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## Author Manuscript

*J Dev Behav Pediatr.* Author manuscript; available in PMC 2013 February 1.

Published in final edited form as:

*J Dev Behav Pediatr.* 2012 February ; 33(2): 112–123. doi:10.1097/DBP.0b013e318241ed23.

## Language Impairment in Children Perinatally Infected with HIV Compared to Children Who Were HIV-Exposed and Uninfected

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### Abstract

**Objective**—To investigate risk for language impairment in children perinatally infected or exposed to HIV.

**Methods**—We evaluated the prevalence of language impairment (LI) in 7–16 year old children with perinatal HIV infection (HIV+) compared to children HIV-exposed and uninfected (HEU), using a comprehensive standardized language test (CELF-4). LI was classified as primary LI (Pri-LI) (monolingual English exposure and no cognitive or hearing impairment), concurrent LI (Con-LI) (cognitive or hearing impairment), or no LI. Associations of demographic, caregiver, HIV disease and antiretroviral treatment (ART) factors with LI category were evaluated using univariate and multivariable logistic regression models.

**Results**—Of 468 children with language assessments, 184 (39%) had LI. No difference was observed by HIV infection status for overall LI or for Pri-LI or Con-LI; mean (SD) CELF-4 scores were 88.5 (18.4) for HIV+ vs 87.5 (17.9) for HEU. After adjustment, Black children had higher odds of Pri-LI vs no LI (aOR=2.43,  $p=0.03$ ). Children who were Black, Hispanic, had a caregiver

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with low education or low IQ, or a non-biological parent as caregiver had higher odds of Con-LI vs no LI. Among HIV+ children, viral load >400 copies/ml (aOR=3.04,  $p<0.001$ ), CDC Class C (aOR=2.19,  $p=0.02$ ) and ART initiation <6 months of age (aOR=2.12,  $p=0.02$ ) were associated with higher odds of Con-LI vs. no LI.

**Conclusions**—Children perinatally exposed to HIV are at high risk for LI, but such risk was not increased for youth with HIV. Risk factors differed for Pri-LI and Con-LI.

### Keywords

Pediatric HIV infection; language impairment; antiretroviral therapy

## INTRODUCTION

Children perinatally-infected with Human Immunodeficiency Virus (HIV) are at risk for impairments in cognitive functioning<sup>1-2</sup>. Increased risk for language impairment is also reported, which can affect academic performance or adherence to medication<sup>3-6</sup>. Impaired verbal functioning has been shown to be associated with HIV disease progression<sup>7</sup> and greater immunosuppression<sup>8</sup>. In a sample of children infected with HIV who were evaluated prior to the availability of antiretroviral (ARV) drug therapy, the prevalence of language impairment (LI) was 10%<sup>9</sup>. Treatment with one or two nucleoside reverse transcriptase inhibitors (NRTIs) in the pre-HAART (highly active antiretroviral therapy) era has been associated with improvement, though not normalization, of overall cognitive and specific language measures in some studies<sup>5,10</sup>. However, Wolters et al found that over the course of a 24-month ART regimen, cognitive abilities remained stable while language abilities continued to decline, suggesting differential effects on specific brain functions<sup>8</sup>. Initiation of HAART has been associated with stabilization in measures of overall cognitive and language function<sup>11-14</sup>. However, studies focused on assessment of language function in school-aged children in the HAART era are lacking.

It is not clear if language impairments in children with HIV infection are indications of a global developmental impairment, including non-verbal and verbal intelligence, or whether language impairment can be a selective deficit. Another possible source of language impairment is related to risk for hearing loss, possibly as a consequence of mitochondrial dysfunction. Prior studies suggest that HIV and its treatment are associated with mitochondrial dysfunction<sup>15</sup> and it has been demonstrated that mitochondrial dysfunction/mutation is associated with sensorineural hearing loss<sup>16-17</sup>.

In healthy children without HIV exposure, language impairments appear in children whose general cognitive abilities are well within or even above age expectations. The condition of Specific Language Impairment (SLI) is defined as language impairments without other developmental impairments. In a study of 7,218 kindergarten children to determine the prevalence of SLI, Tomblin et al<sup>18</sup> reported 7.4% with SLI and 12% of the children with language sparing, children who scored low on nonverbal IQ assessment (in the range of 70–87) but demonstrated language performance within normal limits<sup>19</sup>, suggesting a dissociation of language acquisition and nonverbal intelligence. Similarly, Rice et al<sup>20</sup> documented that children with low nonverbal IQ levels can have grammatical skills within or above typical levels. On the other hand, children who have both language impairments and nonverbal cognitive impairments scored lower, and grew more slowly in language skills between 6 and 10 years, than children with SLI. In effect, language impairments are not necessarily part of a global developmental impairment in healthy children but if both language and cognition are low, the combination yields lower language performance than language impairment alone, and slower growth over time. The prevalence of speech or

language impairments among children is relatively high and comprises a high proportion of children who receive special education services at school entry (62%)<sup>21</sup>. This diagnosis has a reciprocal relationship to services for children with learning disability. In kindergarten, 11% of children with special education services are characterized as having learning disabilities, whereas in 5<sup>th</sup> grade, the age level for many of the children in this study, 60% of children receiving special education services are diagnosed with learning disabilities and the percent of children receiving services for speech or language impairment drops to 14%<sup>21</sup>. The shift seems to be related to a high risk of reading impairment in children with early language impairments, with later diagnosis of reading impairments<sup>22</sup>. The diagnosis of language impairment tends to occur at a younger age than that of reading impairment, and the later reading impairment is identified in academic tasks and targeted as a priority for remediation, even though the language impairments are likely to persist<sup>23</sup>. Children exposed to or living with HIV who have language impairments may be at risk for poor or delayed academic achievement<sup>3</sup>.

Understanding the sources of low performance on language assessments in children with HIV or under HAART treatment for HIV requires differentiation of language impairments associated with cognitive impairments, or as a consequence of hearing impairment. Here we adopt the terminology of Primary impairment (Pri-LI) for children with language impairments with no other known impairments<sup>24</sup>, versus Concurrent impairment, (Con-LI, sometimes referred to as “Secondary LI”<sup>24</sup>), for children with language impairment along with possible hearing and/or cognitive impairment<sup>25</sup>. Children with HIV could be at higher risk for these concurrent impairments due to the ongoing or intermittent exposure of the developing brain to chronic immune dysregulation that characterizes HIV infection, or due to HIV treatment or other complications of HIV disease. Alternatively, risk for Pri-LI could be increased as a result of HIV infection or other environmental influences that can impair language acquisition. Comparison of the prevalence and risk factors for LI in children with HIV infection as compared to those perinatally HIV-exposed but HIV-uninfected can clarify whether an increased risk of LI is attributable to HIV infection.

Evaluation of risk factors for language impairment, both Pri-LI and Con-LI, is needed to identify possible contributions of HIV disease, disease severity and treatments, while controlling for demographic and caregiver characteristics<sup>26</sup>. This study evaluated the relationship between language ability and nonverbal cognitive ability, and the prevalence of Pri-LI and Con-LI in children perinatally infected with HIV (HIV+) compared to children exposed and uninfected (HEU), and the relationships of HIV-disease characteristics along with environmental risk factors on language impairment.

## METHODS

### Study Population

This investigation used data collected in the Adolescent Master Protocol (AMP), a component of the Pediatric HIV/AIDS Cohort Study (PHACS). AMP is a prospective cohort study conducted at 15 sites in the United States, including Puerto Rico, designed to evaluate the impact of HIV infection and ART on the development of children and adolescents with perinatal HIV exposure. The study protocol was approved by the institutional review board (IRB) of each participating site; written informed consent was obtained from each child’s parent/legal guardian or from older participants as allowed by the local IRB. Written assent was obtained as appropriate. The study opened to enrollment in March 2007.

Children ages 7–16 years born to women with HIV infection were eligible. The study design included both children infected with HIV (HIV+) and children exposed and uninfected (HEU). At each semi-annual study visit, information about study participants and their

families was gathered through clinical interviews, medical record reviews, and neurodevelopmental testing. The current study is a cross-sectional analysis of language data collected at the first six-month follow up visit, the first time language was assessed. Lifetime health and treatment histories were obtained through chart reviews and current health status was ascertained through physical and laboratory evaluations.

### Assessment of Language Impairment

Language functioning was evaluated using the comprehensive Clinical Evaluation of Language Functioning-Fourth Edition (CELF-4)<sup>27</sup>. Language Impairment (LI) was defined as scoring more than one standard deviation (SD) below the reference mean (CELF-4 Core Language Standard Score less than 85, equivalent to the 16<sup>th</sup> percentile). This criterion was motivated by the observation that the norming samples for CELF-4 (reported in the test manual, p. 207) included children from bilingual homes (15%) as well as children receiving special services (9.5% overall, 4.8% for learning disability or intellectual disability, and 7.0% for speech or language services). Further, the criterion of one standard deviation below the mean is commonly used in studies of children with SLI, allowing comparison across studies<sup>28</sup>.

The age range of the AMP study crosses two versions of the CELF-4 protocol. Children ages 7 and 8 years completed the following subtests: Concepts and Following Directions; Word Structure, Recalling Sentences, and Formulated Sentences. Children ages 9 and older completed these subtests: Concepts and Following Directions, Recalling Sentences, Formulated Sentences, Receptive Word Classes and Expressive Word Classes. The Core Language Standard Score was computed for the age appropriate subtests, yielding a comparable standard score across age levels.

LI was classified as Pri-LI (LI with no cognitive or hearing impairment) or Con-LI (LI with cognitive or hearing impairment). Audiometric hearing examinations or hearing screens were requested according to the study protocol for children who scored in the LI range; 72% of those with LI received audiometric exams, 7% received routine hearing screenings, and 21% had a caregiver report of presence or absence of permanent hearing loss or concerns regarding the child's hearing. In some cases caregiver reports were based on prior audiometric exams. Nonverbal cognitive impairment was defined as a standard score less than 85, one standard deviation below the mean ( $< -1$  SD), on the Perceptual Reasoning Index (PRI) of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)<sup>29</sup>. The possible confounding effect of multilingual exposure on LI was considered. For those children administered the CELF-4 in English, multilingual exposure was defined as exposure to non-English language either at home or outside the home. The CELF-4 (as well as the WISC-IV) was given in Spanish to children whose primary language was Spanish, based on parent report and/or examiner judgment. For these children, exposure to other languages was not collected and they were classified as monolingual. For the analyses of Pri-LI and Con-LI, children with LI who also had multilingual exposure could not be classified as Pri-LI; they were classified as Con-LI only if they met the criteria for cognitive or hearing impairment. See further detail in the Results section.

### Assessment of Other Risk Factors for Language Impairment

The ART regimen at the time of CELF administration was determined from medication regimen data collected in AMP. Age at ART initiation was based on the earliest date of ARV use, excluding neonatal prophylaxis in the first two months of life and treatment durations less than a week, determined by review of individual records. HIV viral load and CD4+ T-lymphocyte count and percent, two widely used indicators of HIV disease severity (see guidelines at [http://aidsinfo.nih.gov/contentfiles/Pediatric\\_Guidelines.pdf](http://aidsinfo.nih.gov/contentfiles/Pediatric_Guidelines.pdf)) were

obtained as part of routine medical care; results closest to the CELF administration were used in our analysis. Current or past diagnosis with an AIDS-defining condition was based on CDC clinical classification, determined by pediatric surveillance definitions for participants younger than 13 years of age (1994) and the revised adult case definition of AIDS-defining conditions for participants 13 years of age or older (1993).

Factors widely considered as predictors of children's language acquisition were also evaluated as potential confounders in our analysis. Caregiver's education (low level defined as less than high school degree), household income (low level defined as <\$20,000 annual income), marital status, and relationship to child (biological parent or other) are potential influences on children's development<sup>30</sup> although environmental prediction of language impairments has yielded mixed outcomes in large population samples<sup>31</sup>. These variables were obtained by caregiver self-report at study entry. Maternal ARV drug use during pregnancy was obtained at entry in PHACS or from previous studies in which the child and/or mother participated. Caregiver's performance IQ (PIQ) was included as an index of nonverbal cognitive functioning, obtained by direct assessment with the Wechsler Abbreviated Scale of Intelligence, with impairment defined as <70<sup>32</sup>.

## Statistical Methods

The relationship of language and nonverbal intelligence across the full sample was examined based on Pearson correlation coefficients and inspection of bivariate distributions. Children in the HIV+ and HEU groups were compared with respect to demographic and caregiver characteristics. The prevalence of Pri-LI, Con-LI, and no LI was summarized by demographic and caregiver characteristics, and by HIV disease characteristics among the children with HIV. T-tests or ANOVAs and Fisher's Exact tests were used to compare characteristics between HIV+ and HEU groups and across language impairment categories, as appropriate. Univariate and multivariable logistic regression models were used to evaluate the association of HIV status and other factors with the presence of Pri-LI and Con-LI, each versus No LI, both overall and within the HIV+ group. Risk factors considered for the HIV+ group also included measures of HIV disease severity. Initial multivariable models included all covariates with  $p < 0.20$  in univariate models. To be as inclusive as possible, final adjusted models retained all covariates with  $p < 0.15$ . Because of the specific interest in evaluating the association of HIV infection status with LI, this variable was included in all of the models for the overall population.

To provide additional power for detecting differences in language functioning by HIV infection status, sensitivity analyses were conducted by considering the continuous CELF scores and comparing the HIV+ to HEU group using linear regression models adjusted for other confounders. These models were fit with and without child cognitive impairment to address scientific interest in primary versus concurrent impairment. Analyses were conducted using SAS Version 9 (SAS Institute, Cary, NC), and were based on data submitted as of March 1, 2010.

## RESULTS

A total of 468 children (306 HIV+ and 162 HEU) had a valid and complete language assessment, at a median age of 12 years (range 7–16); the children were 52% male, 69% Black and 26% Hispanic. Table 1 displays demographic and caregiver characteristics by HIV infection status for the 437 children in whom Pri-LI, Con-LI and no LI could be distinguished (excluding 8 children due to missing WISC-IV PRI scores and 23 children with LI and multilingual exposure but no other concurrent hearing or nonverbal cognitive impairment). The children with HIV in our study were more likely to be older, female, Black, and non-Hispanic than HEU children. While there were no significant differences in

most caregiver characteristics (education, marital status, or performance IQ) between the HIV+ and HEU groups, children with HIV were less likely to be from a low income household and to have their biological parent as their caregiver. As expected, children with HIV were less likely to have been exposed to ARV drugs *in utero*, as compared to children in the HEU group (18% vs. 85%).

Most children (93%) were administered the CELF-4 in English. Of the 437 children, 153 (35%) scored more than one SD below the general population mean on the CELF-4 Core Language Score (CELF < 85). The rates of LI were comparable between the HIV+ and the HEU groups (34% vs 37% respectively) and the mean Core Language scores were also similar (88.5 vs 87.5). Overall, 32 children (7%) had hearing impairment, 88 (19%) had multilingual exposure, and 137 (29%) had low nonverbal cognitive scores (<85).

Among the 437 children for whom LI category could be identified 48 (11%) had Pri-LI and 105 (24%) had Con-LI. Concurrent conditions for the children with Con-LI included a low nonverbal cognitive score for 94 (90%), hearing impairment for 20 (19%) and both low nonverbal cognitive score and hearing impairment for nine (9%). Multilingual exposure was present in combination with either low nonverbal cognitive score or hearing impairment for 18 (17%). Of the children without LI, 43 (15%) had low nonverbal cognitive score, 12 (4%) had abnormal hearing, and 47 (17%) had multilingual exposure. One child (<1%) of the 284 without LI had both a low nonverbal cognitive score and hearing impairment.

The percent within each language impairment category by HIV infection status and demographic factors is summarized in Table 2. The prevalence of Pri-LI and Con-LI were similar in the HIV+ and HEU groups, with 10% vs 12% for Pri-LI, and 24% vs 25% for Con-LI, respectively. The mean CELF-4 Core Language standard scores were highest for those with no LI (98.7) and slightly higher for those with Pri-LI as compared to Con-LI (74.2 vs 65.8). The Pearson correlation between nonverbal IQ and CELF Core Language Standard Scores was 0.63 among all subjects, but higher for those with Con-LI (0.51) and those with no language impairment (0.37) than for children with Pri LI (0.29). Most children had consistent levels of nonverbal IQ and language functioning, with 54% scoring above 85 for both the nonverbal WISC and CELF-4 and 24% scoring below 85 for both (i.e., Con-LI). However, 91 children (21%) had inconsistent measures of functioning, with 11% showing only language deficits and 10% observed with normal language functioning but low nonverbal IQ. These inconsistencies in the general continuum of severity motivate separate evaluation of predictor relationships for Con-LI and Pri-LI, to examine possible differences between the two groups of children with LI.

A summary of HIV disease severity by language impairment group is provided in Table 3 and illustrated in Figure 1. Children with Con-LI were significantly more likely than those with Pri-LI or no LI to have initiated ART by 6 months of age, to have a prior CDC Class C diagnosis, a detectable viral load, and CD4% < 25%. Most children were on HAART with protease inhibitor (PI) at the six-month visit (72%) with no differences in ART regimen by LI group.

Table 4 summarizes the results of univariate and final adjusted multivariable logistical regression models for Pri-LI vs no impairment, both overall (upper panel) and within the group of children with HIV (lower panel). For the overall study population, the final adjusted model indicated no significant difference in the odds of Pri-LI vs No LI for HIV+ as compared to HEU groups of children; however, children who were Black had over twice the odds of Primary LI vs. no LI (aOR=2.43,  $p=0.03$ ).

Table 5 presents the results of analogous models for Con-LI vs no LI groups, again both overall (upper panel) and within the group of children with HIV (lower panel). Univariate

logistic models for Con-LI versus No LI among HIV + and HEU revealed a significant effect of caregiver education ( $p=0.01$ ) and a marginal effect of low caregiver nonverbal IQ ( $p=0.06$ ), but no significant association with HIV status or other characteristics. However, in the final adjusted model, a significant increase in the odds of Con-LI was observed for children who were Black (aOR=3.7,  $p=0.003$ ) or Hispanic (aOR=3.2,  $p=0.01$ ), who had a less educated caregiver (aOR=1.8,  $p=0.04$ ) or a caregiver with low cognitive score (aOR=3.3,  $p=0.05$ ) or had a caregiver who was not the biological parent (aOR=1.9,  $p=0.02$ ). There was no significant effect of HIV infection status on odds of Con-LI vs no LI.

In a sensitivity analysis based on the continuous CELF-4 scores reported in Table 6, linear regression models indicated no difference in adjusted mean scores between HIV+ vs HEU (mean difference =0.44, 95% CI: -3.20, 4.08,  $p=0.81$ ). However, participants of Black race had an adjusted mean CELF-4 score which was 6.3 points lower than those of non-Black race ( $p=0.002$ ), and those of lower socioeconomic status had lower mean scores, as reflected by having a caregiver without high school education (4.9 points lower,  $p=0.02$ ) and an annual household income below \$20,000 (3.4 points lower,  $p=0.06$ ). In addition, low caregiver cognitive score based on PIQ<70 was associated with significantly lower adjusted mean scores (10.0 points lower,  $p=0.04$ ). Further adjustment for child's cognitive level led to slight attenuation of differences in adjusted means noted above, but race, caregiver education, and low caregiver nonverbal IQ remained significantly associated with CELF-4 scores while HIV status remained clearly non-significant (mean difference=0.8,  $p=0.62$ ).

Within the HIV+ group, univariate and adjusted logistic regression models investigating disease severity measures are summarized in Table 4 (bottom panel) for Pri-LI vs no LI and Table 5 (bottom panel) for Con-LI vs no LI. In univariate models, none of the disease measures reached statistical significance for predicting the odds of Pri-LI vs no LI. In the multivariate model, only age at ART initiation reached significance indicating a two-fold increase in odds of Pri-LI for those with later ART initiation. In contrast, those with detectable viral load, prior CDC Class C diagnosis, or earlier ART initiation had two to three-fold higher odds of Con-LI vs no LI. Within the HIV+ subgroup, children who were male or had a biological parent as caregiver had significantly lower odds of Con-LI, while those who were Black or had a caregiver with lower education had significantly higher odds. Although children with HIV with lower CD4% (<25%) had significantly increased odds of Con-LI in univariate models, this association did not persist after adjustment for other measures of HIV disease severity. Similarly, in sensitivity analyses based on linear regression models for the continuous CELF-4 score restricted to participants with HIV, only HIV viral load>400 copies/mL and CDC Class C were associated with lower mean CELF scores (5.8 and 4.3 points lower, respectively). While children with low CD4% had marginally lower mean scores in unadjusted models, this finding did not persist after adjustment for viral load and CDC Class. After further adjustment for child's nonverbal IQ, CDC Class C was no longer associated with CELF scores, but child's nonverbal IQ was associated with a 19.1 point lower adjusted mean CELF-4-4 score (see Table 6).

## DISCUSSION

Language impairment in this cohort was common among children in both HIV+ and HEU groups, with impairment observed among almost 40% of participants as compared to an expected rate of 16% in the US population<sup>27</sup>. The elevated risk is especially noteworthy given that recent studies note that the practice of including children with language impairments in the norming data of tests such as CELF-4 reduces test sensitivity for identifying children with language impairments<sup>33</sup>. The rate of LI was similar for children in HIV+ and HEU groups, both overall and within sub-classifications of Pri-LI or Con-LI. The rates of LI in this study are higher than the rates of LI reported in other studies. For example,

the overall prevalence of SLI, psychometrically defined similarly to Pri-LI, was 7.4% in a study of healthy five- to six-year-old children<sup>18</sup>. Prevalence of SLI for urban African-American children and for primarily urban Hispanic children (both groups were primarily low SES) in that study was 11% and 8%, respectively. An additional 5% of the cohort demonstrated low nonverbal cognitive functioning accompanied by language impairment, while 12% performed at low nonverbal cognitive levels (70–87 IQ) without language impairment<sup>19</sup>. In our study, we found that 10% of the children without LI had low nonverbal cognitive scores (<85). Low nonverbal cognitive abilities thus could occur with or without accompanying language impairment and vice-versa.

Results from the logistic regression models indicate that factors predictive of LI differ for Pri-LI and Con-LI, yet risk of both types of LI was not different for children in HIV+ and HEU groups. The risk factors examined in these analyses revealed very little about the sources of risk for Pri-LI in children perinatally exposed to HIV. Other studies report genetic linkage and association for SLI<sup>28,34–35</sup>, suggesting that genetic influences may contribute to risk in the children exposed to HIV. In the HIV+ and HEU groups of children in this sample, the established demographic and psychosocial risk factors for Con-LI were notably elevated relative to reference norms. For the HIV+ group, markers of greater disease severity and poorer current control were additional risk factors for Con-LI, suggesting that the HIV disease process may produce more global impairments as seen in Con-LI; the lack of association of these measures with Pri-LI suggests that advanced HIV disease is less likely to cause language impairment in isolation. It is notable that 25 of the 59 children with CDC Class C diagnoses had prior reported diagnoses of encephalopathy<sup>36–37</sup>. It is also possible that the smaller number of children with Pri-LI reduced power to detect associations; however, a sensitivity analysis for the continuous CELF-4 scores offered some confirmation of this finding in that few HIV disease severity measures were associated with mean CELF-4 scores after adjustment for children's low nonverbal cognitive status, akin to lower mean CELF-4 scores not explained by children's cognitive status. With approximately 275 HIV+ and 150 HEU subjects, the linear regression approach had 80% power to detect differences of 4.3 points or more in mean CELF-4 scores.

Age at initiation of ART was associated with both Pri-LI and Con-LI but the effect was in opposite directions. Early ART was associated with higher odds of Con-LI, but significantly lower odds of Pri-LI. The negative effects of HIV infection on the central nervous system can occur prior to birth and during infancy<sup>38</sup>, before many of the participants in this study initiated ART. Though current guidelines recommend routine treatment from early infancy, our study population consisted primarily of older children born at a time when they would have more likely initiated ART early if they manifested neurologic impairment and other serious HIV-related disease in infancy. Thus, ART initiation before 6 months of age may be associated with Con-LI because it is a marker for those children who experienced more severe neurologic involvement from an early age. Among children who did not exhibit overt neurologic problems in infancy, subclinical brain involvement was nonetheless likely. For these children, early ART may have limited or prevented development of neurodevelopmental problems like Pri-LI, while later initiation of ART ensured survival but may have permitted a longer pre-treatment period of HIV-related effects on brain function that placed them at higher risk for more subtle or focused problems, such as Pri-LI. On the other hand, early ART in the current study may reflect early and perhaps more consistent access to comprehensive medical and psychological care and support, including referrals to appropriate early intervention and special education services if delays or deficits are recognized early. There may also be uncontrolled confounding by disease, treatment or temporal factors associated with age at ART initiation that underlie these associations, but none were evident in the current analysis. Early identification of HIV infection with routine



initiation of HAART in young infants in the United States, as currently recommended and practiced, may result in different language outcomes in future cohorts.

We did not identify an association between current ART with increased risk of either Primary or Concurrent LI among youth with perinatal HIV. However, our ability to detect associations may have been limited by the relatively small percentage of youth not receiving HAART. Additionally, the majority of children were fairly HAART-experienced (86% had over 5 years of HAART) which limited our ability to distinguish language functioning by duration on HAART. Despite widespread HAART use in our study population, 46% of those with Con-LI had viral load >400 copies/mL, suggesting adherence difficulties or the possibility of drug resistance. Detectable viral load at the time of language testing was associated with significantly higher odds of language impairment concurrent with hearing and/or low nonverbal cognitive scores. This finding suggests that effectiveness of HAART in reducing deficits in language functioning observed in the pre-HAART era may depend on careful monitoring of both adherence and resistance patterns to guide optimal therapy.

There were some limitations of our study. Our analysis was a cross-sectional evaluation of language functioning at a single time point. Future longitudinal follow-up of these children is necessary to determine the persistence of Pri-LI and Con-LI and possible long-term risks associated with disease status, treatment, and other risk factors. In addition, despite attempts to enroll a comparable control group of uninfected children, the HEU children tended to be younger and living in lower income households. While adjustment for these factors addressed these imbalances to the extent possible, this illustrates the difficulty of identifying a comparable control group of children with perinatal HIV exposure. In addition, we were unable to obtain formal audiometric exams on all children with hearing impairment. Nevertheless, to our knowledge, this is the first study which specifically addresses hearing impairment in evaluation of language functioning among children with HIV. The major strengths of this study include the focus on language impairment, particularly with respect to its classification into Primary and Concurrent groups, the relatively large sample size, the use of a group of HEU children for comparison, and the ability to control for potential confounders.

Several conclusions apply to clinical practice. Physicians providing primary and specialty care to children perinatally exposed to HIV need a heightened awareness of the high rates of LI among children of mothers with HIV, interactions between the disease and its treatment, and routine preventive screening, including hearing assessments. Although Con-LI may be more salient and readily ascertained, children without cognitive problems with HIV infection and children exposed but uninfected experience Pri-LI that may be equally impairing but less easily recognized. Ongoing studies of LI are needed for children with HIV as temporal changes in antiretroviral therapy may lead to different patterns of LI in the future. Those providing care to children and youth growing up with perinatal HIV infection or exposure to HIV should be aware of their substantial risk of LI and potential for difficulties in school and careers that such impairments may produce. Early and ongoing intervention could reduce the negative impact of language impairment.

## Acknowledgments

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS.

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP in 2010, in alphabetical order: **Baylor College of Medicine:** William Shearer, Norma Cooper, Lynette Harris; **Bronx Lebanon Hospital Center:** Murlı Purswani, Mahboobullah Baig, Anna Cintron; **Children's Diagnostic & Treatment Center:** Ana Puga, Sandra Navarro, Doyle Patton; **Children's Hospital, Boston:** Sandra Burchett, Nancy Karthas, Betsy Kammerer; **Children's Memorial Hospital:** Ram Yogeve, Kathleen Malee, Scott Hunter, Eric Cagwin;

**Jacobi Medical Center:** Andrew Wiznia, Marlene Burey, Molly Nozyce; **St. Christopher's Hospital for Children:** Janet Chen, Elizabeth Gobs, Mitzie Grant; **St. Jude Children's Research Hospital:** Katherine Knapp, Kim Allison, Patricia Garvie; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University Health Sciences Center:** Margarita Sileo, Cheryl Borne, Medea Jones; **University of California, San Diego:** Stephen Spector, Kim Norris, Sharon Nichols; **University of Colorado Denver Health Sciences Center:** Elizabeth McFarland, Emily Barr, Robin McEvoy; **University of Maryland, Baltimore:** Douglas Watson, Nicole Messenger, Rose Belanger; **University of Medicine and Dentistry of New Jersey:** Arry Dieudonne, Linda Bettica, Susan Aduabato; **University of Miami:** Gwendolyn Scott, Lisa Himic, Elizabeth Willen

Funding: 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 National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute of Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, and the National Institute on Alcohol Abuse and Alcoholism through cooperative agreements with the Harvard University School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (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).

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.

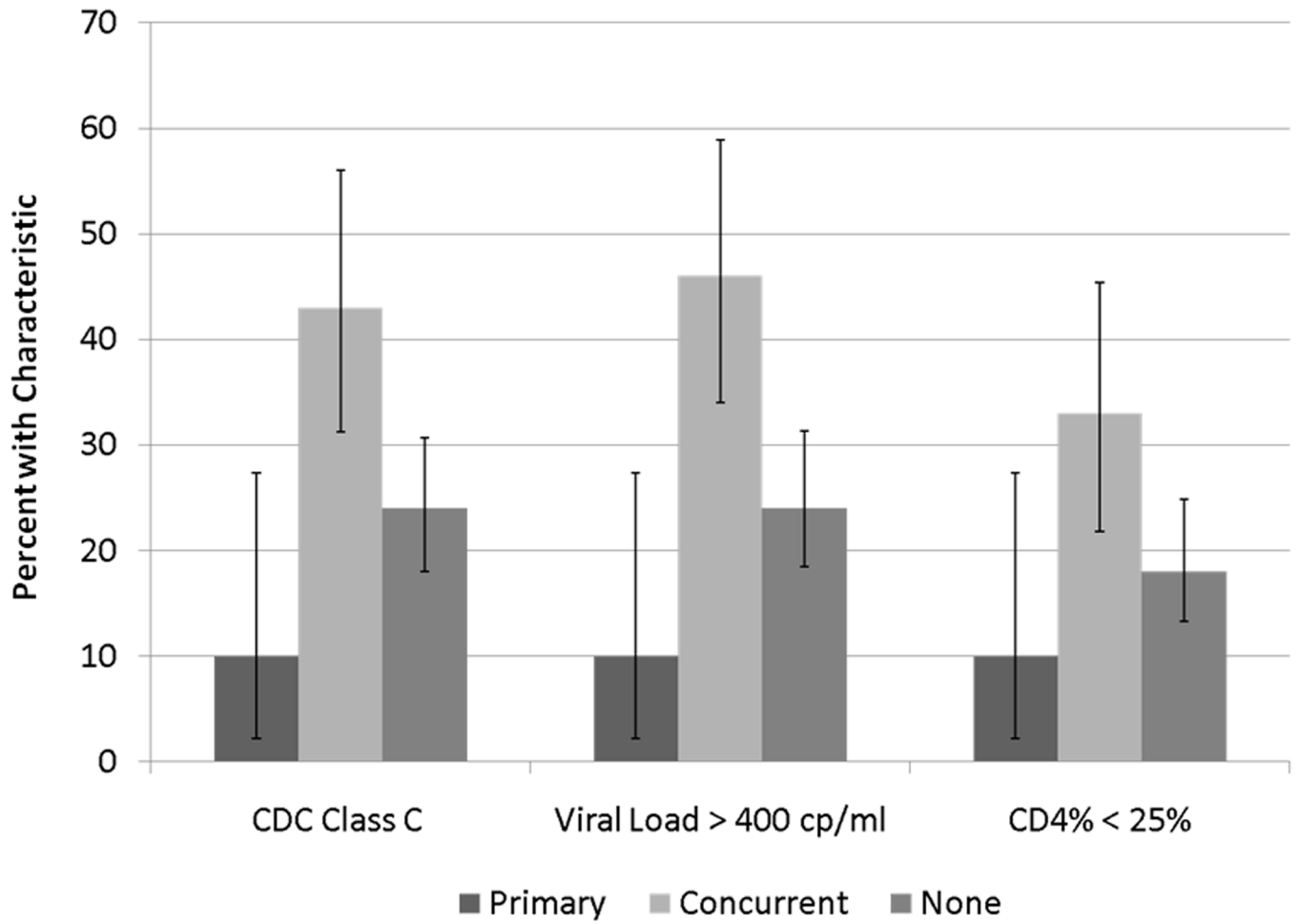
Disclosure: Funded by the National Institutes of Health

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**Figure 1.** Percent with Certain Indicators of HIV Disease Severity among Perinatally HIV-infected Children within each Language Impairment Category, with 95% Confidence Intervals.

Demographic characteristics and Language Impairment Category by HIV Status for 437 HIV -infected or HIV-Exposed but Uninfected Children in the Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study

**Table 1**

Characteristic <sup>1</sup>	HIV Status			P-Value <sup>2</sup>	
	HIV+ (N = 284)	HEU (N = 153)	Total (N = 437)		
CELf Score	Mean (SD)	88.5 (18.4)	87.5 (17.9)	88.1 (18.2)	0.57
Language Impairment	Primary	29 (10%)	19 (12%)	48 (11%)	0.71
	Concurrent	67 (24%)	38 (25%)	105 (24%)	
	None	188 (66%)	96 (63%)	284 (65%)	
Age (years)	Mean (SD)	12.6 (2.6)	11.0 (2.5)	12.0 (2.7)	<0.001
	7 – 8	31 (11%)	43 (28%)	74 (17%)	<0.001
	9 – 12	120 (42%)	80 (52%)	200 (46%)	
	13 – 16	133 (47%)	30 (20%)	163 (37%)	
Birth Year	Before 1995	109 (38%)	22 (14%)	131 (30%)	<0.001
	1995–1999	145 (51%)	84 (55%)	229 (52%)	
	2000 and Later	30 (11%)	47 (31%)	77 (18%)	
Male		134 (47%)	87 (57%)	221 (51%)	0.06
Race	White or Other	56 (20%)	53 (35%)	109 (25%)	0.002
	Black or African American	214 (75%)	97 (63%)	311 (71%)	
Hispanic or Latino Ethnicity		54 (19%)	49 (32%)	103 (24%)	0.003
Caregiver Not High School Graduate		66 (23%)	39 (25%)	105 (24%)	0.64
Annual Household Income ≤ 20K		121 (43%)	97 (63%)	218 (50%)	<0.001
Caregiver Married		111 (39%)	51 (33%)	162 (37%)	0.25
Caregiver is Biological Parent		119 (42%)	124 (81%)	243 (56%)	<0.001
Caregiver's WASI Performance IQ					
	N	219	112	331	
	Mean (SD)	92.9 (14.9)	90.9 (14.3)	92.2 (14.7)	0.25
	Impairment (IQ <70)	7 (2%)	8 (5%)	15 (3%)	0.16
Maternal ARV use in pregnancy		50 (18%)	130 (85%)	180 (41%)	<0.001

CELf= Clinical Evaluation of Language Functioning; WASI=Wechsler Adult Scales of Intelligence; IQ= Intelligence Quotient; ARV=Antiretrovirals

<sup>1</sup> 17 children did not report race; 3 children did not report their ethnicity; 13 caregivers did not report their income; 106 children were missing their caregiver's performance IQ; ART use during pregnancy was unknown for 56 children; 1 child did not consent to share their maternal ART history. Percentages are based on total sample.

<sup>2</sup> P-value calculated by Fisher's Exact Test for categorical variables and by T-Test for continuous variables.

Table 2

Prevalence of Language Impairment by HIV Status and Demographic Characteristics for 437 HIV-Infected or HIV-Exposed but Uninfected Children in the Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study

Characteristic <sup>1</sup>	Language Impairment Classification				P-Value <sup>2</sup>	
	Primary (N=48)	Concurrent (N=105)	None (N=284)	Total (N=437)		
<b>CELF Score</b>	Mean (SD)	74.2 (9.6)	65.8 (12.7)	98.7 (10.3)	88.1 (18.2)	<0.001
<b>HIV Status</b>	HIV-Infected	29 (10%)	67 (24%)	188 (66%)	284	0.71
	HIV-Exposed, Uninfected	19 (12%)	38 (25%)	96 (63%)	153	
<b>Age (years)</b>	Mean (SD)	11.8 (2.7)	11.8 (2.8)	12.2 (2.6)	12.0 (2.7)	0.33
	7 – 8	11 (15%)	23 (31%)	40 (54%)	74	0.25
	9 – 12	19 (10%)	48 (24%)	133 (67%)	200	
	13 – 16	18 (11%)	34 (21%)	111 (68%)	163	
<b>Birth Year</b>	Before 1995	14 (11%)	25 (19%)	92 (70%)	131	0.27
	1995–1999	23 (10%)	57 (25%)	149 (65%)	229	
	2000 or Later	11 (14%)	23 (30%)	43 (56%)	77	
<b>Sex</b>	Male	27 (12%)	48 (22%)	146 (66%)	221	0.45
	Female	21 (10%)	57 (26%)	138 (64%)	216	
<b>Race</b>	White or Other	8 (7%)	20 (18%)	81 (74%)	109	0.06
	Black or African American	40 (13%)	79 (25%)	192 (62%)	311	
<b>Ethnicity</b>	Hispanic or Latino	6 (6%)	32 (31%)	65 (63%)	103	0.04
	Not Hispanic or Latino	42 (13%)	73 (22%)	216 (65%)	331	
<b>Caregiver Education</b>	Not a HS Graduate	10 (10%)	36 (34%)	59 (56%)	105	0.02
	At least a HS Graduate	38 (11%)	69 (21%)	225 (68%)	332	
<b>Annual Household Income</b>	≤ 20K	26 (12%)	57 (26%)	135 (62%)	218	0.37
	> 20K	21 (10%)	44 (21%)	141 (68%)	206	
<b>Caregiver Marital Status</b>	Married	14 (9%)	36 (22%)	112 (69%)	162	0.33
	Not Married	34 (12%)	69 (25%)	172 (63%)	275	
<b>Caregiver is Biological Parent</b>						



Characteristic <sup>1</sup>	Language Impairment Classification			Total (N=437)	P-Value <sup>2</sup>
	Primary (N=48)	Concurrent (N=105)	None (N=284)		
Yes	25 (10%)	52 (21%)	166 (68%)	243	0.25
No	23 (12%)	53 (27%)	118 (61%)	194	
<b>Caregiver's WASI Performance IQ</b>					
N	40	68	223	331	
Mean (SD)	89.8 (13.1)	87.7 (14.2)	94.0 (14.9)	92.2 (14.7)	0.004
Impairment (IQ<70)	2 (13%)	6 (40%)	7 (47%)	15	0.12
No Impairment	38 (12%)	62 (20%)	216 (68%)	316	
<b>Maternal ARV Use In Pregnancy</b>					
Yes	17 (9%)	49 (27%)	114 (63%)	180	0.39
No	26 (13%)	45 (23%)	129 (65%)	200	

CELFF= Clinical Evaluation of Language Functioning; WASI=Wechsler Adult Scales of Intelligence; IQ= Intelligence Quotient; ARV=Antiretrovirals; HS=high school

<sup>1</sup> 17 children did not report their race; 3 children did not report their ethnicity; 13 caregivers did not report their household income; 106 children were missing their caregiver's performance IQ; ART use during pregnancy was unknown for 56 children, and 1 child did not consent to share their maternal ART history. Percentages are based on total sample and display the prevalence of Pri-LI, Con-LI and no LI within each characteristic.

<sup>2</sup> P-value calculated using Fisher's Exact Test for categorical variables and by analysis of variance for comparison of means for continuous variables.

HIV Disease Markers, Current Antiretroviral (ART) Regimen, and ART History by Language Impairment Category for 284 HIV-Infected Children in the Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study

**Table 3**

Characteristic <sup>1</sup>	Language Impairment			P-Value <sup>2</sup>	
	Primary (N = 29)	Concurrent (N = 67)	None (N = 188)		Total (N = 284)
HIV Viral Load > 400 copies/mL	3 (10%)	31 (46%)	46 (24%)	80 (28%)	<0.001
CD4% < 25%	3 (10%)	22 (33%)	35 (18%)	60 (21%)	0.02
CDC Class C	3 (10%)	29 (43%)	45 (24%)	77 (27%)	0.001
Nadir CD4% ≥25%	10 (34%)	14 (21%)	51 (27%)	75 (26%)	0.36
Peak log <sub>10</sub> HIV RNA (copies/mL)					
Mean (SD)	5.2 (1.1)	5.6 (0.7)	5.3 (0.8)	5.4 (0.8)	0.004
Duration on HAART					
Mean (SD)	9.5 (2.6)	9.4 (2.8)	8.7 (2.9)	9.0 (2.9)	0.12
≤ 5 years	2 (7%)	8 (12%)	29 (15%)	39 (14%)	0.47
Age at ART Initiation					
Mean (SD)	2.1 (2.0)	1.0 (1.6)	1.7 (2.0)	1.6 (1.9)	0.01
Before 6 months	6 (21%)	37 (55%)	71 (38%)	114 (40%)	0.004
ART regimen					0.83
HAART w/ PI	23 (79%)	46 (69%)	136 (72%)	205 (72%)	
HAART w/o PI	4 (14%)	11 (16%)	32 (17%)	47 (17%)	
Non-HAART ART	0 (0%)	4 (6%)	9 (5%)	13 (5%)	

ART=Antiretroviral Therapy; HAART=Highly Active ART, defined as at least 2 ARV drugs from at least 2 drug classes, PI=Protease Inhibitor, SD=standard deviation; CDC=Centers for Disease Control and Prevention

<sup>1</sup> CD4 and viral load measurement closest to the time of the CELF administration were used. One child did not give permission to share their ART history; 1 child was never on ARTs; 12 children were never on HAART; 18 children were not on ARTs at the time of the CELF administration. Percentages are based on total sample.

<sup>2</sup> P-value calculated by Fisher's Exact Test for categorical variables and by analysis of variance for comparison of means for continuous variables.

Logistic Regression Models of Primary Language Impairment vs. No Language Impairment Among All Children and Within HIV-Infected Children

Table 4

	Univariate Logistic Regression Models			Final Adjusted Logistic Regression Model			
	N	Odds Ratio	95% Confidence Interval	P-value	Adjusted Odds Ratio	95% Confidence Interval	P-value
<b>Overall Sample (HIV+ and HEU)</b>							
HIV Status (HIV+ vs HEU)	332	0.78	(0.42, 1.46)	0.44	0.75	(0.40, 1.41)	0.37
Black Race	332	2.40	(1.08, 5.32)	0.03	2.43	(1.09, 5.43)	0.03
Age ≥ 13 years	332	0.94	(0.50, 1.76)	0.84	-	-	-
Birth Year (vs 1995-1999)	332			0.41			
Before 1995		0.99	(0.48, 2.01)	0.97	-	-	-
2000 and Later		1.66	(0.75, 3.67)	0.21	-	-	-
Male	332	1.22	(0.66, 2.25)	0.54	-	-	-
Hispanic Ethnicity	329	0.47	(0.19, 1.17)	0.10	-	-	-
Caregiver not HS Graduate	332	1.00	(0.47, 2.13)	0.99	-	-	-
Household Income ≤ 20K	323	1.29	(0.69, 2.41)	0.42	-	-	-
Caregiver Married	332	0.63	(0.32, 1.23)	0.18	-	-	-
Caregiver is Biological Parent	332	0.77	(0.42, 1.43)	0.41	-	-	-
Caregiver PIQ < 70 <sup>l</sup>	332	1.62	(0.33, 8.12)	0.56	-	-	-
ARVs during Pregnancy <sup>l</sup>	332	0.74	(0.38, 1.43)	0.37	-	-	-
<b>HIV+ Youth<sup>2</sup></b>							
HIV Viral load > 400 copies/mL	217	0.36	(0.10, 1.23)	0.10	0.36	(0.10, 1.25)	0.11
CDC Class C	217	0.37	(0.11, 1.27)	0.11	0.37	(0.11, 1.30)	0.12
Age at ART Initiation ≤ 6 mo	215	0.42	(0.16, 1.09)	0.07	0.38	(0.15, 0.99)	0.05
CD4% < 25%	217	0.50	(0.14, 1.76)	0.28	-	-	-
Peak Viral Load > 750,000 copies/mL	217	1.04	(0.34, 3.25)	0.94	-	-	-
Nadir CD4% ≥ 25%	217	1.41	(0.62, 3.24)	0.41	-	-	-
Duration on HAART ≤ 5 yrs	206	0.41	(0.09, 1.84)	0.25	-	-	-

	Univariate Logistic Regression Models				Final Adjusted Logistic Regression Model			
	N	Odds Ratio	95% Confidence Interval	P-value	Adjusted Odds Ratio	95% Confidence Interval	P-value	
Regimen (vs HAART with PI)	216			0.75				
HAART without PI		0.74	(0.24, 2.29)	0.60	-			
Non-HAART or No ART		0.62	(0.14, 2.85)	0.54	-			

PI=Protease Inhibitor; SD=standard deviation; CDC=Centers for Disease Control and Prevention

<sup>1</sup> Missing data indicator method used in this model.

<sup>2</sup> Final adjusted model was not adjusted for any demographic factors.

**Table 5** Logistic Regression Models of Concurrent Language Impairment vs. No Language Impairment Among All Children and Within HIV-Infected Children

	Univariate Logistic Regression Models			Final Adjusted Logistic Regression Model (N = 386)			
	N	Odds Ratio	95% Confidence Interval	P-value	Adjusted Odds Ratio	95% Confidence Interval	P-value
<b>Overall Sample (HIV+ and HEU)</b>							
HIV Status (HIV+ vs HEU)	389	0.90	(0.56, 1.44)	0.66	0.86	(0.50, 1.50)	0.60
Age ≥ 13 years	389	0.75	(0.46, 1.20)	0.23	-		
Birth Year (vs 1995–1999)	389			0.14			0.11
Before 1995		0.71	(0.42, 1.22)	0.21	0.65	(0.36, 1.15)	0.14
2000 and Later		1.40	(0.77, 2.53)	0.27	1.42	(0.75, 2.67)	0.28
Male	389	0.80	(0.51, 1.25)	0.32	-		
Black Race	389	1.46	(0.88, 2.42)	0.15	3.66	(1.57, 8.55)	0.003
Hispanic Ethnicity	386	1.46	(0.88, 2.40)	0.14	3.16	(1.35, 7.37)	0.01
Caregiver not HS Graduate	389	1.99	(1.21, 3.26)	0.01	1.77	(1.03, 3.02)	0.04
Household Income ≤ 20K	377	1.35	(0.86, 2.14)	0.20	-		
Caregiver Married	389	0.80	(0.50, 1.28)	0.35	-		
Caregiver is Biological Parent	389	0.70	(0.44, 1.09)	0.12	0.54	(0.32, 0.92)	0.02
Caregiver PIQ < 70 <sup>l</sup>	389	2.99	(0.97, 9.21)	0.06	3.25	(0.99, 10.66)	0.05
ARVs during Pregnancy <sup>l</sup>	389	1.23	(0.76, 1.98)	0.39	-		
<b>HIV+ Youth<sup>2</sup></b>							
HIV Viral Load > 400 cp/ml	255	2.66	(1.48, 4.77)	0.001	3.04	(1.57, 5.87)	<0.001
CDC Class C	255	2.43	(1.35, 4.37)	0.003	2.19	(1.14, 4.22)	0.02
Age at ART Initiation ≤ 6 mo	253	2.00	(1.14, 3.52)	0.02	2.12	(1.13, 3.97)	0.02
CD4% < 25%	255	2.14	(1.14, 4.01)	0.02	-		
Peak Viral Load >750,000 cp/ml	255	1.72	(0.84, 3.55)	0.14	-		
Nadir CD4% ≥ 25%	255	0.71	(0.36, 1.39)	0.32	-		
Duration on HAART ≤ 5 yrs	244	0.73	(0.31, 1.68)	0.46	-		

	Univariate Logistic Regression Models			Final Adjusted Logistic Regression Model (N = 386)		
	N	Odds Ratio	95% Confidence Interval	P-value	Adjusted Odds Ratio	95% Confidence Interval
Regimen (vs HAART w/PI)	254			0.58		
HAART w/o PI		1.02	(0.47, 2.18)	0.97	-	
Non-HAART or no ART		1.56	(0.67, 3.59)	0.30	-	

HS=High School, HAART=Highly Active Antiretroviral Therapy, PI=Protease Inhibitor, CDC=Centers for Disease Control and Prevention, PIQ=Performance IQ

<sup>1</sup> Missing data indicator method used in this model.

<sup>2</sup> Final adjusted model was also adjusted for males vs females (aOR = 0.52, p = 0.05), Black race (aOR = 3.0, p = 0.02), low caregiver's education (aOR = 2.2, p = 0.03), and biological parent as caregiver (aOR = 0.53, p = 0.06).

Linear regression models for the continuous CELF score, adjusted for other covariates as needed, for all subjects and restricted to HIV+ subjects

**Table 6**

	Adjusted Linear Regression Models, without child's cognitive impairment				Adjusted Linear Regression Models, with child's cognitive impairment			
	N	Adjusted mean difference	95% CI	P-value	Adjusted mean difference	95% CI	P-value	
<b>Overall Sample (HIV+ and HEU)</b>								
HIV Status (HIV+ vs HEU)	437	0.44	(-3.20, 4.08)	0.81	0.79	(-2.33, 3.91)	0.62	
Black Race	437	-6.29	(-10.14, -2.43)	0.002	-4.14	(-7.45, -0.83)	0.01	
Caregiver not HS Graduate	437	-4.86	(-8.97, -0.72)	0.02	-4.28	(-7.79, -0.77)	0.02	
Household Income ≤ 20K	424	-3.39	(-6.94, 0.15)	0.06	-1.63	(-4.67, 1.41)	0.29	
Caregiver PIQ < 70 <sup>I</sup>	437	-10.01	(-19.31, -0.71)	0.04	-6.85	(-14.72, 1.01)	0.09	
Child's cognitive impairment	413	---	---	---	-20.02	(-23.16, -16.89)	<0.001	
<b>HIV+ Youth</b>								
HIV Viral Load > 400 cp/ml	284	-5.76	(-10.36, -1.15)	0.02	-4.80	(-8.82, -0.78)	0.02	
CDC Class C	284	-4.30	(-10.36, -1.15)	0.07	-1.30	(-5.41, 2.80)	0.53	
Black Race	284	-8.71	(-13.52, -3.90)	<0.001	-4.77	(-9.00, -0.43)	0.03	
Caregiver not HS Graduate	284	-6.92	(-11.86, -1.98)	0.01	-5.53	(-9.79, -1.27)	0.01	
Child's cognitive impairment	277	---	---	---	-19.14	(-23.08, -15.20)	<0.001	

HEU=HIV-exposed uninfected; HS=high school; CDC=Centers for Disease Control and Prevention; PIQ=Performance IQ Score from the Wechsler Adult Scales of Intelligence

<sup>I</sup>Missing data indicator method used in this model.