The Pediatric Infectious Disease Journal Publish Ahead of Print
DOI: 10.1097/INF.0b013e31829b80ee

Evaluation of Risk for Late Language Emergence after *In Utero* Antiretroviral Drug Exposure in HIV-Exposed Uninfected Infants

Mabel L. Rice[1], PhD, Bret Zeldow[2], MS, George K. Siberry[3], MD, MPH, Murli Purswani[4], MD, Kathleen Malee[5], PhD, Howard J. Hoffman[6], MA, Toni Frederick[7], PhD, MSPH, Ashley Buchanan[2], MS, Patricia A. Sirois[8], PhD, Susannah M. Allison[9], PhD, and Paige L Williams,[2] PhD, for the Pediatric HIV/AIDS Cohort Study (PHACS)

Abbreviated title: Maternal ARV Use and Infant Language Emergence

Running head: Maternal ARV Use and infant language delay

Corresponding author: Mabel L. Rice, PhD

1000 Sunnyside Avenue, 3031 Dole Human Development Center, University of Kansas

Lawrence, KS 66045 Phone: 785-864-4570 Fax: 785-864-4571 Email: mabel@ku.edu

Affiliations:

1 – Speech, Language, Hearing Department, University of Kansas, Lawrence, KS

2 – Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

3 – Maternal and Pediatric Infectious Disease Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

4 – Bronx-Lebanon Hospital Center, Albert Einstein College of Medicine, Bronx, NY

5 – Northwestern University Feinberg School of Medicine, Psychiatry and Behavioral Sciences, Chicago, IL

6 – Epidemiology and Statistics Program, Division of Scientific Programs, National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health, Bethesda, MD

7 – Maternal, Child and Adolescent Program for Infectious Diseases and Virology, Department of Research Pediatrics, Keck School of Medicine of USC, Los Angeles, CA

8 – Tulane University School of Medicine, Department of Pediatrics, New Orleans, LA

9 – National Institute of Mental Health, National Institutes of Health, Bethesda, MD

Key words: Pregnancy, HIV-exposed infants, antiretroviral, cohort study, language delay

Preliminary results from this analysis were presented at the 18th Conference on Retroviruses and Opportunistic Infections, Boston, MA, Feb 27-Mar 2, 2011, Abstract #751.

Funding:

The Pediatric HIV/AIDS Cohort Study (PHACS) was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (HD052102, 3 U01 HD052102-05S1, 3 U01 HD052102-06S3) and the Tulane University School of Medicine (HD052104, 3U01HD052104-06S1). Note: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

Disclosures: The authors have no conflicts of interest or funding to disclose.

ABSTRACT:

Background: Combination antiretroviral (cARV) regimens are recommended for pregnant women with HIV to prevent perinatal HIV transmission. Safety is a concern for infants who were HIV-exposed but uninfected (HEU), particularly for neurodevelopmental problems, such as language delays.

Methods: We studied late language emergence (LLE) in HEU children enrolled in a US-based prospective cohort study. LLE was defined as a caregiver-reported score ≤ 10th percentile in any of 4 domains of the MacArthur-Bates Communicative Development Inventory for one-year-olds and as ≥1 standard deviation below age-specific norms for the Ages and Stages Questionnaire for two-year-olds. Logistic regression models were used to evaluate associations of *in utero* cARV exposure with LLE, adjusting for infant, maternal, and environmental characteristics.

Results: 1,129 language assessments were conducted among 792 one- and two-year-old children (50% male, 62% black, and 37% Hispanic). Overall, 86% had *in utero* exposure to cARV and 83% to protease inhibitors. LLE was identified in 26% of one-year-olds and 23% of two-year-olds, with higher rates among boys. In adjusted models, LLE was not associated with maternal cARV or ARV drug classes in either age group. Among cARV-exposed one-year-olds, increased odds of LLE was observed for those exposed to atazanavir (aOR=1.83, 95% CI=1.10-3.04), particularly after the first trimester (aOR=3.56, p=0.001), compared with atazanavir-unexposed infants. No associations of individual ARV drugs with LLE were observed among two-year-olds.

Conclusions: *In utero* cARV exposure showed little association with LLE, except for a higher risk of language delay observed in one-year-old infants with atazanavir exposure.

Early language acquisition appears during the first year as gestures (showing intent to communicate), rudimentary understanding of spoken language, and first spoken words at 12-18 months, with rapid vocabulary growth from two years onward. Delayed onset of language can be described as late talking and/or late understanding of spoken language, relative to age expectations. The term "Late Language Emergence" (LLE) defines a delayed onset of language as low performance, relative to age norms, for first word use or understanding, or both, in the general population of young children, controlling for multilingual exposures[1]. In the general population, predictors of early gestural communication include maternal, environmental, and child factors[1-3], and are not necessarily the same as predictors of early verbal productions[2], perhaps due to different neurologic requirements for gestures versus spoken words. Recent studies highlight the vital importance of the prenatal period on infants' subsequent development[4,5]. For example, maternal alcohol use during pregnancy is known to influence children's neurodevelopment, including risk for language impairments[6,7].

In a previous study, we found that school age children with perinatal HIV infection (PHIV) and those HIV-exposed but uninfected (HEU) had a higher risk for language impairments compared to children without HIV exposure[8]. The risk for language impairments was higher for children with concurrent cognitive or hearing impairments, but the PHIV group did not differ from the HEU group. Among children with PHIV, those with poorly controlled HIV or with cognitive or hearing impairments had three times the risk for language impairments compared to those with controlled HIV and those with no cognitive or hearing impairments.

For children born more recently to mothers with HIV, *in utero* exposure to combination antiretroviral drugs (cARV) is common[9], resulting in very low risk for HIV transmission to the infant. Increasingly, newer generations of drugs within existing classes of antiretrovirals (ARV),

and newer classes of ARVs are being used as part of these cARV regimens. Among studies that have been conducted to evaluate neurodevelopmental functioning in children born to mothers with HIV infection, none have specifically addressed language impairment, despite the fact that language and hearing impairments may reflect some of the most sensitive indicators of ARV-associated toxicities[10]. Hence, as these regimens evolve over time, it is important to understand whether *in utero* exposure to cARV, or to particular drugs in the regimen, increases a child's risk for language impairment. If so, it is important to know if the risk is evident early in development given the known benefits of early intervention[10].

A recent study[11] of HEU infants ages 9-15 months reported no consistent association of individual ARVs with any domain of the Bayley Scales of Infant and Toddler Development, Third Edition (Bailey-III)[12], except for the Language domain. One drug, atazanavir, was associated with lower scores on the Language domain in both primary analyses and in sensitivity analyses omitting the intermediaries of prematurity and small for gestational age (SGA). This study was conducted with the same cohort under investigation here. Further investigation is needed to determine if the association of atazanavir and early language acquisition is evident with more detailed measurements of early language acquisition and if exposure to atazanavir predicts risk of LLE when controlled for other factors, such as cognitive delay and hearing impairment. Selective impairment of language acquisition in infancy would help clarify whether language impairment is apparent from onset or if it reflects a cumulative effect apparent only later in development. Further evidence of an association with an individual drug in cARV could clarify possible mechanisms of drug effects early in development. The overall objective of the current study was to evaluate further the safety of maternal ARV use on language acquisition in the first two years of life, by considering the association of LLE with cARV, ARV drug classes,

and individual ARV drugs, controlling for other relevant caregiver, environmental, and child factors.

MATERIALS AND METHODS

***Participants*:** This investigation used data collected in the Surveillance Monitoring of ART Toxicities (SMARTT) study, a prospective cohort study conducted by the Pediatric HIV/AIDS Cohort Study (PHACS) network at 22 sites in the United States including Puerto Rico. SMARTT is designed to identify potential ARV-related toxicities, including language impairment, through an ongoing surveillance system among infants and children who are HEU[13]. The study protocol was approved by institutional review boards at participating sites, and written informed consent was obtained from each child's parent/legal guardian. Beginning in 2007, the study recruited two HEU cohorts: the ongoing Dynamic Cohort, which prospectively enrolled pregnant women and their newborns from week 22 of gestation through 72 hours after birth, and the Static Cohort (closed to further accrual in 2009), which included children < 12 years of age at entry who participated in a previous cohort study where data regarding the mother's ARV exposures during pregnancy were collected. Children and their mothers (or caregivers) are seen at annual study visits around the time of the child's birthday, and language assessments are conducted at specific ages, beginning at age 12 months. The sequence of participant eligibility based on the schedule of data collection and availability of language measures is presented in the Figure.

Language Assessments: We analyzed prospectively-collected language assessments based on caregiver report obtained by trained neuropsychologists at ages 12 and 24 months. At the 12-month visit, the MacArthur-Bates Communicative Development Inventory (CDI)[14] was

administered to yield age-adjusted, gender-specific, percentile scores in four domains: Phrases Understood, Vocabulary Comprehension, Word Production, and Total Gestures. Consistent with previous studies[2], LLE was defined as a score ≤ 10th percentile in any of the four domains, and severe LLE was defined as a score ≤ 5th percentile in at least two domains. A summary score on the CDI was calculated by summing the percentile scores of the four domains (range 0-396). At the 24-month visit, the Communication scale of the Ages and Stages Questionnaire (ASQ) was administered in place of the CDI, due to the time constraints at that study visit. The assessment consists of six items that ask about following directions, receptive vocabulary, expressive vocabulary, and imitation/spontaneous production of word combinations. The summative score is a Total Score (range 0-60). LLE was defined as a Total Score one standard deviation (SD) or more below the mean, based on age-specific means and SDs provided in the ASQ manual. Severe LLE was defined as a Total Score below 26.5 regardless of age (approximately two SDs below the mean). Spanish-speaking children received Spanish versions of the CDI and ASQ.

Maternal ARV history during pregnancy was collected through medical record review and from prior studies where PHACS had received permission to obtain participant-level data. Maternal combination ARV use, or "cARV", was defined as use of at least three drugs from at least two different ARV drug classes during pregnancy, whether for treatment of maternal HIV infection or for prevention of mother-to-child transmission of HIV. ARV drug classes evaluated for cARV included non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Exposures to cARV, ARV drug classes, and individual ARV agents were recorded as any exposure and exposure for each trimester.

Risk factors evaluated for LLE included infant characteristics (age, sex, race, ethnicity, multilingual exposure, hearing problems [based on hearing screening or caregiver report],

gestational age at birth, birth weight, cognitive delay [based on Bayley-III scores], and neonatal ARV prophylaxis), caregiver characteristics (marital status, education and income levels, verbal and nonverbal IQ), maternal substance use during pregnancy (tobacco, alcohol, illicit drug use), maternal immune status during pregnancy (latest CD4 count, CD4%, and viral load [VL] prior to labor and delivery and earlier in pregnancy, when available), and caregiver health limitations (difficulty caring for child, difficulty doing housework, and positive screen for depression). Demographic characteristics were obtained at study entry and subsequent visits through chart review, standardized assessments, and interviews with caregivers. Maternal substance use during pregnancy was based on self-report, validated in this SMARTT sample via meconium assay[15].

***Statistical Methods*:** Demographic and maternal characteristics were summarized by LLE status for 12- and 24-month old children. Logistic regression models were used to assess the association of LLE with *in utero* cARV exposure and by ARV drug class, comparing those exposed versus unexposed at any time during pregnancy. The regimens during pregnancy were also classified into one of three categories: cARV with PIs, cARV without PIs, and non-cARV (which also included a regimen of 3 or more nucleoside reverse transcriptase inhibitors [NRTIs]). The non-cARV group includes three or more NRTIs, other non-cARV regimens, and not on ARVs. In order to reduce confounding by indication, analyses of associations between LLE and individual ARV agents were restricted to infants with *in utero* cARV exposure. For agents or drug classes with p-value < 0.10 in adjusted models, further analyses were conducted based on the time of first reported exposure (first trimester, second/third trimester, or no exposure).

Potential confounders of the relationship between LLE and *in utero* ARV exposure were identified by fitting univariate logistic regression models to evaluate demographic, infant, and

caregiver/maternal factors as predictors of LLE at both 1 and 2 years of age. Variables with unadjusted p-values <0.20 were considered in a backward selection procedure and those with p-values < 0.15 were retained to create a 'core' model. We did not consider inclusion of characteristics reflecting concurrent impairment (cognitive delay, hearing problems) or birth characteristics (preterm birth[16-18], SGA) in the core model due to concerns that they may be on the causal pathway between *in utero* ARV exposure and LLE [19].

We evaluated the association of *in utero* ARV exposures with LLE based on the CDI and ASQ using logistic regression models, adjusting for the core covariates described above. In addition, we conducted several sensitivity analyses. The first set of sensitivity analyses included adjustment for birth characteristics (prematurity, SGA), concurrent impairment (cognitive delay, hearing problems), or both, in addition to the core model covariates, since these factors may be on the causal pathway. Second, we conducted sensitivity analyses on the ASQ restricted to children within a narrower age range corresponding to expected visit windows (21-27 months) to make sure that the results we saw with the full cohort were comparable to the results within the intended age range of the ASQ. Additional sensitivity analyses were conducted to evaluate the potential effect of clinical research site, by fitting models with a random effect of site to account for within-site correlation in LLE outcomes.

To provide additional power and descriptive information, analyses of the association of language functioning with *in utero* ARV exposures were performed using the continuous CDI summary score for one-year-olds and ASQ Total Score for two-year-olds. A linear regression model was fit using a robust Generalized Estimating Equation (GEE) approach to evaluate differences in the mean summary score for those with versus without each ARV exposure. For both CDI and ASQ, new core models were developed using the modeling approach described

above. Two subscales of the CDI--Word Production and Total Gestures--were considered separately using the same modeling strategy. All analyses were based on data submitted as of April 1, 2011 and were conducted using SAS Version 9.2 (SAS Institute Inc., Cary, NC). Two-sided p-values < 0.05 were considered statistically significant. Because this was a safety study, there was no correction for multiple comparisons in order to minimize the Type II error rate (eg, the probability of not detecting true associations between ARV exposures and language outcomes). Due to the numerous ARV exposures evaluated, observed associations will require confirmation in further studies.

RESULTS

Study Population and Language Functioning: The CDI and ASQ were obtained from groups with similar backgrounds (Table 1). For the CDI, 51% were female, 70% black, and 33% Hispanic; 71% had annual household income below $20,000; 98% of caregivers were the infants' biological mothers and 32% of caregivers had not graduated from high school. The percent of children from the Dynamic cohort was higher for those assessed by the CDI (71%) than for the ASQ (51%). Within both age groups, 43% were exposed to cARV in the first trimester, increasing to 86% by the third trimester. For the CDI, 12% were exposed *in utero* to an NNRTI, and 83% to a PI. ARV exposures were similar for two-year-olds.

Valid data were obtained for 577 children on the CDI at the 12-month visit (age range: 9.0-18.9 months) and for 552 children on the ASQ at the 24-month visit (age range: 20.1-34.2 months) (see Figure). Some children (n=215) in the Static cohort were enrolled into the study at the 24 month visit and did not have the 12-month CDI assessment; others (n=240) had not yet reached 24 months of age and had only the 12 month visit. A total of 337 children had both the

CDI and ASQ assessments. Mean (standard deviation [SD] and 95% confidence intervals [CI]) percentiles on CDI subtests were: Phrases Understood, 54.1 (27.7, 51.8-56.4); Vocabulary Comprehension, 44.5 (30.0, 42.0-47.0); Word Production, 47.6 (21.3, 45.9-49.3); and Total Gestures, 46.9 (28.3, 44.6-49.2). The mean percentiles were significantly below the population norms of 50 for the latter three CDI subtests, but above norms for the Phrases Understood subtest. The mean (SD) summary score was 193.0 (83.9, 186.1-199.9). A total of 149 (26%, 22.3-29.6%) one-year-olds met the criteria for LLE; 6% (4.1-8.1%) (n=34) were classified with severe LLE. For the 552 ASQ assessments, the mean (SD) Total Score was 45.3 (15.6, 44.0-46.6). Among these 2-year olds, 128 (23%, 19.7-26.9%) were classified with LLE; 78 (14%, 11.3-17.3%) with severe LLE. Among the 337 children with both CDI and ASQ assessments, the correlations between CDI subtests at 12 months and the ASQ Total Score were as follows (Spearman's ρ): Phrases Understood (0.29), Vocabulary Comprehension (0.29), Total Gestures (0.32), Word Production (0.27), and Summary Score (0.37), all of which were statistically significant.

Association of LLE with In Utero ARV Exposure and Other Factors: Among 1-year olds, boys had higher odds of LLE (adjusted odds ratio [aOR]=1.54, p=0.03) than girls (Table 2). Infants whose caregiver had a verbal IQ <85 had over twice the odds of LLE (aOR=2.10, p=0.003). Other variables associated with higher odds of LLE and retained in the adjusted model at the 12-month visit were multilingual exposure, combination neonatal ARV prophylaxis (vs zidovudine alone), and low maternal CD4% prior to labor and delivery; also retained was maternal VL>400 copies/mL early during pregnancy, associated with lower odds of LLE. Boys also had higher odds of LLE at the 24-month visit (aOR=2.00, p=0.002). Low maternal CD4% during pregnancy and caregiver health problems were associated with increased odds of LLE at

24 months, but infants whose caregivers reported that poor health limited their daily activities had lower odds of LLE. At both the 12-month and 24-month visits, there was no association of LLE with cARV or ARV drug class in either unadjusted or adjusted models (Table 3).

Association of LLE with Exposure to Individual ARVs: Among 1-year old children with *in utero* cARV exposure, the odds of LLE were increased for those exposed to atazanavir (aOR=1.83, p=0.02) but the association was not significant at 24 months (Table 3). There was also an increased odds of LLE associated with saquinavir exposure at 12 months (aOR=2.74, p=0.03) but at 24 months the effect changed directions and was not statistically significant (aOR = 0.15, p=0.06). Drug exposure differed for atazanavir and saquinavir; 21% of 1 year-olds and 19% of 2 year-olds had *in utero* exposure to atazanavir compared to only 5% of both age groups for saquinavir. When examining the timing of atazanavir exposure, there was a threefold increase in odds of LLE associated with later atazanavir use (first use during the second/third trimester) compared to absence of atazanavir exposure (aOR=3.56, p=0.001). Among two-year-olds with *in utero* cARV exposure, there were no significant associations between LLE and any individual ARV drug based on either overall exposure (Table 3) or first trimester exposure (data not shown).

Sensitivity Analyses: The association of LLE with atazanavir based on the CDI remained in sensitivity analyses adjusting for preterm birth and SGA (aOR=1.83, p=0.02) but was attenuated when adjusted for cognitive delay and hearing problems (aOR=1.67, p=0.06). There was no association of LLE with first trimester exposure to any individual ARV (data not shown). When ASQ analyses were restricted to those between 21 and 27 months of age (corresponding to the visit window for the ASQ; n=485) results were essentially unchanged. In sensitivity analyses accounting for study site effects on the CDI, we observed weak within-site correlations in LLE at

1 year (r=0.03) and the associations between LLE and ARV exposures remained similar in magnitude and significance. The association of atazanavir with LLE remained significant (aOR=1.86, p=0.04) while the association with saquinavir was no longer significant (aOR=2.95, p=0.08).

Among 2-year olds with *in utero* cARV exposure, there were no significant associations between LLE and any individual ARV based on either any exposure (Table 3) or first trimester exposure (data not shown).

Association of Language Scores with In Utero ARV Exposure and Other Factors: A summary of GEE linear regression models for the CDI summary score for 1-year olds and the ASQ Total Score for 2-year olds is shown in Table 4. In both unadjusted models (not shown) and after adjustment for potential confounders, there was no association of *in utero* cARV exposure or ARV class exposure, either at any time during pregnancy or during the first trimester, on mean scores within either age group. In addition, there was no significant difference in mean scores by regimen (cARV with PI vs. cARV without PI vs. non-cARV regimens, data not shown). Exposure to a cARV regimen without PI was associated with a marginally higher mean Total Score on the ASQ (6.7 points higher, p=0.07) as compared to a non-cARV regimen.

In evaluation of separate subscales of the CDI (data not shown), there was a significant decrease of 7.7 points (p=0.02) for the Total Gestures subscale among 1-year olds exposed to PIs; this decrease in mean score was observed in those with exposure to PIs later in pregnancy (second or third trimester) compared to those not exposed to PIs. For the Word Production subtest, atazanavir exposure was associated with a significantly lower score in both unadjusted and adjusted models (adjusted mean decrease = 4.9 points, p = 0.04). In contrast, no association was observed with the Total Gestures subscale for atazanavir or any other ARV drug. Among

cARV-exposed 2-year olds, no significant associations between individual ARV agents and mean ASQ Total Score were observed after adjustment for other covariates.

Most of the covariates identified as predictive of LLE in the logistic regression models (Table 2) were associated with the continuous summary scores (Table 4). Boys had lower mean language scores than girls and significantly higher odds of LLE. Maternal/caregiver performance IQ <85 was associated with significantly lower CDI summary scores. Maternal immune status during pregnancy (low CD4% or detectable VL) was associated with the CDI summary score and the ASQ Total Score consistent with the logistic regression models, although the relationship with viral load was counterintuitive (early maternal VL>400 copies/mL was associated with higher mean scores). Limitations in caregiver health, including fatigue and difficulty caring for the child, were associated with lower mean scores on the CDI and ASQ and with increased odds of LLE. Maternal alcohol use during pregnancy was associated with a 21.3 point decrease in mean CDI summary score after adjustment for other factors but was not a risk factor for LLE within either age group.

DISCUSSION

An earlier study of school age children enrolled in PHACS found that children perinatally exposed to HIV were at high risk for language impairments (39%), and the risk was similar for children with and without HIV infection.[8] The results of the current study extend the concern for language delay to HEU infants and toddlers. LLE was identified in 26% of one-year-olds and in 23% of two-year-olds, prevalence estimates somewhat higher than reported in previous studies in the general population[1,2]. Reilly et al [2] reported 20% with LLE based on the CDI at age 2, for a sample of children which included those with multilingual exposure (6.6%, similar to the 6.8%

in this study). Zubrick et al[1] reported 13% with LLE on the ASQ at age 2, excluding children with multilingual exposure.

The associations of LLE with some demographic and maternal characteristics were generally consistent with previous studies of infants in the general population and of those enrolled in SMARTT[11]. Boys had lower language scores and were more likely to be identified with LLE at both 12 and 24 months of age [1,2]. Multilingual exposure has been associated with LLE in 2-year olds [2]. We observed that lower maternal/caregiver verbal ability was associated with higher risk of LLE for 1-year old infants, while Feldman et al[3] found lower maternal education to be associated with higher scores on the CDI in 1-year olds and noted similar outcomes in other studies. The apparent discrepancy may be attributable to different patterns of prediction for the low end of performance versus the full range of performance in one-year-old infants, or for greater sensitivity of maternal verbal intellectual functioning as a predictor variable. Although maternal alcohol use was associated with a decrease in mean CDI score at 12 months, it was not a risk factor for LLE within either age group. This may be because adverse effects of maternal alcohol use on children's early language acquisition are more likely to occur for children with cognitive impairment or hearing loss, factors controlled for in the LLE analyses. Maternal ARV use during pregnancy showed little association with LLE, except that atazanavir was associated with significantly increased odds of LLE at age 12 months: the effects were more evident for word productions than for gestural communications. This finding is of particular importance because use of this medication during pregnancy is increasing (from 2% in 2004 to 20% in 2009)[9] and atazanavir is recommended as a preferred ARV drug for use in pregnancy[20]. Increased usage of atazanavir is a reflection of its once daily dosing regimen, low pill burden and lower rate of metabolic, particularly lipid, adverse effects. Further, an association

of *in utero* atazanavir exposure with lower scores on the Bayley-III[12] language domain was observed in a separate investigation of neurodevelopmental outcomes at age 12 months among 374 infants from the same cohort studied here[11]. This association should be examined in other cohorts of HEU infants.

Atazanavir crosses the placenta at an estimated ratio of 20%[21]. In pregnant women, as in non-pregnant adults and children, atazanavir (usually in combination with boosting ritonavir) is commonly associated with elevated serum unconjugated bilirubin[22] . Normally, fetal unconjugated bilirubin crosses the placenta to maternal circulation and then is conjugated and eliminated by the mother's liver. However, atazanavir-related impairment of maternal bilirubin conjugation and elevated maternal unconjugated bilirubin levels may result in higher levels of fetal unconjugated bilirubin levels through much of the latter half of pregnancy. Neonatal hyperbilirubinemia at varying levels has been associated with risk of developmental delay in multiple domains, including language[23-25]. Neurodevelopmental problems associated with neonatal hyperbilirubinemia in some of these studies include milder and variable deficits (unlike classic kernicterus) and may be detected in the first year of life but often are not in evidence at older ages. Fetal and neonatal elevations in bilirubin associated with maternal atazanavir use[20] are lower than the extreme neonatal hyperbilirubinemia linked to neurologic injury. Neither maternal nor infant bilirubin measurements were collected in our study. It is possible that chronic fetal exposure to milder elevations of bilirubin during the second and third trimesters could result in subtle neurotoxicity detected later as LLE in these language evaluations. This is further supported by data from animal studies of developing neurons suggesting potential neurotoxicity at much lower bilirubin levels,[26] mediated, in part, through mitochondrial toxicity[27]. These mechanistic hypotheses should be tested.

The absence of association of atazanavir exposure with LLE at 24 months of age is reassuring, suggesting that the effect is transient, mild or compensated with ongoing development. In our sample, among 83 one-year-olds with LLE and available for follow-up assessment at two years, 34 (41%) still had LLE (data not shown). Some of those with resolution of LLE may have improved language functioning due to receipt of early intervention services, which increased from 6% to 10% between ages one and two years in our cohort. An alternative explanation is that the ASQ is not as sensitive as the CDI for detecting associations with individual ARV exposures, a limitation of our study protocol. The CDI assesses four domains, and multiple items on each domain, whereas the ASQ provided a total score from six items; the greater amount of information from the CDI could result in greater variation in the individual scores thereby increasing sensitivity as compared to the ASQ. Longer-term language outcomes in this cohort and investigation of associations of atazanavir exposure with language, hearing, and other developmental outcomes in other cohorts will be essential.

Our data suggest careful clinical screening for LLE in infants who are HEU in the first two years of life. As new ARV agents are approved and become more widely used, in combination with NRTIs or other regimens, continued evaluation of language functioning and other neurodevelopmental outcomes are warranted for ensuring the safety of treatments for pregnant women with HIV.

Acknowledgements:

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (HD052102, 3 U01 HD052102-05S1, 3 U01 HD052102-06S3) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104, 3U01HD052104-06S1) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2011, in alphabetical order: **Baylor College of Medicine**: William Shearer, Mary Paul, Norma Cooper, Lynette Harris; **Bronx Lebanon Hospital Center:** Murli Purswani, Emma Stuard, Anna Cintron; **Children's Diagnostic & Treatment Center**: Ana Puga, Dia Cooley, Doyle Patton, Deyana Leon; **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; **New York University**

School of Medicine: William Borkowsky, Sandra Deygoo, Helen Rozelman; **St. Jude Children's Research Hospital**: Katherine Knapp, Kim Allison, Megan Wilkins; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; **SUNY Downstate Medical Center**: Hermann Mendez, Ava Dennie, Susan Bewley; **Tulane University Health Sciences Center**: Russell Van Dyke, Karen Craig, Patricia Sirois; **University of Alabama, Birmingham**: Marilyn Crain, Newana Beatty, Dan Marullo; **University of California, San Diego**: Stephen Spector, Jean Manning, Sharon Nichols; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Emily Barr, Robin McEvoy; **University of Florida/Jacksonville:** Mobeen Rathore, Kristi Stowers, Ann Usitalo; **University of Illinois, Chicago:** Kenneth Rich, Delmyra Turpin, Renee Smith; **University of Medicine and Dentistry of New Jersey:** Arry Dieudonne, Linda Bettica, Susan Adubato; **University of Miami:** Gwendolyn Scott, Claudia Florez, Elizabeth Willen; **University of Southern California:** Toinette Frederick, Mariam Davtyan, Maribel Mejia; **University of Puerto Rico Medical Center**: Zoe Rodriguez, Ibet Heyer, Nydia Scalley Trifilio.

REFERENCES

1. Zubrick SR, Taylor CL, Rice ML, Slegers D. Late language emergence at 24 months: An epidemiological study of prevalence, predictors, and covariates. *J. Speech Lang. Hear. Res.* 2007;50:1562-1592.

2. Reilly S, Bavin EL, Bretherton L, et al. The Early Language in Victoria Study (ELVS): A prospective, longitudinal study of communication skills and expressive vocabulary development at 8, 12 and 24 months. *International Journal of Speech-Language Pathology.* 2009;11(5):344-357.

3. Feldman HM, Dollaghan CA, Campbell TF, Kurs-Lasky M, Janosky JE, Paradise JL. Measurement properties of the MacArthur Communicative Development Inventories at ages one and two years. *Child Dev.* 2000;71(2):310-322.

4. Bloomfield FH. Epigenetic modifications may play a role in the developmental consequences of early life events. *J. Neurodev. Disord.* 2011;3(4):348-355.

5. Quigley MA, Poulsen G, Boyle E, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Archives of Disease in Children: Fetal & Neonatal Edition* 2011.

6. Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL. Neuropsychological comparison of alcohol-exposed children with or without physical features of Fetal Alcohol Syndrome. *Neuropsychology.* 1998;12:146-153.

7. Taylor AN, Chiappelli F, Tritt SH, Yirmiya R. Maternal alcohol consumption and neuroendocrine-immune interactions in the offspring. In: Hodgson DM, Coe DL, eds. *Perinatal programming: early life determinants of adult health and disease*: Taylor & Francis; 2006.

8. Rice ML, Buchanan AL, Siberry GK, et al. Language impairment in children perinatally infected with HIV compared to children who were HIV-exposed and uninfected. *Journal of Developmental & Behavioral Pedatrics.* 2012;33:112-123.

9. Griner R, Williams PL, Read JS, et al. In utero and postnatal exposure to antiretrovirals among HIV-exposed but uninfected children in the United States. *AIDS Patient Care STDS.* 2011;25(7):385-394.

10. LeDoare K, Bland R, Newell ML. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. *Pediatrics.* 2012;130(5).

11. Sirois PA, Huo Y, Williams PL, et al. Safety of perinatal exposure to antiretroviral mediations: Developmental outcomes in infants. *Pediatr. Infect. Dis. J.* 2013.

12. Bayley N. *Bayley Scales of Infant and Toddler Development--Third Edition.* San Antonio, TX: Harcourt Assessment; 2006.

13. Williams PL, Seage GRr, Van Dyke RB, et al. A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. *Am. J. Epidemiol.* 2012;175(9):950-961.

14. Fenson L, Marchman VA, Thal DJ, Dale PS, Reznick JS, Bates E. *MacArthur-Bates Communicative Development Inventories.* Baltimore, Maryland: Paul H. Brookes; 2007.

15. Tassiopoulos K, Read JS, Brogly S, et al. Substance use in HIV-infected women during pregnancy: Self-report versus meconium analysis *AIDS Behav.* 2010;14 1269-1278.

16. van Noort-van der Spek IL, Franken MJP, Weisglas-Kuperus N. Language functions in preterm-born children: A systematic review and meta-analysis. *Pediatrics.* 2012;129:745-754.

17. Sibiude J, Warszawski J, tubiana R, et al. Premature delivery in HIV-infected women startingprotease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin. Infect. Dis.* 2012;54(9):1348-1360.

18. Powis KM, Kitch D, Ogwu H, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J. Infect. Dis.* 2011;204:506-514.

19. Wilcox JJ, Weinberg CF, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am. J. Epidemiol.* 2011;174(9):1062-1068.

20. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of PerinatalTransmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. . 2013.

21. Mandelbrot L, Mazy F, Floch-Tudal C, et al. Atazanavir in pregnancy: impact on neonatal hyperbilirubinemia. *European Journal of Obstetrics and Gynecology and Reproductive Biology.* 2011;157(1):18-21.

22. Conradie F, Zorrilla C, Josipovic D, et al. Safety and exposure of once-daily ritonavir-boosted atazanavir in HIV-infected pregnant women. *HIV Med.* 2011;12(9):570-579.

23. Newman TB, Liljestrand P, Jeremy RJ, et al. Jaundice and infant feeding study team. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. *N. Engl. J. Med.* 2006;354(18):1889-1900.

24. Ip S, Chung M, Kulig J, et al. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatr. Rev.* 2004;114(1):e130-153.

25. Jangaard KA, Fell DB, Dodds L, Allen AC. Outcomes in a population of healthy term and near-term infants with serum bilirubin leavels of > or = 325 micromol/L (>or=19 mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000. *Pediatrics.* 2008;122(1):119-124.

26. Hanko E, Hansen TW, Almaas R, Lindstad J, Rootwelt T. Bilirubin induces apoptosis and necrosis in human nT2-N neurons. *Pediatr. Res.* 2005;57:57-179.

27. Rodrigues CM, Sola S, Brites D. Bilirubin induces apoptosis via the mitochondrial pathway in developing rat brain neurons. *Hepatology.* 2002;35:1186.

FIGURE LEGEND

Figure. Participant enrollment and language evaluations completed in the Surveillance Monitoring of ART Toxicities (SMARTT) study as of April 2011; CDI stands for MacArthur-Bates Communicative Development Inventories; ASQ for Ages and Stages Questionnaire

Table 1. Child and Maternal Characteristics of HIV-exposed uninfected SMARTT Study Infants by Late Language Emergence (LLE) at the 12-Month and 24-Month Visit

Characteristic	LLE on the CDI at 12-month visit		LLE on the ASQ at 24-month visit	
	Yes (N=149)	No (N=428)	Yes (N=128)	No (N=424)
Infant Demographic and Birth Characteristics				
Age at assessment (in months), Mean (SD)	12.8 (1.5)	13.0 (1.5)	24.3 (1.8)	25.1 (1.8)
Male sex	84 (56%)	200 (47%)	78 (61%)	197 (46%)
Black race	93 (69%)	283 (70%)	84 (69%)	269 (68%)
Latino/Hispanic ethnicity	53 (36%)	81 (19%)	43 (34%)	142 (34%)
Multilingual exposure	39 (26%)	78 (18%)	40 (31%)	106 (25%)
Gestational age <37 weeks	53 (36%)	81 (19%)	40 (31%)	91 (22%)
Small for gestational age	18 (12%)	31 (7%)	19 (15%)	32 (8%)
Cognitive delay	18 (15%)	10 (3%)	11 (15%)	6 (3%)
Hearing problems	18 (12%)	15 (4%)	21 (16%)	13 (3%)
Combination neonatal prophylaxis (vs. zidovudine alone)	10 (7%)	10 (2%)	4 (3%)	12 (3%)
Caregiver Characteristics				
Household income <$20,000	107 (74%)	295 (70%)	91 (72%)	306 (73%)
Lack of high school education (or equivalent)	55 (37%)	128 (30%)	45 (35%)	135 (32%)
Low verbal IQ (<85)	60 (57%)	129 (41%)	46 (49%)	143 (49%)
Performance IQ (<85)	41 (39%)	95(30%)	39(42%)	99(34%)
Health problems	133 (90%)	363 (87%)	116 (95%)	371 (90%)
Too tired for activities of daily living	43 (29%)	113 (27%)	47 (39%)	133 (32%)
Difficulty caring for child	26 (18%)	27 (11%)	22 (18%)	71 (17%)
Cannot do other activity*	8 (5%)	23 (5%)	4 (3%)	32 (8%)
Maternal Exposures/Health Characteristics During Pregnancy				
Earliest maternal VL >400 copies/mL	83 (58%)	275 (66%)	76 (61%)	261 (62%)

Latest maternal VL >400 copies/mL	29 (20%)	73 (17%)	25 (20%)	73 (17%)
Earliest maternal CD4% < 25	59 (47%)	154 (40%)	52 (47%)	150 (40%)
Latest maternal CD4% < 25	52 (39%)	122 (30%)	41 (34%)	109 (27%)
Tobacco use	29 (20%)	73 (18%)	18 (16%)	72 (18%)
Alcohol use	15 (10%)	41 (10%)	8 (7%)	31 (8%)
Illicit drug use	8 (6%)	33 (8%)	9 (8%)	23 (6%)

*Other activity refers to all non-work and non-housework activities.

VL=viral load

LLE=Late Language Emergence

CDI= Communicative Development Inventory

ASQ=Ages and Stages Questionnaire

For the CDI: 37 were missing data on race; 2 on ethnicity; 2 on multilingual exposure. Four were missing gestational age; 116 were missing information on verbal IQ and 156 on performance IQ; 1 on hearing status; and 2 on neonatal prophylaxis. Twelve were missing household income; 154 caregivers did not have a verbal IQ; and 11 caregivers were missing all health status variables. Fourteen mothers did not have a VL on record during pregnancy, 70 did not have a measure for early CD4%, 32 were missing CD4% before delivery, and 11 were missing alcohol, tobacco, and drug exposures during pregnancy.

For the ASQ: 27 were missing data on race; 2 on ethnicity; 2 on multilingual exposure. Three were missing gestational age; 193 were missing information on verbal IQ and 169 on performance IQ; and 10 on neonatal prophylaxis. Six were missing household income; 168 caregivers did not have a verbal IQ; and 16 caregivers were missing all health status variables. Nine mothers did not have a VL on record during pregnancy, 70 did not have a measure for early CD4%, 31 were missing CD4% before delivery, and 29 were missing alcohol, tobacco, and drug exposures during pregnancy.

Table 2. Final Adjusted Logistic Regression Models for Association of Late Language Emergence (LLE) among HIV-exposed uninfected children with Infant and Maternal Factors at the 12-month and 24-month Visit

	LLE on the CDI at 12-Month Visit			LLE on the ASQ at 24-Month Visit		
Covariate	**% in category**	**aOR (95% CI)**	***P*-value**	**% in category**	**aOR (95% CI)**	***P*-value**
Male sex	51%	1.54 (1.03, 2.33)	0.03	51%	2.00 (1.28, 3.13)	0.002
Age at assessment						
18-23 months	---	---	---	12%	(ref)	---
23-25 months	---	---	---	49%	0.61 (0.32, 1.14)	0.12
>25 months	---	---	---	40%	0.23 (0.12, 0.46)	<0.001
Multilingual exposure	20%	1.60 (0.98, 2.59)	0.06	---	---	---
Combination neonatal prophylaxis (vs. zidovudinealone)	4%	3.07 (1.18, 7.97)	0.02	---	---	---
Caregiver VIQ<85	33%	2.10 (1.29, 3.41)	0.003	---	---	---
Latest maternal CD4%<25‡	32%	1.62 (1.05, 2.49)	0.03	29%	1.49 (0.93, 2.37)	0.09
Earliest maternal VL>400 cp/mL‡	64%	0.63 (0.41, 0.97)	0.04	---	---	---
Caregiver health problems	---	---	---	91%	2.13 (0.85, 5.32)	0.11
Caregiver too tired for ADL	---	---	---	34%	1.44 (0.90, 2.29)	0.13
Caregiver unable to do other activities*	---	---	---	7%	0.31 (0.10, 0.96)	0.04

*Other activities refer to all non-work and non-housework activities.

‡Measures reflect earliest and latest measures recorded during pregnancy.

aOR=adjusted Odds Ratio, CI=confidence interval, LLE=late language emergence, VIQ=verbal intelligence quotient, VL=viral load, ADL=activities of daily living.

Table 3. Adjusted Logistic Regression Models for Association of Late Language Emergence (LLE) with *in utero* Antiretroviral Exposure among HIV-exposed uninfected children

	LLE on the CDI at 12-month visit			LLE on the ASQ at 24-month visit		
Exposure	**% Exposed**	**aOR (95% CI)**	***P*-value**	**% Exposed**	**aOR (95% CI)**	***P*-value**
Exposure at any time during pregnancy						
	N=535			**N=503**		
cARV vs no cARV	86%	0.79 (0.43, 1.44)	0.44	86%	0.69 (0.37, 1.28)	0.24
NNRTI vs no NNRTI	12%	0.69 (0.36, 1.33)	0.27	13%	1.12 (0.58, 2.13)	0.74
PI vs no PI	83%	1.20 (0.68, 2.11)	0.54	82%	0.95 (0.53, 1.71)	0.86
Exposure During the 1st Trimester of Pregnancy						
cARV vs no cARV	43%	0.77 (0.50, 1.19)	0.23	43%	1.13 (0.72, 1.75)	0.60
NNRTI vs no NNRTI	9%	0.87 (0.43, 1.78)	0.71	10%	1.08 (0.53, 2.20)	0.84
PI vs no PI	37%	0.98 (0.64, 1.51)	0.94	39%	1.23 (0.79, 1.92)	0.36
Exposure to Individual ARV Agents (among children with *in utero* cARV exposure)						
	N=464			**N=431**		
Zidovudine	75%	0.90 (0.54, 1.51)	0.70	76%	1.01 (0.57, 1.79)	0.97
Lamivudine	76%	1.01 (0.59, 1.71)	0.97	78%	0.87 (0.49, 1.56)	0.65
Abacavir	14%	1.23 (0.67, 2.25)	0.50	18%	0.75 (0.40, 1.42)	0.38
Didanosine	3%	1.86 (0.56, 6.19)	0.31	4%	0.98 (0.29, 3.27)	0.98
Stavudine	2%	2.14 (0.45, 10.23)	0.34	3%	1.69 (0.49, 5.78)	0.40
Tenofovir	37%	1.14 (0.72, 1.80)	0.59	33%	0.98 (0.58, 1.64)	0.94

	LLE on the CDI at 12-month visit			LLE on the ASQ at 24-month visit		
Exposure	**% Exposed**	**aOR (95% CI)**	***P*-value**	**% Exposed**	**aOR (95% CI)**	***P*-value**
Emtricitabine	35%	1.03 (0.64, 1.64)	0.92	30%	1.12 (0.66, 1.90)	0.67
Efavirenz	6%	1.11 (0.44, 2.81)	0.83	6%	1.83 (0.58, 4.91)	0.23
Nevirapine	7%	0.47 (0.18, 1.21)	0.12	9%	0.81 (0.34, 1.92)	0.63
Atazanavir	21%	1.83 (1.10, 3.04)	0.02	19%	1.23 (0.69, 2.19)	0.49
Nelfinavir	21%	0.96 (0.54, 1.71)	0.90	30%	0.94 (0.55, 1.59)	0.81
Saquinavir	5%	2.74 (1.09, 6.91)	0.03	5%	0.15 (0.02, 1.12)	0.06
Lopinavir/ritonavir	54%	1.06 (0.68, 1.66)	0.79	49%	0.99 (0.62, 1.60)	0.98

LLE=late language emergence, aOR=adjusted odds ratio, CI=confidence interval, cARV=combination antiretroviral, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, PI=protease inhibitor,CDI=Communicative Development Inventory; ASQ=Ages and Stages Questionnaire.

Each row represents a separate logistic regression model evaluating the odds of LLE for those exposed to the ARV regimen, drug class, or individual drug noted as compared to unexposed, adjusted for covariates as follows: **At 12-month visit**: sex, multilingual exposure, combination neonatal prophylaxis, low caregiver verbal IQ, latest maternal CD4%<25 prior to labor and delivery, and early maternal VL>400 cp/mL during pregnancy; **At 24-month visit**: age at assessment, sex, latest maternal CD4%>25, caregiver health problems, caregiver too tired for everyday activities, caregiver inability to do other activities.

Table 4. Adjusted mean differences in summary scores for language performance at 12-month and 24-month visit by *in utero* antiretroviral exposure among HIV-exposed uninfected children

	Summary CDI Score, 12-month visit			ASQ Total Score, 24-month visit		
Exposure	**Adjusted mean difference**	**(95% CI)**	***P*-value**	**Adjusted mean difference**	**(95% CI)**	***P*-value**
Exposure at any time during pregnancy						
	N=533			**N=467**		
cARVvs no cARV	-8.58	(-29.41, 12.25)	0.42	2.49	(-2.29, 7.27)	0.31
NNRTI vs no NNRTI	4.05	(-16.47, 24.58)	0.70	0.87	(-3.41, 5.15)	0.69
PI vs no PI	-14.33	(-32.80, 4.14)	0.13	-1.39	(-5.09, 2.30)	0.46
Exposure During the 1st Trimester of Pregnancy						
cARVvs no cARV	8.95	(-5.44, 23.35)	0.22	0.13	(-2.89, 3.15)	0.93
NNRTI vs no NNRTI	-12.14	(-36.40, 12.11)	0.33	1.62	(-3.12, 6.36)	0.50
PI vs no PI	5.18	(-9.24, 19.61)	0.48	-1.19	(-4.07, 1.69)	0.42
Exposure to Individual ARV Agents (among children with *in utero*cARV exposure)						
	N=462			**N=413**		
Zidovudine	-14.24	(-32.15, 3.68)	0.12	0.51	(-2.76, 3.77)	0.76
Lamivudine	-21.36	(-40.08, -2.65)	0.03	1.25	(-2.25, 4.75)	0.49
Abacavir	-15.07	(-34.49, 4.35)	0.13	2.54	(-0.85, 5.92)	0.14
Didanosine	-15.46	(-55.72, 24.80)	0.45	-1.84	(-8.63, 4.96)	0.60
Stavudine	-26.05	(-71.95, 19.86)	0.27	-6.20	(-15.62, 3.21)	0.20

	Summary CDI Score, 12-month visit			ASQ Total Score, 24-month visit		
Exposure	**Adjusted mean difference**	**(95% CI)**	***P*-value**	**Adjusted mean difference**	**(95% CI)**	***P*-value**
Tenofovir	8.70	(-7.17, 24.56)	0.28	0.49	(-2.57, 3.55)	0.75
Emtricitabine	11.48	(-4.36, 27.32)	0.16	-0.55	(-3.71, 2.60)	0.73
Efavirenz	-11.78	(-39.86, 16.31)	0.41	-2.00	(-9.05, 5.04)	0.58
Nevirapine	4.84	(-21.69, 31.38)	0.72	3.82	(-0.81, 8.44)	0.11
Atazanavir	-8.52	(-27.18, 10.14)	0.37	-1.05	(-4.62, 2.52)	0.56
Nelfinavir	2.26	(-14.53, 19.05)	0.79	-1.09	(-4.15, 1.97)	0.49
Saquinavir	-3.71	(-36.33, 28.92)	0.82	3.19	(-2.86, 9.24)	0.30
Lopinavir/ritonavir	-9.73	(-24.57, 5.11)	0.20	0.29	(-2.57, 3.14)	0.84

cARV=combination antiretroviral, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, CDI=Communicative Development Inventory; ASQ=Ages and Stages Questionnaire.

Each row represents a separate linear regression model evaluating the language score for those exposed to the ARV regimen, drug class, or individual drug noted as compared to unexposed, adjusted for:: **At 12-month visit:** multilingual exposure, caregiver's education level, caregiver's performance IQ<85, maternal alcohol use during pregnancy, early maternal VL>400 cp/mL during pregnancy, and caregiver's difficulty caring for the child; **At 24-month visit:** sex, age at assessment, caregiver's performance IQ<85, earliest maternal CD4%<25 during pregnancy, earliest maternal viral load>400 cp/mL during pregnancy, caregiver too tired for everyday activities, and caregiver inability to do other activities.