) cases of established or possible mitochondrial dysfunction (MD) among nearly 1,800 ARV-exposed HEU infants in contrast to zero cases among an approximately equal number of ARV-unexposed HEU infants.[4] Of note, five of the eight cases had neurologic symptoms, and three of these five also had persistent hyperlactatemia.

Further epidemiologic surveillance and evaluation by the FPCS identified 18 more children with established or possible MD, with most again having neurologic symptoms.[5] Seizures were also prominent in the cohort, seen in 81 (1.8%)

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subjects.[6] The risk of first febrile seizure was higher with perinatal ARV exposure, and a similar trend was seen for nonneonatal seizures but not for neonatal seizures.[6] The most recent FPCS analysis found that there were four neurologic defects among 13,124 live births from 1994 to 2010; neurologic defects were only found to be associated with the first trimester efavirenz use.[7]

Data from the PACTG 219/219C included 20 cases of possible MD among 1,037 HEU subjects, 19 of whom had neurologic/neurodevelopmental signs, including 9 with seizures, and found an increased risk of MD associated with maternal initiation of 3TC or ZDV/3TC in the third trimester of pregnancy.[8] While the overall prevalence of possible MD in the PACTG 219/219C cohort was higher than that seen in the French cohort (0.3% in the FPCS, 1.8% in 219/219C ARV-exposed HEU subjects, and 2.9% in 219/219C ARV-unexposed HEU subjects),[8] more recent data from the US IMPAACT P1025 cohort reported a 0.3% prevalence of possible MD, but the number of cases was too small ($n=3$) to analyze the association between ARV exposure and the clinical findings.[9]

Beyond the IMPAACT P1025 results, findings from the initial FPCS were not supported by results from many other groups, including investigators from several US cohorts who reviewed >20,000 HEU subjects and found no deaths due to MD.[10–13] However, these US-based studies were limited to evaluating causes of mortality and were not able to assess neurologic morbidity.

Groups in Africa and other parts of Europe have not found an increased incidence of neurologic conditions (NCs) in ARV-exposed HEU subjects compared to those not exposed to ARV.[14,15] Specifically, the PETRA study, a randomized, double-blind, placebo-controlled trial of three short-course regimens of ZDV/3TC versus placebo that was conducted in Tanzania, South Africa, and Uganda, found no difference in the rate of neurologic adverse events across the study arms.[14] In addition, the European Collaborative Group analyzed data from 2,414 subjects (1,008 exposed to ARV) at 26 centers in 9 countries and found a very low rate of neurologic events among all subjects (1.5%).[15]

Our prospective cohort study is one of the first to look at the association between *in utero* ARV exposure and head circumference among HEU infants in addition to analyzing the association between ARV exposure and neurologic diagnoses. Around the world, more widespread use of ARV during pregnancy to prevent mother-to-child transmission has made the safety of *in utero* ARV exposure a critical public health issue.

Materials and Methods

Study population

From 2002 to 2009, HEU infants were prospectively followed from birth to 6 months of age at 24 sites included in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) study from Latin America and the Caribbean (Brazil, Argentina, Peru, Mexico, Bahamas, and Jamaica). Details of this cohort have been previously described.[16,17] The Institutional Review Board approval was obtained from the NICHD, the data management and statistical center (Westat), clinical sites, and in-country ethics boards (Brazil), as required. Signed informed consent was obtained from participating pregnant women.

Data on maternal demographics, health, HIV disease status, and a complete history of ARV use during pregnancy were collected in a systematic manner using standardized questionnaires. Infant data included measurement of head circumference at 6–12 weeks and 6 months and recording of medical diagnoses and laboratory data at birth, 6–12 weeks, and 6 months. Infant head circumference measurements were recorded at birth, but these results were not analyzed because of potential distortion from molding that might occur during the birth process.

Head circumference was obtained in a standardized manner using a flexible, nonstretchable, measuring tape positioned at the most prominent part of the back of the head and just above the eyebrows. Only infants with maternal exposure to combination ARV therapy (cART) (defined as three or more drugs from at least two drug classes) during pregnancy were included in the analysis since this was considered most relevant to the current clinical recommendations.

Definitions

Two primary outcomes were considered for this analysis. Microcephaly was defined using the World Health Organization (WHO) criteria of head circumference for age z-score less than -2.[18] Head circumference z-score for infants born with a gestational age <37 weeks was based on chronologic age corrected for gestational age at birth by subtracting the number of weeks of prematurity (40 weeks for term delivery minus gestational age at birth, in weeks) from their age. For example, if a child was born 4 weeks early, the child's head circumference z-score at 26 weeks of age would be determined using the WHO standards for a 22-week-old child. The second outcome was based on the diagnosis of at least one NC, inclusive of microcephaly, neurologic diagnoses, lactic acidosis, neuro-ophthalmologic conditions, and MD, as identified clinically and obtained through a chart review.

Statistical analyses

Frequencies and proportions were used to describe categorical scaled characteristics of the study population and means and standard deviations for continuous scaled characteristics. The proportion of participants developing microcephaly or at least one NC during study follow-up was determined, and the 95% confidence interval (CI) was calculated using the Clopper–Pearson (exact) method. Bivariable relationships between covariates and the outcomes were first examined using the chi-square and Fisher's exact test for categorical covariates and the two-sample t-test for continuous covariates. Covariates with $p<0.10$ were considered as candidates to enter into multivariable models.

Odds ratios (ORs) and corresponding CIs for associations of microcephaly and NC with individual ARVs and other covariates of interest were generated using multivariable logistic regression modeling. The final models were selected based on likelihood ratio tests. Multiple factors were considered in the modeling, including maternal and infant demographics and delivery-, infant-, maternal HIV-, and infant HIV treatment-related covariates, such as congenital and infant infections, obstetric complications, and maternal infections. A sensitivity analysis was conducted with microcephaly as the outcome, but with no age adjustment of z-scores for those infants who were born prematurely, to determine whether the results would differ based on this less conservative definition of microcephaly.

Results

A total of 1,400 HEU infants were included in this analysis born to mothers with an average maternal age at delivery of 28.5 years (range, 14–46 years). The majority of mothers were from Brazil (64.1%); most had more than 6 years of formal education (69.4%), and nearly a third reported substance abuse during pregnancy (30.9%). Maternal infectious diseases during pregnancy occurred among 181 (12.9%) births and included sexually transmitted infection ($n=98$), cytomegalovirus ($n=28$), rubella ($n=25$), toxoplasmosis ($n=22$), tuberculosis ($n=21$), group B streptococcal infection ($n=19$), influenza ($n=4$), varicella-zoster virus ($n=3$), pneumonia ($n=3$), dengue fever ($n=1$), and primary Epstein–Barr virus infection ($n=1$); mothers could experience more than one type of infection during pregnancy.

Obstetric complications occurred in 158 (11.3%) births and included vaginal bleeding ($n=38$), gestational/pregestational diabetes ($n=35$), preeclampsia ($n=33$), oligohydramnios ($n=27$), intrauterine growth restriction ($n=15$), cardiovascular conditions ($n=9$), chorioamnionitis ($n=9$), renal failure ($n=6$), placenta previa ($n=6$), and polyhydramnios ($n=2$). Many infants were born prematurely (11.1%), and 15.7% had birth weight <2.5 kg. Finally, infections were reported in 124 (8.9%) infants, including sepsis/sepsis inflammatory response syndrome ($n=85$), congenital syphilis ($n=28$), congenital cytomegalovirus ($n=6$), toxoplasmosis ($n=4$), and hepatitis ($n=2$; 1 presumed case of hepatitis B and 1 proven case of hepatitis C).

A total of 134 (9.6%; 95% CI: 8.1–11.2) HEU infants in this cohort had at least one NC reported (Table 1). There were 105 (7.5%; 95% CI: 6.2–9.0) cases of microcephaly and 33 (2.4%; 95% CI: 1.6–3.3) cases with at least one specific neurologic diagnosis reported; four infants with microcephaly also had a neurologic diagnosis. The most commonly reported neurologic diagnoses were neonatal seizures ($n=7$), hypotonia ($n=6$), perinatal hypoxia ($n=4$), and hypertonia ($n=3$). It was not possible to get further clarification on whether or not the seizures were febrile or afebrile. No cases of lactic acidosis or MD were reported.

The majority of women who used cART during pregnancy initiated ARV during the second trimester of their pregnancy (47.7%), while 32.2% were on ARV before the study pregnancy (data not shown). The most common maternal ARVs used during pregnancy were 3TC (98.1%), ZDV (94.2%), NFV (40.6%), LPV/r (28.4%), and nevirapine (35.9%). Of note are 343 (25%) women with viral loads ≥400 copies/ml before delivery and 164 (12%) with CD4 cell counts ≤200 cells/mm^3 before delivery, indicating insufficient viral control in a portion of the study population.

All infants received ZDV prophylaxis at birth. Neither microcephaly nor NCs were significantly associated with any specific ARV analyzed in either the bivariable analyses or multivariable models ($p>0.05$); the specific ARVs analyzed are detailed in Supplementary Table 1 (Supplementary Data are available online at www.liebertpub.com/aid).

In bivariable analyses, a higher proportion of male than female infants ($p<0.005$) and infants with birth weight <2.5 kg ($p<0.0001$), Apgar score <7 ($p<0.05$), congenital infections ($p<0.0001$), presence of maternal noninfectious obstetric complications ($p<0.005$), and with infections ($p<0.001$) experienced microcephaly or NC (Table 2). The mean gestational age at birth was also significantly lower ($p<0.05$) among those experiencing microcephaly or NC.

Microcephaly and NC were not associated with mother's age or educational status, infant prematurity, maternal substance use during pregnancy, or presence of maternal infectious disease ($p>0.05$). Microcephaly and NC also were not associated with the trimester of cART exposure, mother's most complex ARV regimen received for ≥28 days during pregnancy, maternal HIV viral load or CD4+ cell count during pregnancy, or maternal CDC HIV disease classification at delivery.

Several demographic and clinical covariates were found to be associated with significantly increased odds of microcephaly and NCs in multivariable modeling (Table 3). The odds of microcephaly were significantly higher for males (OR = 1.9; 95% CI: 1.2–2.9), infants with birth weight <2.5 kg (OR = 4.0; 95% CI: 2.5–6.2), and infants experiencing infections (OR = 2.1; 95% CI: 1.2–3.7). The odds of having an NC were higher for males (OR = 1.9; 95% CI: 1.3–2.8), those with birth weight <2.5 kg (OR = 3.1; 95% CI: 2.1–4.8), those with 1-min Apgar score <7 (OR = 2.5; 95% CI: 1.4–4.4), and those with infant infections (OR = 2.5; 95% CI: 1.5–4.1).

In sensitivity analyses, an additional 51 infants were identified as having microcephaly when no age adjustment was applied for infants born prematurely, for a total of 156 cases. Modeling results with this increased number of events were generally consistent with the primary analysis findings, although gender was now only of borderline significance in the model ($p=0.06$) and the odds of microcephaly associated with birth weight <2.5 kg more than doubled (OR = 9.7; 95% CI: 6.6–14.3) (data not shown). No individual ARV was associated with microcephaly determined without the age adjustment.

Discussion

This study assesses microcephaly and a wide range of neurologic outcomes among HEU infants exposed to ARVs *in utero*. Among cART-exposed HEU infants from Latin America and the Caribbean, no individual ARV analyzed was significantly associated with the risk of microcephaly or NCs.

We found a relatively high prevalence of NCs (9.6%) in this cohort of cART-exposed HEU infants, which is higher than that reported in previous studies. While some studies have reported less than 1% prevalence,[4,5,19] most studies have reported prevalence rates of 1%–3%.[6,8,14,15,20] Although our prevalence is higher, this may be because the NISDI study was designed specifically to detect both adverse and serious adverse events among HEU infants, and thus, the neurologic outcomes included were much broader (including head circumference to ascertain microcephaly) compared to previous studies that looked only at MD as an outcome. In fact, excluding microcephaly, our observed prevalence of other specific neurologic diagnoses was only 2.4%, which is more in line with the 1%–3% prevalence frequently reported.

In addition, many previous studies compared HEU infants exposed to ARVs to those unexposed to ARVs. Our analysis included only infants with exposure to three or more ARV drugs *in utero* since this is the treatment regimen most relevant to the current international treatment guidelines for HIV-positive pregnant women and because women not on ARVs during pregnancy likely differ in important ways from those who have access to care and are treated with ARVs.

TABLE 1. ASSOCIATIONS OF CHARACTERISTICS OF STUDY POPULATION WITH STUDY OUTCOMES (N= 1400)

	Microcephaly			*Any neurologic conditions*		
Characteristic	*Yes* n *(%)*	*No* n *(%)*	p	*Yes* n *(%)*	*No* n *(%)*	p
Sex						
Male	67 (9.3)	652 (90.7)	0.001	86 (12.0)	633 (88.0)	0.002
Female	38 (5.6)	643 (94.4)		48 (7.1)	633 (93.0)	
Country						
Brazil	65 (7.3)	832 (92.8)	0.33	84 (9.4)	813 (90.6)	0.09
Argentina	25 (7.3)	319 (92.7)		28 (8.1)	316 (91.9)	
Mexico	4 (18.2)	18 (81.8)		5 (22.7)	17 (77.3)	
Bahamas	3 (7.3)	38 (92.7)		3 (7.3)	38 (92.7)	
Jamaica	1 (3.0)	32 (97.0)		3 (9.1)	30 (90.9)	
Peru	7 (11.1)	56 (88.9)		11 (17.5)	52 (82.5)	
Gestational age at birth (weeks)						
Mean (SD)	37.8 (2.1)	38.3 (1.8)	0.02	37.7 (2.3)	38.3 (1.7)	0.0004
Mother's age at delivery (years)						
Mean (SD)	28.9 (6.0)	28.5 (5.8)	0.43	28.9 (6.0)	28.4 (5.8)	0.39
>6 years of formal education completed by mother						
Yes	70 (7.2)	902 (92.8)	0.52	93 (9.6)	879 (90.4)	0.99
No	35 (8.2)	393 (91.8)		41 (9.6)	387 (90.4)	
Substance use during pregnancy						
Alcohol						
Yes	16 (9.5)	153 (90.5)	0.34	23 (13.6)	146 (86.4)	0.07
No	89 (7.4)	1,118 (92.6)		111 (9.2)	1,096 (90.8)	
Missing	0	24		0	24	
Tobacco						
Yes	31 (9.0)	312 (91.0)	0.20	39 (11.4)	304 (88.6)	0.18
No	72 (6.9)	968 (93.1)		93 (8.9)	947 (91.1)	
Missing	2	15		2	15	
Marijuana						
Yes	4 (12.9)	27 (87.1)	0.28	5 (16.1)	26 (83.9)	0.21
No	96 (7.2)	1,229 (92.8)		124 (9.4)	1,201 (90.6)	
Missing	5	39		5	39	
Cocaine/crack						
Yes	4 (11.4)	31 (88.6)	0.32	4 (11.4)	31 (88.6)	0.57
No	96 (7.3)	1,221 (92.7)		124 (9.4)	1,193 (90.6)	
Missing	5	43		6	42	
Heroin/opiate						
Yes	0	0	—	0	0	—
No	99 (7.4)	1,239 (92.6)		127 (9.5)	1,211 (90.5)	
Missing	6	56		7	55	
Any substance						
Yes	36 (8.3)	396 (91.7)	0.43	47 (10.9)	385 (89.1)	0.27
No	69 (7.1)	899 (92.9)		87 (9.0)	881 (91.0)	
Missing	0	0		0		
Severely premature (gestational age <32 weeks)						
Yes	2 (18.2)	9 (81.8)	0.20	3 (27.3)	8 (72.7)	0.08
No	103 (7.4)	1,285 (92.6)		131 (9.4)	1,257 (90.6)	
Missing	0	1		0	1	
Premature (gestational age <37 weeks)						
Preterm	13 (8.4)	142 (91.6)	0.66	19 (12.3)	136 (87.7)	0.23
Full term	92 (7.4)	1,152 (92.6)		115 (9.2)	1,129 (90.8)	
Missing	0	1		0	1	
Birth weight (kg)						
<2.5	41 (18.6)	179 (81.4)	<0.0001	48 (21.8)	172 (78.2)	<0.0001
≥2.5	64 (5.4)	1,115 (94.6)		86 (7.3)	1,093 (92.7)	
Missing	0	1		0	1	
Apgar scores at 1 min						
<7	11 (12.9)	74 (87.1)	0.04	21 (24.7)	64 (75.3)	<0.0001
≥7	91 (7.0)	1,201 (93.0)		109 (8.4)	1,183 (91.6)	
Missing	3	20		4	19	

(*continued*)

TABLE 1. (CONTINUED)

Characteristic	*Microcephaly*			*Any neurologic conditions*		
	Yes n *(%)*	*No* n *(%)*	p	*Yes* n *(%)*	*No* n *(%)*	p
Maternal infectious diseases present						
Yes	13 (8.2)	145 (91.8)	0.71	18 (11.4)	140 (88.6)	0.41
No	92 (7.4)	1,150 (92.6)		116 (9.3)	1,126 (90.7)	
Congenital infections						
Yes	22 (17.7)	102 (82.3)	<0.0001	31 (25.0)	93 (75.0)	<0.0001
No	83 (6.5)	1,193 (93.5)		103 (8.1)	1,173 (91.9)	
Obstetric complications (noninfectious) present						
Yes	37 (11.6)	283 (88.4)	0.002	48 (15.0)	272 (85.0)	0.0002
No	68 (6.3)	1,012 (93.7)		86 (8.0)	994 (92.0)	
Infant infections						
Yes	22 (17.7)	102 (82.3)	<0.0001	31 (25.0)	93 (75.0)	0.0004
No	83 (6.5)	1,193 (93.5)		103 (8.1)	1,173 (91.9)	
Timing of initiation of cARV						
Before pregnancy	34 (7.5)	417 (92.5)	0.62	44 (9.8)	407 (90.2)	0.87
1st trimester	5 (7.5)	62 (92.5)		8 (11.9)	59 (88.1)	
2nd trimester	55 (8.2)	613 (91.8)		64 (9.6)	604 (90.4)	
3rd trimester	11 (5.2)	201 (94.8)		18 (8.5)	194 (91.5)	
Missing	0	2		0	2	
Most complex maternal ARV regimen used ≥28 days during pregnancy						
2 NRTIs +1 PI	64 (6.9)	868 (93.1)	0.47	86 (9.2)	846 (90.8)	0.90
2 NRTIs +1 NNRTI	38 (8.5)	407 (91.5)		44 (9.9)	401 (90.1)	
Other ARVs	1 (6.3)	15 (93.8)		1 (6.3)	15 (93.8)	
No ARVs used for ≥28 days during pregnancy[a]	2 (28.6)	5 (71.4)		3 (42.9)	4 (57.1)	
First viral load during pregnancy (copies/ml)						
<400	51 (7.5)	634 (92.5)	0.98	66 (9.6)	619 (90.4)	0.92
≥400	53 (7.5)	656 (92.5)		67 (9.5)	642 (90.5)	
Missing	1	5		1	5	
Last viral load before delivery (copies/ml)						
<400	78 (7.4)	973 (92.6)	0.91	99 (9.4)	952 (90.6)	0.79
≥400	26 (7.6)	317 (92.4)		34 (9.9)	309 (90.1)	
Missing	1	5		1	5	
First CD4 count during pregnancy (cells/mm^3)						
<200	21 (10.3)	183 (89.7)	0.16	27 (13.2)	177 (86.8)	0.12
200–499	48 (6.5)	695 (93.5)		63 (8.5)	680 (91.5)	
≥500	36 (8.1)	407 (91.9)		43 (9.7)	400 (90.3)	
Missing	0	10		1	9	
Last CD4 count before delivery (cells/mm^3)						
<200	15 (9.2)	149 (90.9)	0.61	18 (11.0)	146 (89.0)	0.68
200–499	46 (7.0)	615 (93.0)		59 (8.9)	602 (91.1)	
≥500	44 (7.8)	521 (92.2)		56 (9.9)	509 (90.1)	
Missing	0	10		1	9	
Maternal CDC clinical classification at delivery						
A	89 (7.5)	1,097 (92.5)	0.93	114 (9.6)	1,072 (90.4)	1.00
B	6 (6.8)	82 (93.2)		8 (9.1)	80 (90.9)	
C	10 (7.9)	116 (92.1)		12 (9.5)	114 (90.5)	
Postnatal ARV use at birth						
ZDV alone (oral and/or IV)	99 (7.5)	1,220 (92.5)	1.00	127 (9.6)	1,192 (90.4)	1.00
Others	6 (7.4)	75 (92.6)		7 (8.6)	74 (91.4)	
Duration of ZDV use from birth to up to 6 months (days)						
Mean (SD)	44.3 (17.1)	41.8 (11.0)	0.15	42.5 (17.0)	42.0 (10.9)	0.75

[a]These seven participants received cART but not for ≥28 days.

ARV, antiretroviral; cART, combination ARV therapy; SD, standard deviation; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ZDV, zidovudine.

Table 2. Frequencies of Outcomes in Study Population (N= 1,400)

Outcome	*Frequency (%; 95% CI)*[a]
Microcephaly	105 (7.5%; 6.2–9.0)
At least one neurologic diagnosis	33 (2.4%; 1.6–3.3)
Specific neurologic diagnoses reported	
Neonatal seizures	7
Hypotonia	6
Perinatal hypoxia	4
Hypertonia	3
Neuropathy	2
Motor development delay	2
Non-HIV encephalopathy	2
Central nervous system structural defect	2
Epilepsy	1
Facial palsy and hypotonia	1
Myelopathy	1
Neuro-ophthalmologic condition	1
Unspecified	1
Total neurologic conditions[b]	134 (9.6%, 8.1–11.2)

[a]CIs are calculated using the Clopper–Pearson exact binomial method.

[b]There were 4 infants diagnosed with both microcephaly and a neurologic diagnosis, including a diagnosis of non-HIV encephalopathy, central nervous system structural defect, neonatal seizure, and hypotonia.

CI, confidence interval.

The findings of this investigation are consistent with those of previous studies that found no association between *in utero* ARV exposure and neurologic outcomes, such as MD,[10–13,20,21] neurologic events,[14,21] and congenital abnormalities[15] among HEU infants. However, there are other studies that did find associations between *in utero* ARV exposure and MD,[4,8] hyperlactatemia,[22] febrile seizures,[6] and neurologic dysfunction.[7] Our analysis examined differences by specific ARV drug among all cART-exposed infants, while other studies compared cART-exposed infants to those unexposed. It may be that cART is associated with neurologic disorders overall, but that no particular ARV is associated with increased risk.

While this analysis focused on safety of ARVs during pregnancy, there is a large body of literature demonstrating that infections during pregnancy can have both short- and long-term neurodevelopmental consequences.[23] The list of infections includes rubella, herpes simplex virus, cytomegalovirus, toxoplasmosis, and influenza. In a study by Ezra Susser *et al.*,[24] based on data from the Child Health and Development Study, in a population-based cohort born between 1959 and 1967 in California, the risk of schizophrenia was increased sevenfold following maternal influenza during the first trimester and twofold in those exposed to elevated maternal toxoplasmosis immunoglobulin G.[25,26]

In addition to demonstrating a potential link between these infections and neurodevelopmental outcomes, these results also emphasize that infections during pregnancy may have long-term consequences since schizophrenia is usually diagnosed after childhood.

These results also raise questions about whether these infections act in unique ways to bring about these outcomes or whether they act through a common pathway likely involving neuroinflammation. If the latter, then there is a strong basis to hypothesize that HIV infection during pregnancy itself may be a risk factor for untoward neurodevelopmental outcomes in offspring and that the use of potent ARVs during pregnancy may help protect against this effect. Using this logic, one explanation for the findings from the PACTG 219/219C study, that demonstrated that initiation of 3TC or ZDV/3TC in the third trimester was associated with neurologic/neurodevelopmental abnormalities, could be that uncontrolled HIV infection earlier in pregnancy, rather than a toxic effect of the ARVs started in the third trimester, was the contributing factor for the findings in these children.[8]

With regard to covariates, the odds of NC was higher among male infants and those with lower birth weight, lower Apgar scores, maternal infectious disease, and infant infections themselves. These findings are not unexpected and are in line with previous studies finding higher rates of microcephaly and more NCs associated with these risk factors.

Table 3. Examination of Associations of Covariates with Study Outcomes Using Multivariable Logistic Regression Modeling

Covariate	*Microcephaly OR (95% CI)*	p[a]	*Any neurologic conditions, OR (95% CI)*	p[a]
Sex				
Male	1.9 (1.2–2.9)	0.005	1.9 (1.3–2.8)	0.001
Female (reference)	1.0		1.0	
Birth weight (kg)				
<2.5	4.0 (2.5–6.2)	<0.0001	3.1 (2.1–4.8)	<0.0001
≥2.5 (reference)	1.0		1.0	
Apgar scores at 1 min				
<7	1.2 (0.6–2.5)	0.56	2.5 (1.4–4.4)	0.002
≥7 (reference)	1.0		1.0	
Infant infections				
Yes	2.1 (1.2–3.7)	0.01	2.5 (1.5–4.1)	0.0004
No (reference)	1.0		1.0	

[a]*p* values were obtained from the Wald chi-square test from the multivariable logistic regression model.

OR, odds ratio.

Limitations of this analysis include limited follow-up to 6 months of age and lack of independent verification of the NC outcome by a neurologist. However, it seems unlikely that outcomes, such as microcephaly, would be overreported or differentially reported according to ARV exposure and may potentially be underreported. In addition, very few infants in this study were unexposed to 3TC or ZDV, limiting the ability to detect associations between NC and these exposures. Finally, one quarter of the women had viral loads ≥400 copies/ml, indicating potential nonadherence to ARVs.

This study benefits from a number of strengths, including a relatively large number of subjects with the outcomes of interest, standardized data collection forms and procedures, and a prospective design. In addition, this study also benefits from looking at various neurologic outcomes, which may be associated with cART exposure, not just MD, and includes the objective outcome of head circumference.

This study confirms previous research and finds no association between specific ARV exposures *in utero* and NCs among HEU infants and did not find any HIV-related covariates associated with higher odds of NC. The infant- and maternal-related factors found to be associated with higher odds of NC in this study population highlight the need to implement additional interventions to address these factors among HIV-positive pregnant women. Better overall prenatal care and maternal/infant follow-up are needed to reduce low birth weight, low Apgar score, and infant infections. Although no ARV investigated in this study was associated with the outcomes, continued investigation of such associations appears warranted, particularly as new ARVs are used during pregnancy and exposure to cART during the first trimester of pregnancy becomes increasingly common.

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