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Safety of Perinatal Exposure to Antiretroviral Medications: Developmental Outcomes in Infants

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Abstract

Background—This study evaluated effects of perinatal exposure to antiretroviral (ARV) medications on neurodevelopment of HIV-exposed, uninfected infants.

Methods—HIV-exposed, uninfected infants (age 9–15 months) enrolled in SMARTT, a multisite prospective surveillance study, completed the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III), assessing cognition, language, motor skills, social-emotional development, and adaptive behavior. Linear regression models were used to evaluate associations between Bayley-III outcomes in infants with and without perinatal and neonatal ARV exposure, by regimen (combination ARV [cARV] versus non-cARV), type of regimen (defined by drug class), and individual ARVs (for infants with cARV exposure), adjusting for maternal and infant health and demographic covariates.

Results—As of May 2010, 374 infants had valid Bayley-III evaluations. Median age at testing was 12.7 months; 49% male, 79% black, 16% Hispanic. Seventy-nine percent were exposed to regimens containing protease inhibitors (PIs; 9% of PI-containing regimens also included non-nucleoside reverse transcriptase inhibitors [NNRTIs]), 5% to regimens containing NNRTIs (without PI), and 14% to regimens containing only nucleoside reverse transcriptase inhibitors

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SUPPLEMENTAL DIGITAL CONTENT Supplemental Digital Content 1. Figure showing the comparison of unadjusted mean Bayley-III domain scores between the HIV-exposed infants and the population norm. pdf Supplemental Digital Content 2. Table presenting the comparison of unadjusted mean Bayley-III domain scores for the HIV-exposed and HIV-unexposed infants. pdf

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(NRTIs). Overall, 83% were exposed to cARV. No Bayley-III outcome was significantly associated with overall exposure to cARV, ARV regimen, or neonatal prophylaxis. For individual ARVs, following sensitivity analyses, the adjusted group mean on the Language domain was within age expectations but significantly lower for infants with perinatal exposure to atazanavir ($p=0.01$).

Conclusions—These results support the safety of perinatal ARV use. Continued monitoring for adverse neurodevelopmental outcomes in older children is warranted, and the safety of atazanavir merits further study.

Keywords

HIV; ARV; infant; neurodevelopment; developmental assessment

Use of antiretroviral (ARV) medications during pregnancy has led to a dramatic decline in mother-to-child transmission of human immunodeficiency virus (HIV)¹ while increasing the number of HIV-exposed, uninfected children worldwide.^{2,3} ARVs may have a negative effect on infant and child health and development.^{2,4-6}

Currently, most pregnant women with HIV in the U.S. receive combination ARV (cARV) therapy to prevent mother-to-child transmission.^{2,4,7-9} Investigators conducting human and animal studies of prenatal ARV exposure have noted structural and functional changes in the central nervous system (CNS),¹⁰⁻¹³ suggesting the CNS may be an important target of these agents. *In utero* exposure to NRTIs such as zidovudine (Retrovir; GlaxoSmithKline, Brentford, Middlesex, UK) has been associated with mitochondrial toxicities in animal and human studies.¹⁴⁻²³ Mitochondrial defects adversely affect high-energy organ systems including the brain and peripheral nervous system.²⁴ Conflicting information exists regarding effects of ARV exposure on neurologic and neurodevelopmental functioning. The French Perinatal Cohort study²⁵ examined approximately 1800 children exposed to ARVs and reported 8 with findings compatible with mitochondrial dysfunction, higher than expected in the general population. The European Collaborative Study²⁶ and the Petra study²⁷ found no increase in the rate of severe adverse events in children with perinatal ARV exposure. Among 1037 HIV-exposed, uninfected children, Brogly and colleagues²⁸ identified 20 (1.9%) with possible mitochondrial dysfunction, including 19 with neurological or developmental abnormalities. No clear-cut association with *in utero* NRTI exposure emerged, but results suggested that first exposure to lamivudine (Epivir; GlaxoSmithKline, Brentford, Middlesex, UK) or zidovudine/lamivudine (Combivir; GlaxoSmithKline, Brentford, Middlesex, UK) in third trimester might be associated with clinical findings of mitochondrial dysfunction. Children with clinical abnormalities in this study tended to have laboratory evidence of mitochondrial abnormalities compared to ARV-exposed and ARV-unexposed children without clinical findings.²⁹ A risk-benefit analysis of ARV use in pregnancy³⁰ found the three least effective regimens demonstrated low toxicity, while three-drug ARV regimens initiated in first trimester resulted in fewer HIV infections but slightly more cases of suspected mitochondrial toxicity.

Risk for lowered cognitive performance or increased behavior problems in ARV- and HIV-exposed children is not firmly established.³¹⁻³⁵ The French Perinatal Cohort study²⁵ found evidence of developmental delay in children with prenatal ARV exposure, but other investigators^{26,27,31,32} reported no such association. Some studies did not control adequately for maternal/caregiver and environmental characteristics associated with developmental delays in infants and children, including prenatal exposure to alcohol, drugs, and infections; environmental factors such as poverty, lead exposure, maternal education, and parental medical and psychiatric illness; and, for infants with HIV exposure, severity of maternal HIV disease and pre- and postnatal ARV exposure.^{28,30,36-41}

The primary objective of this analysis was to evaluate safety of *in utero* and neonatal ARV exposure with respect to development in HIV-exposed, uninfected infants during the first year of life. Specific aims were: (1) describe infant development across developmental domains, (2) evaluate prenatal and postnatal factors confounding the relationship between *in utero* ARV exposure and infant development, (3) evaluate effects of type and timing of prenatal ARV exposure on development, and (4) evaluate effects of neonatal ARV exposure on development.

MATERIALS AND METHODS

Participants

The Surveillance Monitoring for ART Toxicities (SMARTT) study is a prospective cohort study designed to evaluate the safety of *in utero* and neonatal exposure to ARVs. All infants were HIV-exposed but uninfected with complete information on perinatal ARV exposure. The study is conducted by the Pediatric HIV/AIDS Cohort Study (PHACS) network at 22 sites in the United States, including Puerto Rico. SMARTT includes infants followed from birth (Dynamic cohort) and infants enrolled in earlier HIV-related studies (Static cohort). The first infants were enrolled in 2007. SMARTT also includes a Reference cohort of infants who were not exposed to HIV or ARVs, drawn from the same demographic background and enrolled at the same research sites in 2010-2011.

Procedures

Developmental assessments were administered according to standardized procedures by licensed psychologists when the infants were 9-15 months of age (the 1-year-old study visit). The institutional review board at each participating site and at Harvard School of Public Health approved the study. Parents or legal guardians provided written informed consent for their own and their infant's participation.

Infant outcomes—The Bayley Scales of Infant and Toddler Development—Third Edition⁴² (Bayley-III) is normed for infants and young children, ages 1-42 months, and provides standardized measures of infant development in five domains: Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior. The cognitive, language, and motor scales were administered via direct testing with the infant; the social-emotional and adaptive behavior scales were administered as face-to-face interviews with mothers/primary caregivers. The Bayley-III is available only in English. Infants were excluded if the mother/primary caregiver was not able to complete the assessment in English; thus the two sites in Puerto Rico did not participate. Scores were not corrected for prematurity to obtain precise assessments of infants' current developmental functioning.

ARV exposures—cARV was defined as any maternal regimen containing at least three ARVs from at least two drug classes. Neonatal prophylaxis was defined as use of ARV medications during the first eight weeks of life, dichotomized into zidovudine monotherapy versus combination neonatal prophylaxis using at least two ARV medications. ARV regimens were defined by ARV drug class, using three mutually exclusive categories: protease inhibitor (PI)-containing (with or without NNRTIs), NNRTI-containing (without PI), and NRTI only. ARV exposure was analyzed by (1) maternal use of cARV, (2) maternal ARV regimen, (3) maternal use of individual ARVs, and (4) neonatal prophylaxis. Use of cARV and ARV regimens were analyzed overall (anytime during pregnancy) and by trimester. To reduce residual confounding, individual ARVs were evaluated for the subset of infants exposed to cARV *in utero*, considering cARV with a specific ARV versus cARV without that ARV. The trimester of first reported use during pregnancy was explored for individual ARVs showing significant overall associations with Bayley-III outcomes.

Covariates and confounders—Potential confounders were identified *a priori*. Infant characteristics included age at testing, sex, race, ethnicity, prematurity (gestational age < 37 weeks), birth weight, small for gestational age (SGA; birth weight < 10th percentile for gestational age), and year of delivery. Maternal and caregiver characteristics included income and educational levels, primary language, and marital status. Several measures of maternal health during pregnancy were included: age at delivery, sexually transmitted disease (STD), use of alcohol, tobacco, or illicit drugs, first CD4% and HIV RNA plasma level (viral load) during pregnancy, and last CD4% and viral load prior to delivery. Demographic and maternal health data were obtained through medical record review and maternal/caregiver interviews at study entry. Measures of maternal/caregiver cognition were obtained with the Wechsler Abbreviated Scale of Intelligence,⁴³ providing a Full Scale IQ (FSIQ) score. Maternal/caregiver mental health status was assessed with the Client Diagnostic Questionnaire (CDQ),⁴⁴ a screening instrument developed and validated for populations affected by HIV. The CDQ was administered as a face-to-face interview to assess presence of symptoms of psychiatric illness, including depression, anxiety, alcohol and illicit substance abuse, post-traumatic stress disorder, and psychosis. Maternal/caregiver FSIQ and CDQ data were collected concurrent with infant testing.

Statistical Methods

Descriptive statistics (means and standard deviations) were calculated for the HIV-exposed and HIV-unexposed infants for each Bayley-III domain, and the two groups were compared using t-tests. Characteristics of each cohort were compared using chi-square tests or t-tests, as appropriate. For HIV-exposed infants, linear regression models were used to evaluate the associations of *in utero* ARV exposures with each Bayley-III outcome, adjusted for potential confounders. Potential confounders were first evaluated in univariate models. A core model was developed separately for each Bayley-III domain by including covariates with $p < 0.20$ in univariate models and reducing to only those covariates with $p < 0.10$ in multivariate models. Infant age at testing was included in each model regardless of its significance. Linear regression models were fit for each Bayley-III subtest separately, adjusting for the same core confounders as the corresponding domain.

Several sensitivity analyses were conducted. First, because ARVs are associated with increased risk of premature birth^{2,45-48} and prematurity is associated with developmental delay,^{49,50} models were fit both with and without adjustment for prematurity and SGA for Bayley-III outcomes that included those variables in their core models. Second, due to the potential for inherent differences among research sites, a sensitivity analysis was conducted to adjust for site.

All analyses were based on data submitted to the PHACS data center as of May 2010 for the SMARTT Dynamic and Static cohorts and March 2012 for the Reference cohort and conducted using SAS Version 9.2 (SAS Institute Inc., Cary, NC). Two-sided p-values < 0.05 were considered statistically significant. Because SMARTT is a safety study, no correction for multiple comparisons was employed to minimize the Type II error rate, thus the findings warrant confirmation in future studies.

RESULTS

Participants

As of May 1, 2010, 574 infants had attended the 1-year-old study visit and were potentially eligible for the analyses. Of those, 384 had both a completed Bayley-III (obtained between the ages of 9 and 15 months) and information available about perinatal ARV exposure. Of these 384, 10 had invalid Bayley-III scores for all five domains and were excluded from the

analyses. Reasons for not including the remaining 190 infants were: missing Bayley-III (n = 175); Bayley-III completed outside the appropriate age range (n = 6); and missing detailed information on perinatal ARV exposure (n = 9). The most common reason for a missing Bayley-III was a primary language at home other than English (n = 85; 49%); remaining reasons included missed appointments and lack of time to complete the Bayley-III. There were differences in demographic and health characteristics between the infants and mothers/caregivers included in the analyses and those not included, but after controlling for primary language, only two differences remained significant: a higher percentage of infants included in the analyses were born before 2009 and lived in households with higher annual income.

Table 1 presents infant and maternal/caregiver demographic characteristics for the HIV-exposed, uninfected infants in the Static and Dynamic cohort (N = 374) and the HIV-unexposed infants in the Reference cohort (N = 49 as of March 1, 2012). The HIV-exposed and HIV-unexposed groups were similar except that the HIV-exposed infants were more likely to have been born in earlier years (due to the later enrollment of the Reference cohort) and were less likely to be SGA. The mothers/caregivers of the HIV-exposed infants were more likely to have had obstetrical complications and functional limitations in daily living at the time of the infant's assessment.

Among the 374 infants with HIV exposure, 79% were exposed to PI-containing regimens (9% of PI-containing regimens also included NNRTIs), 5% to regimens containing NNRTIs without PI, and 14% to regimens containing only NRTIs. Overall, 83% were exposed *in utero* to cARV. The 17% who were not exposed to cARV *in utero* included those whose mothers used no ARVs during pregnancy or had regimens that did not meet criteria for cARV (regimens with one or two ARVs or three NRTIs). This subset of cARV-unexposed infants (n = 62) was excluded from the analyses of individual ARV exposures. Maternal and infant characteristics were similar for cARV-unexposed and cARV-exposed groups except that fewer mothers of cARV-unexposed infants reported illicit drug use during pregnancy (2% vs. 10%, respectively, p = 0.04), and fewer had a CD4% ≥ 25% prior to delivery (24% vs. 40%, respectively, p = 0.02). Mothers/caregivers of cARV-unexposed infants had a lower mean FSIQ than mothers/caregivers of cARV-exposed infants (Mean [M] (standard deviation [SD]) = 83.7 (13.1) vs. 87.7 (13.6), respectively, p = 0.04).

Bayley-III Outcomes

Unadjusted analyses revealed small but significant differences in Bayley-III domain mean scores for HIV-exposed infants (N = 374) compared to the mean of the Bayley-III standardization sample (M = 100, SD = 15) (see Figure, Supplemental Digital Content 1, showing the comparison between the HIV-exposed infants and the population norm; p 0.01 for all comparisons). Infants in this group obtained higher mean scores on the Cognitive (M = 104.1, SD = 14.4) and Social-Emotional (M = 102.3, SD = 17.0) domains and lower mean scores on the Language (M = 93.5, SD = 13.5), Motor (M = 97.8, SD = 13.5), and Adaptive Behavior (M = 95.3, SD = 14.5) domains. There were no significant differences in mean scores for any Bayley-III domain between the HIV-exposed and HIV-unexposed infants (see Table, Supplemental Digital Content 2, and Figure, Supplemental Digital Content 1, presenting the comparison between the HIV-exposed and HIV-unexposed infants).

In multivariate analyses conducted among HIV-exposed infants, several infant and caregiver characteristics were associated with Bayley-III domain scores. Prematurity was associated with lower performance in the Cognitive, Language, Motor, and Adaptive Behavior domains, with mean decreases ranging from 4.5 points in the Adaptive domain to 7.5 points in the Motor domain. Male sex, SGA, and maternal age ≥ 35 at delivery were associated with poorer Adaptive scores (mean decreases of 3.0, 7.6, and 4.8 points, respectively).

Lower maternal/caregiver cognition (FSIQ) was associated with lower mean scores for all Bayley-III domains (mean decreases of 4.5 to 6.6 points for FSIQ = 70-84, and 7.8 to 14.5 points for FSIQ < 70, compared to caregivers with FSIQ ≥ 100). In contrast, maternal viral load > 400 copies/mL prior to delivery was associated with a higher mean score in the Social-Emotional domain (mean increase, 5.4 points). Infants in the Dynamic cohort or whose mothers/caregivers reported illicit substance abuse at the time of infant testing had higher mean Adaptive scores (mean increases of 4.3 and 7.1 points, respectively). Infants born in 2007 had higher scores for all domains except Language compared to those born in 2008-2009 (mean increases of 3.8 to 7.4 points across domains). STD during pregnancy, self-reported illicit substance use during pregnancy, and maternal/caregiver income and educational levels at the time of infant testing were not associated with infant performance.

Analysis of ARV Exposures

cARV—After adjusting for domain-specific covariates with $p < 0.10$, there were no significant differences in mean scores for any Bayley-III domain or subtest between infants with *in utero* exposure to cARV ($n = 309$) and infants whose mothers used either one or two ARVs, three NRTIs, or no ARVs during pregnancy ($n = 62$; Table 2). This lack of difference between infants with and without cARV exposure remained consistent regardless of the timing of exposure to cARV.

ARV regimen—Adjusted mean Bayley-III scores for all domains and subtests were similar for infants with *in utero* exposure to a PI-containing (with or without NNRTI) or an NNRTI-containing (without PI) regimen to those of infants exposed *in utero* to an NRTI-only regimen (Table 3). These findings also remained consistent regardless of the timing of exposure to any regimen.

Individual ARVs—The association of *in utero* exposure to individual ARVs at any time during pregnancy was examined in the infants with cARV exposure. After adjusting for core confounders, 5 of the 14 medications had a significant association with at least one Bayley-III domain (Table 4). Lower performance on the Cognitive, Language, Social-Emotional, and Adaptive Behavior domains was associated with exposure to nelfinavir (Viracept; Pfizer Inc., New York, NY), atazanavir (Reyataz; Bristol-Myers Squibb, New York, NY), tenofovir (Viread; Gilead Sciences, Inc., Foster City, CA), and lopinavir/ritonavir (Kaletra; Abbott Laboratories, Abbott Park, IL), respectively. Higher performance on the Language and Social-Emotional domains was associated with lopinavir/ritonavir and lamivudine, respectively. The absolute differences ranged from 3.1 to 4.9 points across domains (between 0.2 and 0.3 SDs). Lower performance on the Receptive Communication subtest of the Language domain was associated with atazanavir (estimated difference < 1 point).

Neonatal prophylaxis—There was no association of any Bayley-III outcome with neonatal prophylaxis when comparing infants exposed to zidovudine alone with those exposed to zidovudine in combination with other ARVs.

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate potential associations between *in utero* ARV exposures and Bayley-III outcomes without adjustment for prematurity and SGA. There remained no association of cARV exposure or ARV regimen with any Bayley-III outcome. Among individual ARVs, the association of atazanavir exposure with lower mean Language scores and lopinavir/ritonavir exposure with lower mean Adaptive scores remained significant. The differences observed for nelfinavir exposure with lower mean Cognitive scores and lopinavir/ritonavir exposure with higher mean Language scores did not remain significant.

Adjusted models including research site revealed significant differences in mean Bayley-III outcomes for all five domains across the 20 participating sites. Further adjustment for research site had little effect on the findings regarding ARV exposures. There remained no significant association with cARV exposure, ARV regimen, or neonatal prophylaxis for any Bayley-III outcome. For the individual ARVs, only the association of atazanavir with a lower mean Language score remained significant ($p = 0.01$).

DISCUSSION

In this study, there was no association between *in utero* exposure to cARV or to any ARV regimen at any time during pregnancy and any Bayley-III outcome for infants age 9-15 months. These findings support the overall safety of ARVs currently prescribed during pregnancy and the neonatal period.

Analyses of individual ARVs, including zidovudine during the neonatal period, showed no consistent association with any Bayley-III outcome except for the association between *in utero* exposure to atazanavir and a lower mean score on the Language domain, observed in both the primary analyses and in sensitivity analyses adjusting for research site and omitting the intermediates of prematurity and SGA. It is possible that this association would not have been significant had we corrected for multiple comparisons; however, this could be a true association. Atazanavir has lower CNS penetration^{51,52} and poorer transplacental passage⁸ than other ARVs, making it possibly less protective of the developing fetal brain from HIV while less likely to produce direct CNS toxicity. Atazanavir has also been associated with neonatal hyperbilirubinemia,⁵³ a known cause of severe cognitive impairment in neonates. It is also possible that atazanavir has specific interactions with other factors that were not examined in this investigation, such as medications that the infants' mothers took during pregnancy. Therefore, additional research is warranted into the mechanisms by which atazanavir might adversely affect language development in infants.

Mean Bayley-III scores for the HIV-exposed and HIV-unexposed infants were similar and within age expectations, although some variability was observed across domains. Prematurity, SGA, and maternal/caregiver cognition are known to affect infant development in the general population and were also associated with infant development in this study. Maternal illicit substance use during pregnancy and the presence of maternal/caregiver psychiatric disorder at the time of infant testing were not associated with Bayley-III outcomes in this cohort.

The strengths of this study included the large sample of children with perinatal HIV and ARV exposure, the comparison with a reference cohort without these exposures, and valid Bayley-III data for both groups. The study also included detailed information concerning maternal and infant health, ARV history during pregnancy and the neonatal period, and environmental confounders. In SMARTT, maternal self-reports of substance use during pregnancy were confirmed through meconium assay. Discordance between self-report and meconium assay for metabolites of tobacco and illicit substances was uncommon,⁵⁴ thus we have confidence in the self-report data obtained from mothers in this analysis. Earlier investigations were unable to control adequately for these and other important maternal/caregiver characteristics, including maternal viral load,^{2,30} which can be associated with developmental delays in infants and young children. The current study is important, therefore, because it examined the influence of many relevant maternal/caregiver and infant characteristics, enabling us to control for confounders in assessing safety of *in utero* and neonatal exposure to ARVs.

Our findings are consistent with those of Brogly et al.²⁸ but not with those of the French Perinatal Cohort study.²⁵ The difference could be due to methodology and differences in medical treatment at the time of the research. The present study was more narrowly focused on infant development, employed a narrower age range (9-15 months), and included infants with *in utero* exposure to a larger number of ARVs (83% exposed to cARV), several of which were approved and became widely used⁹ after the French study was published in 1999. Changes in ARV use during pregnancy may have contributed to differing results among the studies.

The present study was limited by lack of information concerning adherence to ARV regimens, both maternal and neonatal, lack of information about maternal/caregiver cognition in a subset of the sample, and the large number of infants excluded because of missing Bayley-III data. In addition, the small number of infants who received zidovudine in combination with other ARVs limited the power to detect differences in neonatal prophylaxis regimens. In comparing infants with and without exposure to cARV *in utero*, we had 80% power to detect a difference of 5.8 points (0.39 SD) in mean Bayley-III domain scores. For the subset exposed to cARV *in utero*, depending on the percent exposed to specific ARVs, we had 80% power to detect differences of 4.9 to 8.1 points (0.33 to 0.54 SDs) in mean domain scores. Thus, it is unlikely that we missed important differences in these comparisons.

Although the current findings are encouraging, subtle but important differences as the result of early exposure to HIV and ARVs might emerge in learning, behavior, and adaptive skills as children grow older. Brain development is a dynamic process beginning in the first trimester and continuing into childhood and adolescence. Perinatal exposure to HIV and ARVs could affect developing neuronal systems, with the potential for long-term negative effects on infant and child development. As children grow older, environmental influences play a very significant role. Children require environmental supports to maximize individual potential for both physical and mental development and benefit from enriched environments that include stable homes, good nutrition, routine medical care, and opportunities for learning. Children exposed to HIV and ARVs may not experience these opportunities consistently. They also have the additional challenge of living with parents who may not be able to care for them due to chronic illness or death; they may face multiple changes in caregivers, foster care placement, and frequent disruptions in their lives. Such factors, along with the addition of the effects of *in utero* and neonatal ARV exposure, may create an incremental effect of potentially adverse consequences.

Continued study of infant development is warranted as new ARVs are developed and become more widely used. Future studies are needed to investigate the role of atazanavir in lower language skills in infants exposed to atazanavir *in utero*. Finally, additional prospective studies are necessary to assess both the short- and long-term effects of *in utero* ARV exposure on child development in older children exposed to both HIV and ARVs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Characteristics and ARV Exposure of HIV-exposed and HIV-unexposed Infants Included in the Analyses

Characteristics	SMARTT Cohort		p-value ^a
	Static and Dynamic HIV-exposed (N = 374)	Reference HIV-unexposed (N = 49)	
<u>Infant</u>			
Age (months) at time of testing, Median	12.7	13.3	0.98
(Q1, Q3)	(12.1, 13.7)	(11.6, 14.2)	
Year of delivery			< 0.001
2006	42 (11%)	0 (0%)	
2007	117 (31%)	0 (0%)	
2008	190 (51%)	0 (0%)	
2009	25 (7%)	31 (63%)	
2010	0 (0%)	18 (37%)	
Male sex	184 (49%)	23 (47%)	0.77
Black race	285 (79%)	36 (75%)	0.58
Hispanic ethnicity	61 (16%)	9 (19%)	0.69
Prematurity (< 37 weeks gestational age)	87 (23%)	6 (13%)	0.10
SGA (< 10th percentile for gestational age)	28 (8%)	8 (16%)	0.04
Exposure <i>in utero</i> to cARV	309 (83%)	---	
Exposure <i>in utero</i> to specific cARV regimen			
PI-containing (with or without NNRTIs)	297 (79%)	---	
NNRTI-containing (without PIs)	19 (5%)	---	
NRTI alone	53 (14%)	---	
No ARV exposure	5 (1%)	---	
Neonatal prophylaxis: zidovudine alone	364 (97%)	---	
<u>Maternal/Caregiver</u>			
Age at delivery 35 years	82 (22%)	6 (13%)	0.13
Education: less than high school	112 (30%)	10 (20%)	0.17
Annual household income			0.19
\$20,000	219 (62%)	30 (67%)	
\$20,000 – 40,000	96 (27%)	14 (31%)	
> \$40,000	38 (11%)	1 (2%)	
Single parent	186 (50%)	27 (55%)	0.48
Caregiver identity: biological parent	368 (98%)	47 (96%)	0.23
Any obstetrical complication	228 (61%)	12 (26%)	< 0.001
Any STD in pregnancy	131 (36%)	---	
Tobacco use during pregnancy	73 (20%)	4 (9%)	0.06
Alcohol use during pregnancy	31 (9%)	4 (9%)	0.97
Illicit substance use during pregnancy	31 (9%)	1 (2%)	0.13
FSIQ, Mean (SD)	87.0 (13.5)	89.0	(13.1) 0.33

Characteristics	SMARTT Cohort		p-value ^a
	Static and Dynamic HIV-exposed (N = 374)	Reference HIV-unexposed (N = 49)	
Positive screen for psychiatric disorder at time of infant testing	76 (21%)	12 (26%)	0.44
Positive screen for substance abuse disorder (alcohol or illicit drugs) at time of infant testing	22 (6%)	4 (9%)	0.50
Number of maternal/caregiver functional limitations at time of infant testing			0.03
0	257 (70%)	42 (88%)	
1-3	91 (25%)	4 (8%)	
4 or more	19 (5%)	2 (4%)	
First CD4% during pregnancy 25%	165 (46%)	---	
Last CD4% prior to delivery 25%	128 (37%)	---	
First viral load during pregnancy > 400 copies/mL	230 (62%)	---	
Last viral load prior to delivery > 400 copies/mL	63 (17%)	---	

^a Chi-square tests were used for all comparisons except for infant age at time of testing and maternal/caregiver FSIQ, for which a t-test with equal variance was used.

Missing data. The following numbers of participants in the Static and Dynamic cohort were excluded from the following calculations: race (11), ethnicity (3), prematurity (2), SGA (1), cARV exposure *in utero* (3), maternal age at delivery (1), household income (21), STD during pregnancy (7), obstetrical complications (1), alcohol/tobacco/illicit substance use during pregnancy (11), screening for psychiatric and substance abuse disorders (5), number of maternal/caregiver functional limitations at time of infant testing (7), maternal/caregiver FSIQ (47), first CD4% during pregnancy (18), last CD4% prior to delivery (27), first viral load during pregnancy (5), and last viral load prior to delivery (10). The following numbers of participants in the Reference cohort were excluded from the following calculations: race (1), ethnicity (1), prematurity (2), maternal age at delivery (1), household income (4), obstetrical complications (2), alcohol/tobacco/illicit substance use during pregnancy (3), screening for psychiatric and substance abuse disorders (2), number of maternal/caregiver functional limitations at time of infant testing (1), and maternal/caregiver FSIQ (4). The following characteristics were not collected from or not applicable to the Reference cohort: STD during pregnancy, *in utero* ARV exposures, neonatal prophylaxis, and CD4% and viral load measurements during pregnancy.

Table 2

Adjusted Mean Bayley-III Domain Scores by *In Utero* cARV Exposure for the SMARTT Static and Dynamic Cohort (N = 374)

<u>Adjusted Mean Score (Standard Error)</u>				
Bayley-III Domain	N ^a	cARV-Exposed (n = 309)	cARV-Unexposed (n = 62)	p-value
<u><i>In utero</i> cARV exposure at any time during pregnancy</u>				
Cognitive	367	102.2 (1.3)	101.8 (2.1)	0.82
Language	360	93.1 (1.1)	92.4 (1.9)	0.72
Motor	365	95.7 (1.2)	94.5 (1.9)	0.51
Social-Emotional	351	103.1 (1.7)	102.2 (2.7)	0.71
Adaptive Behavior	352	91.7 (2.5)	93.6 (3.0)	0.33
<u><i>In utero</i> cARV exposure during first trimester</u>				
Cognitive	367	102.5 (1.5)	101.9 (1.4)	0.65
Language	360	92.7 (1.3)	93.2 (1.2)	0.74
Motor	365	95.5 (1.4)	95.5 (1.3)	0.99
Social-Emotional	351	103.2 (2.0)	102.9 (1.8)	0.88
Adaptive Behavior	352	91.8 (2.6)	92.3 (2.6)	0.72

^aNumber of observations used in the multivariate model. Three infants had missing information about cARV exposure and were excluded from these analyses.

The models for each domain were adjusted as follows: Cognitive: infant age at testing, year of delivery, prematurity, maternal/caregiver FSIQ; Language: infant age at testing, prematurity, STD during pregnancy, maternal/caregiver FSIQ; Motor: infant age at testing, sex, year of delivery, prematurity, maternal/caregiver FSIQ; Social-Emotional: infant age at testing, year of delivery, last viral load prior to delivery, maternal/caregiver FSIQ; Adaptive Behavior: infant age at testing, sex, study cohort, year of delivery, prematurity, SGA, maternal/caregiver FSIQ, positive screen for maternal/caregiver substance abuse (alcohol or illicit drugs) at time of infant testing, maternal age at delivery.

Table 3

Adjusted Mean Bayley-III Domain Scores by *In Utero* ARV Regimen Exposure for the SMARTT Static and Dynamic Cohort

Bayley-III Domain	N ^a	<i>In Utero</i> ARV Regimen Exposure ^b	Adjusted Mean Score (Standard Error)	p-value (vs. NRTI only)
Cognitive	365	PI-containing (with or without NNRTI)	102.2 (1.3)	0.63
		NNRTI-containing (without PI)	103.6 (3.2)	0.50
		NRTI only	101.1 (2.2)	(ref)
Language	358	PI-containing (with or without NNRTI)	93.3 (1.1)	0.43
		NNRTI-containing (without PI)	91.9 (3.0)	0.95
		NRTI only	91.7 (2.0)	(ref)
Motor	363	PI-containing (with or without NNRTI)	95.7 (1.2)	0.67
		NNRTI-containing (without PI)	94.1 (3.0)	0.82
		NRTI only	94.9 (2.1)	(ref)
Social-Emotional	348	PI-containing (with or without NNRTI)	103.0 (1.7)	0.35
		NNRTI-containing (without PI)	104.6 (4.0)	0.37
		NRTI only	100.6 (2.8)	(ref)
Adaptive Behavior	350	PI-containing (with or without NNRTI)	91.6 (2.5)	0.19
		NNRTI-containing (without PI)	94.9 (3.9)	0.92
		NRTI only	94.5 (3.1)	(ref)

^a Number of observations used in the multivariate model.

^b ARV regimen categories were mutually exclusive with the following hierarchy: PI-containing regimen (with or without NNRTI), NNRTI-containing regimen (without PI), and NRTI only, in that order. Five infants without perinatal ARV exposure were excluded from the analyses.

The models for each domain were adjusted as follows: Cognitive: infant age at testing, year of delivery, prematurity, maternal/caregiver FSIQ; Language: infant age at testing, prematurity, STD during pregnancy, maternal/caregiver FSIQ; Motor: infant age at testing, sex, year of delivery, prematurity, maternal/caregiver FSIQ; Social-Emotional: infant age at testing, year of delivery, last viral load prior to delivery, maternal/caregiver FSIQ; Adaptive Behavior: infant age at testing, sex, study cohort, year of delivery, prematurity, SGA, maternal/caregiver FSIQ, positive screen for maternal/caregiver substance abuse (alcohol or illicit drugs) at time of infant testing, maternal age at delivery.

Table 4

Individual ARV Medications Associated with Significant Differences in Mean Bayley-III Domain Scores, Based on Adjusted Linear Regression Models, for Infants in the SMARTT Static and Dynamic Cohort with *In Utero* Exposure to cARV

<i>In Utero</i> ARV Exposure (Percent Exposed)	Bayley-III Domain	N ^a	Adjusted Mean Score (Standard Error)		p-value
			Exposed	Unexposed	
Atazanavir (21%)	Language	301	90.5 (1.8)	94.8 (1.2)	0.01
Lamivudine (76%)	Social-Emotional	293	104.2 (1.9)	99.3 (2.5)	0.03
Lopinavir/ritonavir (48%)	Language	301	95.1 (1.3)	92.0 (1.5)	0.04
	Adaptive Behavior	294	90.8 (2.8)	94.5 (2.8)	0.03
Nelfinavir (16%)	Cognitive	306	100.1 (2.1)	104.3 (1.5)	0.04
Tenofovir (36%)	Social-Emotional	293	100.5 (2.2)	104.7 (2.0)	0.04

^aNumber of observations used in the multivariate model.

The models for each domain were adjusted as follows: Cognitive: infant age at testing, year of delivery, prematurity, maternal/caregiver FSIQ; Language: infant age at testing, prematurity, STD during pregnancy, maternal/caregiver FSIQ; Motor: infant age at testing, sex, year of delivery, prematurity, maternal/caregiver FSIQ; Social-Emotional: infant age at testing, year of delivery, last viral load prior to delivery, maternal/caregiver FSIQ; Adaptive Behavior: infant age at testing, sex, study cohort, year of delivery, prematurity, SGA, maternal/caregiver FSIQ, positive screen for maternal/caregiver substance abuse (alcohol or illicit drugs) at time of infant testing, maternal age at delivery.