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Neurodevelopment and In Utero Antiretroviral Exposure of HIV-Exposed Uninfected Infants

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Abstract

OBJECTIVE—Antiretroviral (ARV) drugs are routinely provided to HIV-infected pregnant women to prevent HIV mother-to-child transmission. Although ARV use has significantly reduced mother-to-child transmission to <2% in the United States, it remains crucial to monitor uninfected infants and children for adverse consequences of in utero ARV exposure.

METHODS—We studied neurodevelopmental function in HIV-exposed uninfected children who were enrolled in Pediatric AIDS Clinical Trials Group 219/219C, a multisite, prospective, cohort study. Mental and motor functioning were assessed with the Bayley Scales of Infant Development (BSID), first and second editions. ARV exposure information was collected during pregnancy or within the first years of life. Linear regression methods were used to evaluate the association of in utero ARV exposure on Mental Developmental Index and Psychomotor Developmental Index at 2 years of age, controlling for demographic factors (age, gender, and race/ethnicity) and potential confounders: test version, primary language, primary caregiver, caregiver education level, low birth weight, geographic and urban/rural location, birth year, and maternal illicit drug use.

RESULTS—Among 1840 infants who were born between 1993 and 2006, 1694 (92%) were exposed to ARV in utero and 146 (8%) were not exposed. After controlling for confounders, children who were exposed in utero to any ARV did not have lower Mental Developmental Index and Psychomotor Developmental Index scores than unexposed children. Among low birth weight infants, significantly higher BSID scores were observed for prenatally ARV-exposed than unexposed children. Maternal illicit drug use was reported for 17% of mothers but was not associated with BSID scores.

CONCLUSIONS—Mental and motor functioning scores were not lower for infants with in utero ARV exposure compared with no exposure. Although these results are reassuring, continued evaluation of uninfected children with in utero ARV exposure for long-term adverse outcomes is important.

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Keywords

Bayley scales; mental development; motor development; maternal health; antiretroviral treatment; low birth weight

Antiretroviral (ARV) drugs are routinely provided to HIV-infected pregnant women to prevent HIV mother-to-child transmission (MTCT) and have dramatically reduced MTCT in the United States and other developed countries.[1-4] In particular, use of zidovudine (ZDV) during pregnancy, intrapartum ZDV treatment, and short-term neonatal treatment was demonstrated by the AIDS Clinical Trials Group 076 study to reduce perinatal transmission from 25% to 8%.[1] Treatment with highly active antiretroviral therapy (HAART) in resource-rich countries has further reduced transmission to <2%.[2-4] Perinatal HIV prevention programs are now implemented in many countries across the world, making in utero ARV exposure and its potential consequences a global issue. Since 1998, the US Public Health Service has recommended the use of combination ARV to prevent MTCT of HIV.[5] Despite the clear successes of these programs in reducing transmission rates, concern remains regarding possible adverse consequences of prenatal exposure, given that many ARV drugs readily cross the placenta and some have demonstrated mutagenic and carcinogenic effects in animal studies.[6-8]

In response to such concerns, a number of studies have been conducted to evaluate whether congenital malformations, cancer, growth delay, neurodevelopmental problems, hematologic and lactic acid abnormalities, and potential mitochondrial toxicity could be associated with prenatal ARV exposure in infants who are born to HIV-infected mothers. These studies have generally provided reassuring support for the safety of perinatal regimens,[9,10] showing little evidence of increased risk for congenital malformations,[10-12] early childhood cancers,[9,13,14] or growth abnormalities.[15,16] Several studies have shown that in utero ARV exposure (particularly to combination ARV agents) may be associated with mild but persistent hematologic abnormalities in lymphocytes or neutrophil populations.[17-20] The evidence regarding mitochondrial toxicity in HIV-exposed and ARV-exposed children remains equivocal; some studies support a lack of association of mitochondrial dysfunction with perinatal ARV exposure in uninfected infants,[9-11,21-26] whereas others suggest potential associations with nucleoside reverse transcriptase inhibitors (NRTIs), particularly combinations such as ZDV plus lamivudine (3TC).[27-30]

Few studies have evaluated the effects of prenatal ARV exposure on neurodevelopment in uninfected children. An evaluation of children who were enrolled in the Women and Infants Transmission Study (WITS) compared declines in cognitive and motor functioning between 114 HIV-infected versus 481 HIV-exposed children and found significantly higher risk for decline in the HIV-infected children[31]; however, this study did not address the impact of maternal ARV exposure. An evaluation of the Pediatric AIDS Clinical Trials Group (PACTG) 219/219C cohort compared changes in neurodevelopmental functioning in HIV-infected children who were treated with protease inhibitors with those of uninfected children.[32] Investigators observed no effect of prenatal ARV exposure on cognitive and motor functioning in uninfected children who were younger than 1 year but did not adjust for any potential confounders. One study examined the effect of in utero exposure to HAART on cognitive functioning of HIV-uninfected children.[33] A significant difference was observed in mean mental development scores in 39 HIV-uninfected children who were exposed to HAART compared with 24 control children from an ongoing hepatitis C study; however, after adjustment for maternal substance use, the difference in average mental scores was not statistically significant. Adjustment for other potential confounders was not possible because of the small study size.

We studied neurodevelopmental function in 1840 HIV-exposed uninfected children who were enrolled in PACTG 219/219C, a multisite, prospective, cohort study. Our assessment compared mental and motor development scores between those with and without maternal ARV exposure, controlling for many factors that are associated with cognitive functioning, including primary language, race/ethnicity, birth weight, and caregiver characteristics. We also conducted sensitivity analyses to evaluate the timing and duration of prenatal ARV exposure and specific regimens of interest and their association with neurodevelopmental function.

METHODS

This study was based on data collected as part of the PACTG 219 and 219C cohort studies, which enrolled children in the United States with HIV infection or perinatal HIV exposure between 1993 and 2006. PACTG 219 was initiated to study long-term effects of in utero ARV exposure and complications of HIV infection in children who were co-enrolled in another PACTG treatment trial or whose mother participated in a PACTG perinatal treatment trial. A revised version, PACTG 219C, opened in 2000 and extended enrollment to any youth who was aged ≤21 and had HIV infection or perinatal HIV exposure. Children and adolescents were enrolled at >80 participating sites across the United States, including Puerto Rico. The study protocol was reviewed and approved by the institutional review board at each participating site, and written informed consent was obtained from each child's parent/guardian. The study closed to follow-up in May 2007; additional details of study conduct have been previously reported.[34,35]

Our analysis focused on children who were perinatally HIV-exposed but uninfected and who had at least 1 neurodevelopmental functioning test by using the Bayley Scales of Infant Development (BSID). At the time of enrollment into PACTG 219/219C, clinical records were abstracted to obtain medical and clinical histories. ARV exposure information was collected during pregnancy or within the first years of life (75% enrolled before age 1 and 90% before age 18 months) and was supplemented with data collected in other PACTG studies (primarily perinatal protocols 076, 185, and 316). Maternal HIV RNA levels during pregnancy were not collected in 219/219C but were obtained from these perinatal protocols when available.

Neurodevelopmental functioning in children up to 3 years of age was assessed by using the BSID I[36]; the BSID II replaced the BSID I study-wide in March 1996, after being revised by test developers to address both changes in theory and developmental research and the upward shifts in scores.[37,38] BSID were scheduled to be administered as study-required assessments by trained psychologists according to standardized procedures every 6 months until 36 months of age in PACTG 219 and at 6, 12, 24, and 36 months of age in PACTG 219C. Our analysis included the BSID test conducted closest to 24 months of age. Floor-adjusted scaled scores were used, and results that were judged invalid by the site psychologist and confirmed invalid after review by team psychologists were excluded. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) were used to measure general functioning in mental and motor skills, respectively. The MDI and PDI are well-established measures that are standardized to have a mean 100 and an SD 16 (BSID I)[36] or 15 (BSID II).[37] Our study of 1840 individuals had 90% power to detect differences in BSID test scores of ≥4.2 points between exposed and unexposed subjects.

Linear regression methods were used to estimate the association of in utero ARV exposure on MDI and PDI scores, controlling for demographic factors (age at test, gender, and race/ethnicity) and potential confounders: test version (BSID I or II), primary language, primary caregiver, caregiver education level, low birth weight (LBW; >2500 g), and birth year. In

addition, we controlled for variation on the basis of the size of clinical unit (patient accrual), geographic location in the United States, and urban/rural location. The effects of ARV and other covariates on MDI and PDI scores are summarized by using least squares means; these adjusted means reflect the predicted BSID scores when all other model covariates were set to their average values. Interactions between in utero ARV exposure and other covariates were explored to evaluate possible effect modification. Because of the reported decrease in mean scores for the BSID II as compared with the BSID I test versions,[38] along with the coincident introduction of pro-tease inhibitors,[39] we also conducted a stratified analysis by test version. In addition, subgroup analyses were conducted among the subset of women with information available on maternal substance use (heroin, cocaine, or other stimulants, n = 1162) and among those with maternal viral load measurements (n = 936) during pregnancy.

Comparisons were also conducted of the proportion of children in each group with severe mental or motor impairment, defined as an MDI or PDI score <70, respectively, both overall and adjusted for potential confounders by using logistic regression analysis. Analyses were conducted using SAS 9 (SAS Institute Inc, Cary, NC) and included data submitted as of November 2006. All P values are 2-sided, and $P < .05$ was considered statistically significant.

RESULTS

A total of 2342 uninfected, HIV-exposed infants were enrolled in PACTG 219 or 219C as of November 2006, 2300 of whom were enrolled within the recommended age range for BSID I and II testing. Among these 2300 infants, 1910 had at least 1 BSID test reported, and 1840 (96%) of these had both valid test results and known maternal ARV exposure (47 were judged invalid after review by team psychologists, and 23 were excluded because of missing ARV exposure). These 1840 infants were born between 1993 and 2006 and included 1694 (92%) children who were exposed and 146 (8%) who were not exposed to ARV in utero. Demographic characteristics of the study population are summarized in Table 1. Of the 1840 children, 293 (16%) had LBW. Maternal use of heroin, cocaine, or stimulants during pregnancy was self-reported by 17% of those with information available. Although most characteristics were similar by exposure status, those with in utero ARV exposure were more likely to be born after 1994 (89% vs 22%) and to have been assessed by using the BSID II test (81% vs 21%). There was no significant difference in background characteristics for those who were excluded because of invalid BSID scores, but the 23 who were excluded because of missing ARV exposure were less likely to have a biological parent as caregiver.

Mean MDI and PDI scores are presented in Tables 2 and 3, respectively, both unadjusted and adjusted for all other covariates in a linear regression model. Overall, unadjusted mean MDI and PDI scores were significantly lower than the US population norms of 100. After controlling for confounders, children who were exposed in utero to any ARV agent showed no decrement in MDI and PDI scores as compared with ARV-unexposed children (adjusted mean MDI: 94.8 vs 92.2 [P = .07]; PDI: 93.9 vs 93.5 [P = .82]). Significantly higher adjusted mean MDI and PDI scores were observed among girls, infants of normal birth weight, and those with more highly educated primary caregivers. In addition, significant variation in both MDI and PDI scores was observed across clinical sites on the basis of site size and of geographic and urban location. Significantly lower adjusted MDI and PDI mean scores were observed in children who were tested with the BSID II as compared with the BSID I. Significant differences among race/ethnicity groups and according to primary language were observed for MDI scores but not for PDI scores. Sensitivity analyses for MDI

and PDI scores excluding the effect of birth weight, which may itself be a result of maternal ARV exposure, yielded similar conclusions regarding prenatal exposure (Table 4).

Although no overall effect of maternal ARV exposure was observed, adjusted mean MDI scores were 10 to 12 points higher for ARV-exposed than unexposed among the 293 LBW infants ($P = .01$; Table 4, Fig 1), whereas no significant difference was observed among infants of normal birth weight. No other significant interactions of covariates with maternal ARV exposure were observed. Separate models fit by BSID test version confirmed results of the overall analysis (Table 4, Fig 2); adjusted MDI and PDI means were within 2 to 4 points for ARV-exposed and unexposed children for each version and were not significantly different.

We also considered several different exposure classifications for maternal ARV, again adjusting for all other covariates in Table 1; however, none of the classifications suggested lower MDI or PDI scores with increasing levels of in utero exposure (data not shown). In particular, we compared infants whose mother received HAART during pregnancy (47%) with those whose mother received a non-HAART regimen (45%) or were unexposed prenatally to ARV (8%) and observed no difference in MDI or PDI scores. The non-HAART regimens ($n = 834$) included a single NRTI (primarily ZDV; 59%), 2 NRTIs (15%), and other nonHAART combinations (26%). We addressed the effect of regimens, including ZDV plus 3TC, and observed higher adjusted MDI scores in those who were exposed to regimens that contained ZDV + 3TC (57%) than in those who were not exposed (adjusted MDI means: 95.4 vs 91.9; $P = .04$) but no difference between those who were exposed to other ARV regimens (35%) versus unexposed (mean MDI: 94.2 vs 91.9; $P = .16$). No difference was observed in adjusted PDI means on the basis of ZDV + 3TC exposure (adjusted means: 93.7 vs 94.0 vs 93.6 for ZDV + 3TC-containing, other ARV, and unexposed, respectively).

We found a significant trend of higher mental scores with increasing duration of maternal ARV exposure, with adjusted mean MDI scores of 92.4, 94.5, 95.3, and 95.9 for infants who were exposed 0 weeks (9%), 1 to 13 weeks (23%), 13 to 25 weeks (36%), and ≥26 weeks (32%), respectively ($P = .02$); however, mean scores were only ~3 points higher for those who were exposed for ≥26 weeks as compared with unexposed children. Trimester of in utero exposure could be adequately ascertained for 1614 (88%) infants; mean MDI scores for children whose mother received a ZDV + 3TC- containing regimen were marginally higher for second-trimester exposure and significantly higher (~3 points) for third-trimester exposure, as compared with those who were not exposed during that respective trimester.

Maternal substance use during pregnancy was reported for 17% of mothers with available information but was not associated with MDI or PDI scores (Table 5). Among the subset of 936 (51%) infants with maternal viral load information available from other PACTG perinatal treatment trials, there were slightly lower (but not statistically significant) adjusted MDI scores with increasing viral load, from 93.9 for those with <400 copies per mL to 89.1 for those with >50 000 copies per mL (trend test $P = .09$), and a parallel significant decline in adjusted PDI scores (trend test $P = .03$). In this subset, there was no overall effect of maternal ARV exposure after adjustment for maternal viral load, but the significant increase of ~10 points in MDI scores among LBW infants who were exposed to ARV as compared with unexposed LBW infants was confirmed.

Last, logistic regression models supported a lack of association between in utero ARV exposure and higher percentages of children with mental or motor impairment (defined by BSID scores <70). The prevalence of mental impairment was 13% within each exposure group and for motor functioning was 10% within each group. Multiple logistic regression

models that adjusted for the covariates described previously suggested a decreased odds of mental impairment for ARV-exposed versus unexposed infants (odds ratio: 0.50; $P = .05$) and no difference in motor impairment rates (odds ratio: 0.85; $P = .65$).

DISCUSSION

Our study of >1800 children who were born to HIV-infected mothers found no decrement in neurodevelopmental functioning at 2 years of age associated with in utero exposure to ARV agents. After adjustment for important covariates that are associated with mental and motor functioning, similar or slightly higher mean BSID scores were observed among those with prenatal ARV exposure as compared with those without. These relationships were maintained even in separate models fit for each BSID test version, which is notable given the shift in mean scores between these 2 versions.[38] These results provide additional support to previous studies that found no association between early neurodevelopmental functioning and prenatal ARV exposure and also provide reassurance regarding the safety of in utero ARV exposure.

Alimenti et al[33] observed significantly lower mean MDI scores for 39 HAART-exposed children as compared with 24 unexposed children and consistently lower scores across a number of other developmental assessments; however, their study had unexpected imbalances between their ARV-exposed group and their “control” group in maternal illicit drug use and other important confounders. A previous analysis of >800 children with the BSID II test by Lindsey et al[32] found no difference in mental and motor functioning between infants who were younger than 1 year who did or did not have maternal ARV exposure; however, this was not the primary focus of their evaluation and was not adjusted for any potential confounders.

High rates of illicit drug use during pregnancy have been reported for HIV-infected women,[40–42] which could pose risks for infant neurodevelopment; however, we did not observe a relationship between self-reported maternal illicit drug use and cognitive or motor functioning, which is consistent with findings from a number of other large studies.[31,32,40] The WITS found a delay in mental and motor functioning at 4 months of age but not at 24 months among HIV-exposed uninfected children with maternal hard drug exposure.[40] Similarly, other evaluations of the WITS data have found no effect of prenatal illicit drug exposure on mental or motor scores through the first 30 months of life[31] or on behavioral outcomes.[42] Previous evaluations of the PACTG 219/219C cohort also identified no effect of maternal injection drug use on BSID scores.[32] However, it is possible that self-reported maternal substance use in our study is under-reported because of social desirability, fear of legal consequences, and concerns regarding child custody issues; such underreporting may attenuate associations.[41]

Although we observed slightly higher BSID scores for ARV-exposed children after adjustment for demographic and socioeconomic measures, these differences were small and may reflect incomplete control for other potential confounders, such as household income levels and access to prenatal care. We found significantly higher mental functioning among LBW infants who were prenatally exposed to ARV, which suggests the possibility of greater access to prenatal care as compared with the ARV-unexposed LBW infants. The additional advantages of both prenatal and postnatal care may be most dramatic in situations in which the infant's health is at risk, such as for LBW infants. Such care may include skilled neonatal attention along with health and nutritional counseling for both infants and their mothers, which in turn may create a home environment that is conducive to appropriate neurodevelopment; however, greater access to prenatal care would not be expected for those who originally were randomly assigned to placebo in AIDS Clinical Trials Group 076,

which comprised 68% of the unexposed individuals in our analysis. We also observed a trend suggestive of lower neurodevelopmental functioning with higher maternal viral load, suggesting the possibility of a cytokine response associated with incompletely controlled viral load during pregnancy.[43]

The major strengths of our study are its large size, its prospective nature, and its ability to control for many potential confounders. In addition, the inclusion of a subgroup of ARV-unexposed children is a key strength that is unlikely to be repeated in future studies, at least in high-resource settings; however, the observational nature of the study is a limitation in that there may be unmeasured confounders, which could lead to biases in estimated effects.[44] Assessment of neurodevelopmental functioning among ARV-exposed uninfected children as they age into school years is warranted, along with continued monitoring to address the safety of new ARV agents and combination regimens received by HIV-infected pregnant women.

WHAT'S KNOWN ON THIS SUBJECT

Two previous studies evaluated the effects of prenatal ARV exposure on neurodevelopmental functioning in HIV-exposed uninfected infants and found no association; however, these studies were limited by sample size or lack of adjustment for potential confounders.

WHAT THIS STUDY ADDS

We evaluated the association of prenatal ARV exposure with neurodevelopmental functioning in >1800 HIV-exposed uninfected infants, adjusting for many potential confounders. We found no decrement in functioning of ARV-exposed 2-year-olds, providing reassurance regarding the safety of in utero ARV exposure.

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ABBREVIATIONS

ARV	antiretroviral
MTCT	mother-to-child transmission

ZDV	zidovudine
HAART	highly active antiretroviral therapy
NRTI	nucleoside reverse transcriptase inhibitor
3TC	lamivudine
WITS	Women and Infants Transmission Study
PACTG	Pediatric AIDS Clinical Trials Group
BSID	Bayley Scales of Infant Development
MDI	Mental Developmental Index
PDI	Psychomotor Developmental Index
LBW	low birth weight

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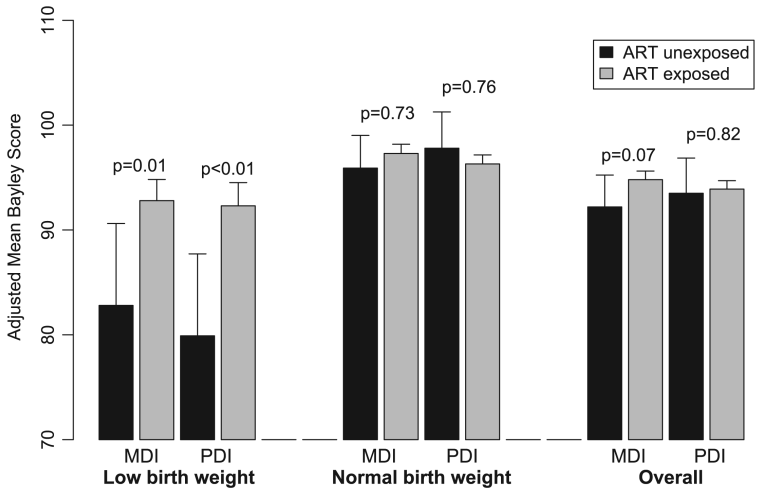

FIGURE 1.

MDI and PDI scores overall and by birth weight; estimated least squares means for 1840 HIV-exposed uninfected children in PACTG 219/219C at age 2 years, by exposure to ARV treatment (ART). Least squares means are adjusted for exact age at test, birth year, gender, race/ethnicity, type of caregiver, caregiver education level, primary language, region of country, site size, rural/urban site classification, and BSID test version.

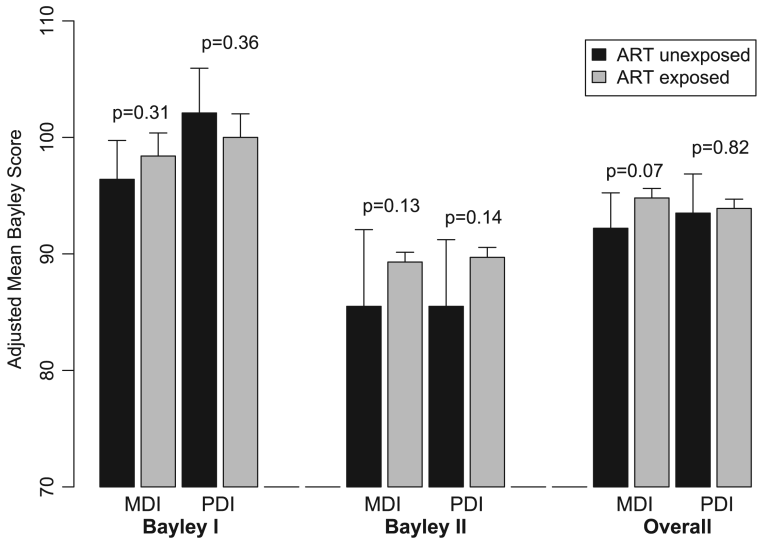

FIGURE 2.

MDI and PDI scores overall and by BSID test version (I or II); estimated least squares means for 1840 HIV-exposed uninfected children in PACTG 219/219C at age 2 years, by exposure to ARV treatment (ART). Least squares means are adjusted for exact age at test, birth year, gender, race/ethnicity, type of caregiver, caregiver education level, primary language, birth weight, region of country, site size, and rural/urban site classification.

TABLE 1

Demographic, Health, and Site Characteristics of 1840 HIV-Exposed Uninfected Study Participants Overall and by In Utero ARV Exposure

Characteristic	All Study Subjects (*N*= 1840)	In Utero ARV Exposure	
		Exposed (*n* = 1694)	Not Exposed (*n* = 146)
Female, *n* (%)	921 (50)	844 (50)	77 (53)
Age at test, median (IQR)	1.8 (1.0–2.0)	1.6 (1.0–2.0)	1.8 (1.5–2.1)
Race/ethnicity, *n* (%)			
White non-Hispanic and other races	242 (13)	219 (13)	23 (16)
Black non-Hispanic	1016 (55)	933 (55)	83 (57)
Hispanic	582 (32)	542 (32)	40 (27)
Non-English primary language, *n* (%)	485 (26)	454 (27)	31 (21)
Biological parent as primary caregiver, *n* (%)	1758 (96)	1624 (96)	134 (92)
Education level of primary caregiver, *n* (%)			
Less than high school	642 (35)	589 (35)	53 (36)
High school graduate	601 (32)	557 (33)	44 (30)
Some college/technical school	401 (22)	365 (21)	36 (25)
College graduate or higher	93 (5)	88 (5)	5 (3)
Other/unknown	103 (6)	95 (6)	8 (6)
LBW, *n* (%)	293 (16)	274 (16)	19 (13)
BSID II used, *n* (%)	1391 (76)	1360 (81)	31 (21)
Child;s year of birth, *n* (%)			
1991–1994	294 (16)	180 (11)	114 (78)
1994–2000	817 (44)	804 (47)	13 (9)
2000–2006	729 (40)	710 (42)	19 (13)
Small Clinical site (<45 accrued infants), *n* (%)	1034 (56)	936 (55)	98 (67)
Region, *n* (%)			
Northeast	579 (32)	546 (32)	33 (23)
South	851 (46)	779 (46)	72 (49)
Midwest	165 (9)	143 (9)	22 (15)
West	245 (13)	226 (13)	19 (13)
Urban site (>1 million population), *n* (%)	1539 (84)	1419 (84)	120 (82)
Maternal substance use (*n* = 1162), *n* (%)	202 (17)	171 (16)	31 (27)
Maternal viral load, *n* (%), copies per mL			
≤400	362 (39)	350 (42)	12 (13)
401–5000	272 (29)	229 (27)	43 (46)
5000–50 000	235 (25)	199 (23)	36 (38)
>50 000	67 (7)	64 (8)	3 (3)
Unknown	904	852	52

IQR indicates interquartile range.

TABLE 2

Unadjusted and Adjusted MDI Scores by ARV Exposure and Other Characteristics

Characteristic	*n*	Unadjusted, Mean ± SD	Least Squares (Adjusted), Mean	*p*[a]
In utero ARV exposure				.070
Not exposed	146	90.6 ± 18.4	92.2	
Exposed	1694	87.7 ± 16.9	94.8	
BSID test version				<.001
BSID I	449	95.4 ± 18.3	100.6	
BSID II	1391	85.5 ± 15.9	86.4	
Primary caregiver				.580
Biological parent	1758	87.9 ± 17.0	93.0	
Other adult (foster, adoptive)	82	87.4 ± 17.1	93.9	
Primary caregiver education level				<.001
Less than high school	642	86.3 ± 17.2	90.8	
High school graduate/equivalency	601	87.8 ± 16.6	92.0	
Some college/technical school	401	89.2 ± 17.1	93.8	
College graduate	93	93.2 ± 18.6	98.9	
Other education	103	89.1 ± 15.8	92.0	
Primary language				.009
English	1355	88.5 ± 17.0	94.8	
Other	485	86.4 ± 17.1	92.2	
Gender				<.001
Male	919	86.0 ± 16.5	91.3	
Female	921	89.8 ± 17.4	95.6	
Age at time of test, mo				<.001
<9	209	95.5 ± 13.2	101.5	
9–15	393	94.2 ± 12.9	100.0	
15–21	285	88.4 ± 15.2	92.2	
21–27	804	84.0 ± 18.2	88.3	
>27	149	80.7 ± 18.7	85.4	
Race/ethnicity				<.001
White Non-Hispanic and other race	242	95.3 ± 17.7	95.7	
Black non-Hispanic	1016	86.5 ± 16.4	91.5	
Hispanic	582	87.4 ± 17.1	93.3	
Birth weight				<.001
LBW (<2500 g)	293	82.2 ± 16.9	90.9	
Normal birth weight (>2500 g)	1547	89.0 ± 16.9	96.1	
Birth year				.019
1991–1994	294	92.7 ± 17.5	90.8	
1994–2000	817	87.2 ± 17.8	94.7	
2000–2006	729	86.8 ± 15.7	95.0	
Region of United States				<.001

Characteristic	*n*	Unadjusted, Mean ± SD	Least Squares (Adjusted), Mean	*P*[a]
Midwest	165	92.0 ± 14.5	96.6	
Northeast	579	84.8 ± 17.9	89.0	
South (including Puerto Rico)	851	87.8 ± 16.7	94.0	
West	245	93.1 ± 16.1	94.4	
Type of site				<.001
Rural (<1 million population)	301	93.6 ± 15.4	97.0	
Urban	1539	86.8 ± 17.1	90.0	
Size of site (total accrual)				<.001
≤45 subjects	1034	90.6 ± 16.5	96.2	
>45 subjects	806	84.5 ± 17.1	90.8	

[a]From type III F test of effect in multiple linear regression model, adjusting for all other covariates shown above at their average levels.

TABLE 3

Unadjusted and Adjusted PDI Scores by ARV Exposure and Other Characteristics

Characteristic	*n*	Unadjusted, Mean ± SD	Least Squares (Adjusted), Mean	*p*[a]
In utero ARV exposure				.820
Not exposed	146	97.9 ± 20.3	93.5	
Exposed	1694	92.9 ± 16.9	93.9	
BSID test version				<.001
BSID I	449	100.3 ± 19.1	98.8	
BSID II	1391	91.0 ± 15.9	88.5	
Primary caregiver				.090
Biological parent	1758	93.5 ± 17.4	95.3	
Other adult (foster, adoptive)	82	89.4 ± 17.2	92.1	
Primary caregiver education level				.040
Less than high school	642	91.9 ± 18.1	91.9	
High school graduate/equivalency	601	94.0 ± 16.4	94.0	
Some college/technical school	401	94.7 ± 16.7	95.0	
College graduate	93	92.7 ± 16.7	94.1	
Other education	103	93.0 ± 18.3	93.5	
Primary language				.530
English	1355	93.2 ± 16.7	93.5	
Other	485	93.4 ± 18.6	94.1	
Gender				.025
Male	919	92.5 ± 17.3	92.8	
Female	921	94.1 ± 17.0	94.5	
Age at time of test, mo				<.001
<9	209	93.6 ± 15.5	95.1	
9–15	393	95.6 ± 14.9	97.1	
15–21	285	94.3 ± 14.4	93.8	
21–27	804	92.6 ± 18.4	92.8	
>27	149	88.7 ± 21.8	89.7	
Race/ethnicity				.490
White Non-Hispanic and other race	242	96.2 ± 16.8	94.7	
Black non-Hispanic	1016	92.8 ± 16.4	93.4	
Hispanic	582	92.9 ± 18.5	93.0	
Birth weight				<.001
LBW (<2500 g)	293	88.2 ± 18.4	91.2	
Normal birth weight (>2500 g)	1547	94.3 ± 16.8	96.1	
Birth year				.450
1991–1994	294	99.0 ± 20.4	92.5	
1994–2000	817	93.2 ± 17.0	94.4	
2000–2006	729	91.1 ± 15.4	94.1	
Region of United States				<.001

Characteristic	*n*	Unadjusted, Mean ± SD	Least Squares (Adjusted), Mean	*P*[a]
Midwest	165	93.9 ± 14.2	94.5	
Northeast	579	89.7 ± 17.3	90.2	
South (including Puerto Rico)	851	95.0 ± 17.3	96.5	
West	245	95.4 ± 17.0	93.7	
Type of site				<.001
Rural (<1 million population)	301	96.9 ± 16.7	95.7	
Urban	1539	92.6 ± 17.2	91.7	
Size of site (total accrual)				<.001
≤45 subjects	1034	94.5 ± 17.2	95.8	
>45 subjects	806	91.7 ± 17.0	91.6	

[a]From type III F test of effect in multiple linear regression model, adjusting for all other covariates shown above at their average levels.

TABLE 4

Adjusted MDI and PDI Scores by ARV Exposure Overall, by Birth Weight, and on the Basis of Separate Models for Each BSID Test Version

Characteristic	*n*	MDI		PDI	
		Adjusted Mean[a]	*p*[b]	Adjusted Mean[a]	*p*[b]
Overall in utero ARV exposure			.07		.82
Not exposed	146	92.2		93.5	
Exposed	1694	94.8		93.9	
Model excluding adjustment for birth weight					
Overall in utero ARV exposure			.07		.82
Not exposed	146	93.8		95.2	
Exposed	1694	96.4		95.5	
Model including interaction by birth weight					
LBW (<2500 g)			.01		<.01
Not exposed	19	82.8		79.9	
Exposed	274	92.8		92.3	
Normal birth weight (≥2500 g)			.73		.76
Not exposed	127	95.9		97.8	
Exposed	1420	97.3		96.3	
Separate models for each BSID test version					
BSID I			.31		.36
Not exposed	115	96.4		102.1	
Exposed	334	98.4		100.0	
BSID II			.13		.14
Not exposed	31	85.5		85.5	
Exposed	1360	89.3		89.7	

[a]Adjusted for age, birth year, sex, race/ethnicity, type of caregiver, caregiver education level, primary language, birth weight (except where indicated), BSID test version (except in separate models by version), region of country, site size, and rural/urban site classification, all at the levels shown in Table 1.

[b]From F test in multiple regression model, adjusting for all of the above covariates.

TABLE 5

Adjusted MDI and PDI Scores by ARV Exposure Within Subsets With Maternal Viral Load and Maternal Substance Use Information

Characteristic	*n*	MDI		PDI	
		Adjusted Mean[a]	*p*[b]	Adjusted Mean[a]	*p*[b]
Among those with maternal substance use data (*n* = 1162)					
In utero ARV exposure			.46		.32
Not exposed	116	92.6		95.3	
Exposed	1046	93.9		93.3	
Maternal substance use			.69		.94
Yes	202	93.0		94.3	
No	960	93.5		94.4	
Among those with maternal viral load data (*n* = 936)					
In utero ARV exposure			.83		.13
Not exposed	94	91.8		92.6	
Exposed	842	92.2		89.0	
Maternal viral load, copies per mL			.12		.06
≤400	362	93.9		93.5	
401–5000	272	92.0		91.0	
5000–50 000	235	93.0		91.6	
>50 000	67	89.1		87.1	

[a] Adjusted for age, birth year, gender, race/ethnicity, type of caregiver, caregiver education level, primary language, birth weight, BSID test version, region of country, site size, and rural/urban site classification, all at the levels shown in Table 1.

[b] From F test in multiple regression model, adjusting for all of the above covariates; for maternal viral load, from trend test of decreasing scores with increasing viral load.