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Atazanavir exposure *in utero* and neurodevelopment in infants: A comparative safety study

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Abstract

Objective—To evaluate the safety of *in utero* exposure to atazanavir and neurodevelopment in perinatally HIV-exposed but uninfected (PHEU) infants.

Design—Prospective cohort study of mother-PHEU infant pairs in the SMARTT protocol of the Pediatric HIV/AIDS Cohort Study.

Methods—Pregnant women living with HIV who initiated an antiretroviral (ARV) regimen during pregnancy were followed from the date of ARV initiation. Women were classified according to whether the ARV regimen contained atazanavir and the trimester of ARV initiation. Neurodevelopment at 9–15 months was evaluated using the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III). We estimated mean differences for the five Bayley-III domains for atazanavir-containing regimens versus all other regimens. Models included baseline covariates and adjustment for failure to complete the Bayley-III using inverse probability weighting.

Results—PHEU infants were exposed *in utero* to atazanavir-containing (n=167) and non-atazanavir-containing (n=750) ARV regimens. The adjusted mean differences (95% CI) in Bayley-III domain scores for initiating an atazanavir-containing regimen in the first trimester were: Cognitive, −1.5 (−6.2, 3.2); Language, −3.3 (−7.6, 1.0); Motor, −2.9 (−7.7, 1.9); Social-Emotional, 0.1 (−6.2, 6.4); and Adaptive Behavior, −0.1 (−4.3, 4.0). The mean differences for the second or

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third trimester were: Cognitive, 0.4 (−3.2, 4.0); Language, −3.4 (−6.2, −0.5); Motor, 0.3 (−2.9, 3.4); Social-Emotional, −5.9 (−9.4, −2.3); and Adaptive Behavior, −2.5 (−5.9, 0.8).

Conclusions—*In utero* exposure to atazanavir-containing regimens compared to non-atazanavir-containing regimens may adversely affect language and social-emotional development in PHEU infants during the first year of life, but the absolute difference is small.

Keywords

atazanavir; antiretrovirals; infant; neurodevelopment; observational study; pregnancy

Introduction

The use of antiretroviral medications (ARVs) during pregnancy has dramatically decreased the incidence of perinatal HIV transmission [1, 2]. Accordingly, U.S. and European guidelines recommend that all pregnant women with HIV take ARVs throughout pregnancy, regardless of CD4 cell count [3, 4]. Despite the growing number of perinatally HIV-exposed but uninfected (PHEU) infants exposed to ARVs [2, 5, 6], the effects of specific regimens on fetal and infant neurodevelopment require further evaluation [7–10].

One U.S.-based observational study found significantly lower language domain scores among 9- to 15-month-old infants exposed to atazanavir compared with those not exposed to atazanavir [11]. Another study in the same cohort, using different measures of language development, found an increased risk of late language emergence (LLE) among 9- to 15-month-old infants exposed to atazanavir [12].

In this study, we estimate the effect of *in utero* exposure to ARV regimens containing atazanavir compared with all other regimens on neurodevelopment at 9–15 months of age using observational data from a cohort of PHEU infants. This comparative safety study follows up on the U.S. studies that identified the need for additional research into the safety of atazanavir [11, 12], and incorporates updated data from the same cohort appropriately adjusting for measured confounding and selection bias. We also examine the safety of prenatal atazanavir exposure separately by trimester of ARV initiation since exposure at different stages of pregnancy may have differential effects on neurodevelopment [13–15].

Methods

Study Population

The Surveillance Monitoring for ART Toxicities (SMARTT) protocol of the Pediatric HIV/AIDS Cohort Study (PHACS) is a prospective cohort study conducted at 22 sites in the U.S., including Puerto Rico [11]. The SMARTT protocol was approved by the institutional review board at each site and the Harvard T.H. Chan School of Public Health. Mothers and primary caregivers provided informed consent for their own and their child's participation.

Our analysis included pregnant women living with HIV enrolled in the dynamic cohort of SMARTT who were not on ARVs at their last antepartum menstrual period and who initiated a potent ARV regimen during pregnancy between October 2006 and April 2013.

Potent ARV regimens were defined as regimens containing either (1) two or more ARVs from at least two drug classes, (2) three nucleoside reverse transcriptase inhibitors (NRTIs), (3) one protease inhibitor (PI), or (4) one nonnucleoside reverse transcriptase inhibitor (NNRTI). Mother-infant pairs were excluded from analyses if they: (1) enrolled at a Puerto Rican site where measures of infant development were not collected; (2) resulted in perinatal HIV transmission (<1% of all pregnancies); (3) did not have a study visit 9–15 months after birth and the infant was less than 15 months of age at the administrative end of follow-up (July 1, 2014).

Exposure ascertainment

For each woman, baseline was defined as the date of initiation of a potent ARV regimen during pregnancy. Women were classified into two groups according to whether the ARV regimen did or did not contain atazanavir. We further classified women according to the trimester in which they initiated ARV (first or second/third) using the date of the last antepartum menstrual period. Since only 10% of women initiated ARV in the third trimester, the second and third trimester were combined.

Outcome ascertainment

We considered developmental outcomes at 1 year of age in our primary analysis. The Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III) [16] were administered by psychologists according to standardized assessment and scoring procedures at the one-year study visit, when the infants were 9–15 months old. The Bayley-III is used to assess problem-solving, receptive and expressive language, fine- and gross-motor skills, social-emotional development and adaptive behavior. The cognitive, motor, and language scales are administered through direct interaction with the infant; the social-emotional and adaptive behavior scales are administered as face-to-face interviews with the primary caregiver. Bayley-III domain scores are age-referenced standard scores with a mean of 100 and standard deviation of 15. All test results were rated by site psychologists for validity. The Bayley-III is only available in English and the scores were not adjusted for prematurity.

To explore how *in utero* exposure to atazanavir-containing regimens may affect infant development, we also assessed several neonatal outcomes thought to be associated with infant development, including low birth weight (< 2500 grams), gestational age, prematurity (gestational age <37 weeks), and neonatal hearing; and head circumference z-score at one year. Newborn hearing screening exams were performed according to local requirements within two months after birth (by otoacoustic emissions or automated auditory brainstem responses). Head circumference z-scores were assessed at 9–18 months and calculated using the Centers for Disease Control and Prevention 2000 growth standards [17]. For infants born premature (<37 weeks of gestational age), z-scores were corrected for completed weeks of gestational age by subtracting weeks of prematurity from the exact age at the time of measurement [18].

Statistical methods

Analyses were conducted separately for each of the five Bayley-III domains. Multivariate adjusted linear regression models were fit to estimate the mean difference in each domain

score for atazanavir-containing regimens compared with non-atazanavir-containing regimens. The mean differences were estimated separately by trimester of ARV initiation (first trimester or second/third trimester). We adjusted for the following baseline maternal covariates, measured at or prior to the date of initiation of a potent ARV regimen: maternal educational attainment (eighth grade or less, completed high school, at least some college, missing or unknown), CD4 cell count (<300, 300–499, 500 cells/ μ l, missing or unknown), HIV RNA (<500, 500–9,999, 10,000 copies/ml, missing or unknown), calendar year (2008, 2009–2010, 2011), race (white, black, other or unknown), ethnicity (Hispanic/Latina, not Hispanic/Latino, unknown), language spoken most often at home (English, Spanish, other or unknown), annual household income (<\$10,000, \$10,001–\$20,000, \$20,001–\$40,000, >\$40,000, unknown or missing), age (<20, 20–29, 30 years, unknown or missing) and maternal Full Scale Intelligence Quotient (FSIQ; <80, 80–89, 90, unknown or missing). Maternal FSIQ was measured at the one-year visit using the Wechsler Abbreviated Scale of Intelligence (WASI) [19]. We also adjusted for self-reported illicit substance use, alcohol use, and tobacco use during the first trimester of pregnancy.

Approximately 40% of eligible study participants had incomplete or invalid results for one or more Bayley-III domains (Figure 1). Restricting our analysis to individuals who had a valid and complete test result could introduce bias if initiating an atazanavir-containing regimen was associated with completing the Bayley-III and if neurodevelopment differed between those who completed the assessment and those who did not. To adjust for this potential selection bias we computed inverse probability of censoring weights. Each infant who completed the domain of interest received a weight inversely proportional to the estimated probability of not being censored (i.e. completing the Bayley-III). To compute the weights, we fit a logistic model using the baseline covariates listed above, the ARV regimen initiated by the mother, and the following additional covariates: mother's last CD4 cell count in pregnancy (<300, 300–499, 500 cells/ μ l, missing or unknown), positive test for sexually transmitted infection (STI) in pregnancy, infant low birth weight (>2,500 grams, 2,500 grams, missing or unknown) and gestational age at delivery (<37, 37–38, 38–39 weeks, 39 weeks, missing or unknown) [20, 21]. The weights were stabilized [20] and used in the final primary models evaluating atazanavir exposure and Bayley-III domain scores. The estimated weights for each of the five outcomes had mean 1.00 (first percentile: 0.40–0.77; 99th percentile: 1.35–1.78). We used robust variance estimators to compute conservative 95% confidence intervals (CIs) for each of our estimates [22].

The analyses of neonatal outcomes and head circumference at 1 year were restricted to the mother-infant pairs for whom the infant was age-eligible for the Bayley-III assessment. For low birth weight, prematurity, and hearing screen referral, we fit a log-binomial regression model [23] to estimate the risk ratio for atazanavir-containing regimens compared with all other regimens, conditional on the previously listed baseline covariates and the mother's pre-pregnancy body mass index (<18.5, 18.5–24.9, 25–29.9, 30 kg/m², missing). For head circumference and gestational age, we fit a linear regression model with the same covariates. To adjust for potential selection bias due to not having a head circumference measurement, we used the same inverse-probability weighting procedure described in the Bayley-III analysis. Because outcome information was largely complete (>97%) for newborn hearing, birth weight and gestational age, IPW was unnecessary.

Several sensitivity analyses were performed. We (1) excluded individuals for whom the mother's FSIQ was missing; (2) included site location (five geographic areas) as a baseline covariate; (3) excluded first trimester illicit substance use, tobacco use, and alcohol use as baseline covariates; (4) adjusted for the correlation between infant siblings; (5) excluded the 149 women who initiated one-PI-only, one-NNRTI-only or three-NRTIs-only regimens; (6) excluded premature infants; (7) adjusted for STI diagnosis and obstetric complications in pregnancy in the analyses of neonatal outcomes and (8) used multiple imputation to account for missing values of the outcome and covariates. Finally, we assessed whether additional adjustment for several environmental factors measured during infancy also known to influence infant development affected our estimates of differences in Bayley-III domain scores: alcohol use in the home, maternal cigarette smoking, maternal health problems other than HIV, maternal mental health, and whether the infant had lived with a primary caregiver other than the biological mother within the first 15 months of life.

Results

Of the 917 mother-infant pairs eligible for our study, 167 (18.2%) mothers initiated ARV regimens with atazanavir and 750 (81.8%) mothers initiated ARV regimens without atazanavir. 282 (30.8%) mothers initiated ARV in the first trimester and 635 (69.2%) initiated ARV in the second or third trimester. Mothers who initiated atazanavir-containing regimens were older at baseline, had lower cognitive scores, and were more likely to be black and initiate ARVs after 2010 (Table 1). The most frequently used ARV regimen containing atazanavir was boosted-atazanavir with tenofovir and emtricitabine (Table 2). ARV regimens initiated in the first trimester were similar to those initiated in the second/third trimester.

Of the 917 eligible mother-infant pairs, 678 attended the one-year study visit and 575 completed the Bayley-III assessment (Figure 1). Mothers who attended the one-year study visit and completed the Bayley-III were more likely to have initiated an atazanavir-containing regimen, be black, speak English at home and have an assessment of cognitive status (Appendix Table 1). Among the 575 infants who completed the Bayley-III assessment, those whose mothers received more education, had higher family annual incomes and higher maternal cognitive status averaged higher scores on each of the 5 domains (Appendix Table 2).

Of the 282 mothers who initiated ARVs in the first trimester, 30% switched to a different ARV regimen or discontinued ARVs before delivery, compared to 22% of mothers who initiated ARVs in the second or third trimester. Among mothers who initiated atazanavir-containing regimens, these proportions were 29% and 15%, respectively. The median (IQR) length of time on the initial ARV regimen was 178.5 (132, 200) days among mothers who initiated ARVs in the first trimester and 109 (67, 140) days among mothers who initiated ARVs in the second/third trimester, but did not vary significantly by atazanavir exposure. The most recent viral load at the time of delivery was below the lower limit of quantification (which ranged from <50 to 400 copies/ml) in 55% of mothers who initiated atazanavir-containing regimens (and below 500 copies/ml in 84% of these mothers) and 58% of

mothers who initiated non-atazanavir-containing regimens (and below 500 copies/ml in 82% of these mothers), indicating that mothers generally adhered to their ARV regimens.

The unadjusted mean Bayley-III domain scores were within age expectations for infants in the U.S. general population (103.1 for Cognitive, 93.1 for Language, 97.6 for Motor, 100.1 for Social-Emotional, 94.4 for Adaptive Behavior). Among infants whose mothers initiated ARVs in the first trimester, the adjusted mean difference (95% CI) in Bayley-III domain score for initiating an atazanavir-containing ARV regimen compared to a regimen without atazanavir was -1.5 (-6.2, 3.2) for Cognitive, -3.3 (-7.6, 1.0) for Language, -2.9 (-7.7, 1.9) for Motor, 0.1 (-6.2, 6.4) for Social-Emotional, and -0.1 (-4.3, 4.0) for Adaptive Behavior. Among infants whose mothers initiated ARVs in the second or third trimester, the adjusted mean differences (95% CI) were 0.4 (-3.3, 4.0) for Cognitive, -3.4 (-6.2, -0.5) for Language, 0.3 (-2.9, 3.4) for Motor, -5.9 (-9.4, -2.3) for Social-Emotional, and -2.5 (-5.9, 0.8) for Adaptive Behavior (Table 3).

Comparing atazanavir-containing regimens with all other regimens, the adjusted risk ratios were 1.2 (0.5, 2.8) for hearing screen referral, 1.1 (0.7, 1.5) for low birth weight, and 1.0 (0.7, 1.5) for prematurity. The adjusted mean difference for gestational age was 0.0 weeks (-0.4, 0.4). These estimates did not vary by trimester of ARV initiation, but the 95% CIs were wide. The adjusted mean differences were -0.5 (-0.7, -0.2) for head circumference z-score at 9–18 months (Table 4).

Results were similar with or without IPW adjustment. The mean difference for head circumference z-score was -0.3 (-0.7, 0.1) among infants whose mothers initiated ARVs in the first trimester and -0.5 (-0.8, -0.2) among those whose mothers initiated in the second/third trimester. Hearing screen referral, low birth weight, and prematurity were associated with lower mean Bayley-III domain scores, whereas larger head circumference and longer gestational age were associated with higher mean scores (Appendix Table 3).

Adjusting for each of the environmental factors measured during infancy did not materially change our estimates (Appendix Table 4). The effect of atazanavir-containing regimens on neurodevelopment was slightly larger when excluding premature infants (Appendix Table 5). None of the other sensitivity analyses yielded appreciably different results (data not shown).

Discussion

Our comparative safety analysis of this U.S. cohort estimated little or no effect of initiation of atazanavir-containing regimens during the first trimester on neurodevelopment in PHEU infants at 9–15 months of age. However, we estimated that atazanavir-containing regimens may lower infants' performance on the Language domain of the Bayley-III by about 3.4 points, regardless of trimester of initiation, and on the Social-Emotional domain by 5.9 points, when initiated in the second/third trimester. The lack of an estimated effect of initiation of atazanavir-containing regimens in the first trimester on social-emotional development may be explained by a high proportion of women (29%) who initiated atazanavir-containing regimens in the first trimester but switched to another ARV regimen

later in pregnancy, perhaps before reaching the window during which atazanavir exerts its effect.

A previous study in this cohort of prenatal exposure to ARVs found lower scores on the Language domain of the Bayley-III but not on the Social-Emotional domain among infants exposed to atazanavir in a cohort of PHEU infants 9–15 months old [11], but our analysis includes data from a larger sample with four more years of data, is restricted to mothers who were not on ARVs at the last antepartum period and who started potent ARV regimens during pregnancy, adjusts for measured confounding and selection bias, and provides separate effect estimates by trimester of initiation. Another observational study conducted in the same cohort, using a lengthy parent interview versus direct observation of the infant, found an increased risk of late language emergence among one-year-old infants exposed to atazanavir, but not among two-year-olds with prenatal atazanavir exposure [12].

ARVs must cross the placenta to impact fetal development, and must further penetrate the fetal blood-brain barrier to have an effect on neurodevelopment. Because atazanavir has poor transplacental passage and low central nervous system penetration [24, 25], our findings are somewhat unexpected. However, the development of the blood-brain barrier is a gradual process [26–28] and its integrity can be compromised by inflammation, toxins, or maternal substance abuse, especially if exposure occurs during the early stages of development [26–28]. Another possibility is that the effect of prenatal atazanavir exposure might be mediated by hyperbilirubinemia, which has been associated with increased risk of suboptimal developmental outcomes [29–36] and hearing impairment [35, 37–40], a risk factor for delays in language and social-emotional development. Many studies have examined the effect of elevated bilirubin levels on developmental outcomes in infants, but the effects of less extreme elevations of bilirubin remain unknown, and few studies have examined this relationship in preterm infants [39–41]. Because elevated serum bilirubin levels are more common in preterm infants [33, 41], and the risk of prematurity in PHEU infants is elevated compared to infants without prenatal exposure to HIV and ARVs [42–44] (18% in our study versus approximately 11% in the U.S. population [45]), *in utero* exposure to atazanavir-containing regimens may not increase bilirubin beyond what is expected in premature infants. In summary, the mechanisms through which atazanavir may affect language and social-emotional development remain poorly understood.

Our study has several limitations. First, as with all observational studies, the validity of our estimates relies on the untestable assumption that the measured covariates were sufficient to adjust for confounding and selection bias. If mothers were more likely to be prescribed atazanavir-containing ARV regimens due to clinical or environmental factors also associated with infant development, then our results could be explained by this confounding by indication. However, we were able to adjust for several important indicators of infant neurodevelopment, including the mother's FSIQ and education level. Adjusting for environmental factors during infancy and toddlerhood that may be associated with both the initiation of an atazanavir-containing regimen and infant development did not materially affect the results. Moreover, the atazanavir-containing regimen most commonly prescribed, boosted-atazanavir with tenofovir and emtricitabine, is not a one-pill regimen that clinicians might consider an easily tolerated regimen. Second, it is difficult to disentangle the effects of

atazanavir from tenofovir, as 75% of atazanavir-containing regimens also included tenofovir. Our results are consistent with previous findings of an association between *in utero* exposure to regimens containing tenofovir and lower head circumference z-scores at 1 year using data from the same SMARTT cohort [46]. Separating an effect of atazanavir from the potential effect of tenofovir was not possible in this analysis. Nevertheless, if atazanavir and tenofovir are commonly prescribed together, these results could still be informative for clinical practice. Third, starting ARVs in the second or third trimester could be related to women's access to health care resources; however, it is unlikely that this possibility would explain the observed differences in infant development found between the initiation of two different types of regimens among women who initiated ARVs later in pregnancy. Fourth, while measurement error for the Bayley-III is possible, psychologists with experience in infant assessment administered the instrument and rated the validity of the results, and any measurement error would likely be non-differential. Finally, since most infants in this study were exposed to ARVs initiated in the second or third trimester, the 95% CIs around our effect estimates for infants exposed to ARVs initiated in the first trimester were wide.

In conclusion, *in utero* exposure to atazanavir-containing regimens may have an adverse effect on the neurodevelopment of PHEU infants. A three-point difference in the Bayley-III Language domain score and a five-point difference in the Social-Emotional domain score may not have large clinical implications, but they add another risk to the constellation of existing biological and socio-environmental risk factors to which these children are often exposed. Future work is needed to evaluate whether the differences observed in this study persist past one year of age, the effects of atazanavir and tenofovir on infant neurodevelopment and growth outcomes, and how bilirubin may mediate the effect of atazanavir on neurodevelopment. These results may be useful in treatment planning for women with HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow chart of individuals in the SMARTT dynamic cohort before and after the start of follow-up, PHACS.

Table 1

Baseline characteristics of 917 mothers* by treatment strategy, PHACS SMARTT.

	No. women (%)	
	Atazanavir-containing regimen (n=167)	Non-atazanavir-containing regimen (n=750)
Baseline characteristic		
ARV initiation		
First trimester	55 (32.9)	227 (30.3)
Second or third trimester	112 (67.1)	523 (69.7)
Highest education level attained		
Eighth grade or less	50 (29.9)	259 (34.5)
High school graduate	60 (35.9)	276 (36.8)
At least some college	56 (33.5)	209 (27.9)
Missing or unknown	1 (0.6)	6 (0.8)
CD4 cell count (cells/ μ l)		
<300	39 (23.4)	222 (29.6)
300 to < 500	54 (32.3)	190 (25.3)
500	45 (27.0)	218 (29.1)
Missing or unknown	29 (17.4)	120 (16.0)
Mean, value	426.7	436.9
HIV RNA (copies/ml)		
<500	28 (16.8)	119 (15.9)
500 to < 10,000	55 (32.9)	263 (35.1)
10,000	53 (31.7)	244 (32.5)
Missing or unknown	31 (18.6)	124 (16.5)
Median (IQR), value	5,345 (662, 23,595)	5,213 (1,030, 24,323)
Calendar year		
2008	47 (28.1)	278 (37.1)
2009–2010	53 (31.7)	281 (37.5)
2011–2014	67 (40.1)	191 (25.5)
Race		
White	30 (18.0)	172 (22.9)
Black	132 (79.0)	543 (72.4)
Other or unknown	5 (3.0)	35 (4.7)
Ethnicity		
Hispanic/Latino	27 (16.2)	151 (20.1)
Not Hispanic/Latino	138 (82.6)	588 (78.4)
Unknown	2 (1.2)	11 (1.5)
Used illicit substances first trimester		
No	140 (83.8)	663 (88.4)

No. women (%)		
	Atazanavir-containing regimen (n=167)	Non-atazanavir-containing regimen (n=750)
Yes	20 (12.0)	74 (9.9)
Missing	7 (4.2)	13 (1.7)
Used alcohol first trimester		
No	144 (86.2)	682 (90.9)
Yes	17 (10.2)	55 (7.3)
Missing	6 (3.6)	13 (1.7)
Used tobacco first trimester		
No	119 (71.3)	592 (78.9)
Yes	42 (25.2)	142 (18.9)
Missing	6 (3.6)	16 (2.1)
Language spoken at home		
English only	133 (79.6)	594 (79.2)
Spanish only	10 (6.0)	62 (8.3)
Other or unknown	24 (14.4)	94 (12.5)
Annual household income		
<\$10,000	82 (49.1)	349 (46.5)
\$10,001–\$20,000	35 (21.0)	148 (19.7)
\$20,001–\$40,000	34 (20.4)	116 (15.5)
>\$40,000	7 (4.2)	43 (5.7)
Unknown or missing	9 (5.4)	94 (12.5)
Age (years)		
<20	7 (4.2)	63 (8.4)
20–<30	95 (56.9)	450 (60.0)
30	64 (38.3)	232 (30.9)
Unknown or missing	1 (0.6)	5 (0.7)
Maternal FSIQ		
< 80	40 (24.0)	144 (19.2)
80–<90	31 (18.6)	120 (16.0)
90	40 (24.0)	181 (24.1)
Unknown or missing	56 (33.5)	305 (40.7)
Mean, value	84.3	86.5

Baseline, date of initiation of a potent ARV regimen.

* Women are not all unique since some had multiple children

Table 2

Most frequently prescribed atazanavir-containing and non-atazanavir-containing regimens, PHACS SMARTT.

	No. of initiators	Type of regimen
Atazanavir-containing regimens		
Atazanavir, emtricitabine, tenofovir, ritonavir	126	Boosted PI with 2 NRTIs
Atazanavir, zidovudine, lamivudine, ritonavir	15	Boosted PI with 2 NRTIs
Atazanavir, abacavir, lamivudine	5	PI with 2 NRTIs
Other atazanavir-containing regimens	21	
Non-atazanavir-containing regimens		
Lopinavir, zidovudine, lamivudine, ritonavir	335	Boosted PI with 2 NRTIs
Zidovudine, lamivudine, abacavir	134	3 NRTIs
Nelfinavir, zidovudine, lamivudine	49	PI with 2 NRTIs
Darunavir, tenofovir, emtricitabine, ritonavir	35	Boosted PI with 2 NRTIs
Other non-atazanavir-containing regimens	197	

PI, protease inhibitor

Boosted PI, protease inhibitor plus ritonavir

NRTI, nucleoside reverse transcriptase inhibitor

Table 3

Mean difference in Bayley-III domain scores for atazanavir exposure by trimester of ARV initiation, PHACS SMARTT

Bayley-III Domain	No. of infants	Adjusted mean difference (95% CI)*	Adjusted mean score (95% CI) standardized to baseline variables**
First Trimester			
<i>Cognitive</i>			
Non-atazanavir regimen	141	0 (reference)	103.1 (100.9, 105.2)
Atazanavir regimen	41	-1.5 (-6.2, 3.2)	101.6 (97.0, 106.1)
<i>Language</i>			
Non-atazanavir regimen	141	0 (reference)	95.0 (92.6, 97.4)
Atazanavir regimen	41	-3.3 (-7.6, 1.0)	91.7 (87.1, 96.2)
<i>Motor</i>			
Non-atazanavir regimen	140	0 (reference)	98.5 (96.4, 100.6)
Atazanavir regimen	41	-2.9 (-7.7, 1.9)	95.6 (91.0, 100.1)
<i>Social-Emotional</i>			
Non-atazanavir regimen	134	0 (reference)	103.7 (100.8, 106.7)
Atazanavir regimen	39	0.1 (-6.2, 6.4)	103.9 (97.7, 110.0)
<i>Adaptive Behavior</i>			
Non-atazanavir regimen	132	0 (reference)	94.4 (91.9, 96.9)
Atazanavir regimen	41	-0.1 (-4.3, 4.0)	94.2 (90.3, 98.2)
Second/Third Trimester			
<i>Cognitive</i>			
Non-atazanavir regimen	308	0 (reference)	103.1 (101.6, 104.5)
Atazanavir regimen	75	0.4 (-3.2, 4.0)	103.5 (100.0, 106.9)
<i>Language</i>			
Non-atazanavir regimen	305	0 (reference)	93.2 (91.7, 94.7)
Atazanavir regimen	74	-3.4 (-6.2, -0.5)	89.8 (87.2, 92.4)
<i>Motor</i>			
Non-atazanavir regimen	302	0 (reference)	97.4 (96.1, 98.6)
Atazanavir regimen	74	0.3 (-2.9, 3.4)	97.6 (94.6, 100.7)
<i>Social-Emotional</i>			
Non-atazanavir regimen	299	0 (reference)	99.6 (97.8, 101.4)
Atazanavir regimen	75	-5.9 (-9.4, -2.3)	93.8 (90.8, 96.7)
<i>Adaptive Behavior</i>			
Non-atazanavir regimen	304	0 (reference)	94.9 (93.4, 96.4)
Atazanavir regimen	76	-2.5 (-5.9, 0.8)	92.4 (89.3, 95.5)

CI, confidence interval.

* Adjusted for maternal baseline covariates (education, CD4 cell count, HIV RNA, calendar year, race, and ethnicity, first trimester use of illicit substances, alcohol and tobacco, language spoken at home, family annual income, age, and FSIQ), mother's last CD4 cell count in pregnancy, diagnosis of a sexually transmitted infection (STI) in pregnancy, infant low birth weight and gestational age at delivery.

**
CIs calculated using 200 bootstrap samples

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Table 4

Risk ratios and mean differences (95% CIs) for atazanavir exposure for neonatal and infant outcomes, PHACS

Outcome and regimen	No. of infants	Mean (SD)	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)
Head circumference z-score				
Non-atazanavir regimen	525	0.5 (1.1)	0 (ref)	0 (ref)
Atazanavir regimen	127	0.1 (1.1)	-0.4 (-0.7, -0.2)	-0.5 (-0.7, -0.2) [*]
Gestational age (weeks)				
Non-atazanavir regimen	742	38.1 (2.0)	0 (ref)	0 (ref)
Atazanavir regimen	164	38.0 (2.3)	-0.0 (-0.4, 0.3)	0.0 (-0.4, 0.4) ^{**}
	No. of infants	No. of outcomes	Unadjusted risk ratio (95% CI)	Baseline-adjusted risk ratio (95% CI)
Hearing screen referral				
Non-atazanavir regimen	733	23	1 (ref)	1 (ref)
Atazanavir regimen	165	8	1.6 (0.7, 3.4)	1.2 (0.5, 2.8) ^{***}
Low birth weight				
Non-atazanavir regimen	745	132	1 (ref)	1 (ref)
Atazanavir regimen	166	31	1.1 (0.7, 1.5)	1.1 (0.7, 1.5) ^{**}
Prematurity (<37 weeks gestational age)				
Non-atazanavir regimen	745	133	1 (ref)	1 (ref)
Atazanavir regimen	166	28	0.9 (0.7, 1.4)	1.0 (0.7, 1.5) [†]

CI, confidence interval.

SD, standard deviation.

^{*} Adjusted for maternal baseline covariates (trimester of ARV initiation, education, CD4 cell count, HIV RNA, calendar year, race, ethnicity, use of illicit substances, use of alcohol, use of tobacco, language spoken at home, family annual income, age, FSIQ), mother's last CD4 cell count in pregnancy, diagnosis of a sexually transmitted infection (STI) in pregnancy, infant low birth weight and gestational age at delivery.

^{**} Adjusted for maternal baseline covariates (trimester of ARV initiation, education, CD4 cell count, HIV RNA, calendar year, race, ethnicity, use of illicit substances, use of alcohol, use of tobacco, language spoken at home, family annual income, age, FSIQ) and the mother's pre-pregnancy BMI.

^{***} Adjusted for a subset of the maternal baseline covariates due to sample size restrictions (trimester of ARV initiation, CD4 cell count, HIV RNA, calendar year, race, first trimester use of illicit substances, language spoken at home, family annual income, FSIQ) and pre-pregnancy BMI.

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⁷ Adjusted for a subset of the maternal baseline covariates due to sample size restriction (trimester of ARV initiation, CD4 cell count, HIV RNA, calendar year, race, ethnicity, use of illicit substances, use of alcohol, use of tobacco, language spoken at home, family annual income, age, FSIQ) and pre-pregnancy BMI.