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 the risk for language impairment (LI) in children perinatally infected or exposed to HIV.** ***Methods:*** **We evaluated the prevalence of LI in 7- to 16-year-old children with perinatal HIV infection (HIV+) compared with HIV-exposed and uninfected children, using a comprehensive standardized language test (Clinical Evaluation of Language Functioning-Fourth Edition [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 factors with LI category were evaluated using univariate and multivariable logistic regression models.** ***Results:*** **Of the 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+ versus 87.5 (17.9) for HIV-exposed and uninfected children. After adjustment, black children had higher odds of Pri-LI versus no LI (adjusted odds ratio [aOR] = 2.43, $p = .03$). Children who were black, Hispanic, had a caregiver with low education or low intelligence quotient, or a nonbiological parent as caregiver had higher odds of Con-LI versus no LI. Among HIV+ children, viral load >400 copies/mL (aOR = 3.04, $p < .001$), Centers for Disease Control and Prevention Class C (aOR = 2.19, $p = .02$), and antiretroviral treatment initiation <6 months of age (aOR = 2.12, $p = .02$) were associated with higher odds of Con-LI versus 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.**

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Children perinatally infected with HIV are at risk for impairments in cognitive functioning.[1,2] Increased risk for language impairment (LI) is also reported, which can affect academic performance or adherence to medication.[3–6] Impaired verbal functioning has been shown to be associated with HIV disease progression[7] and greater immunosuppression.[8] In a sample of children infected with HIV who were evaluated before the availability of antiretroviral (ARV) drug therapy, the prevalence of LI was 10%.[9] Treatment with 1 or 2 nucleoside reverse transcriptase inhibitors in the pre-highly active antiretroviral therapy (HAART) era has been associated with improvement, although not normalization, of overall cognitive and specific language measures in some studies.[5,10] However, Wolters et al[8] found that over the

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course of a 24-month ARV treatment (ART) regimen, cognitive abilities remained stable while language abilities continued to decline, suggesting differential effects on specific brain functions. Initiation of HAART has been associated with stabilization in measures of overall cognitive and language function.[11–14] However, studies focusing on assessment of language function in school-aged children in the HAART era are lacking.

It is not clear whether LIs in children with HIV infection are indications of a global developmental impairment, including nonverbal and verbal intelligence, or whether LI can be a selective deficit. Another possible source of LI is related to risk for hearing loss, possibly as a consequence of mitochondrial dysfunction. Previous studies suggest that HIV and its treatment are associated with mitochondrial dysfunction,[15] and it has been demonstrated that mitochondrial dysfunction/mutation is associated with sensorineural hearing loss.[16,17]

In healthy children without HIV exposure, LIs appear in children whose general cognitive abilities are well within or even above age expectations. The condition of specific LI (SLI) is defined as LIs without other developmental impairments. In a study of 7218 kindergarten children to determine the prevalence of SLI, Tomblin et al[18] reported that 7.4% of the children were identified with SLI. In another report from this sample of children, 12% of the children showed language sparing, with low performance on nonverbal intelligence quotient (IQ) assessment (in the range of 70–87) and language performance within normal limits.[19] These findings suggest a dissociation of language acquisition and nonverbal intelligence. Similarly, Rice et al[20] 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 LIs and nonverbal cognitive impairments scored lower and grew more slowly in language skills between 6 and 10 years, than children with SLI. In effect, LIs 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 LI 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%).[21] 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 fifth 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 impairments drops to 14%.[21] The shift seems to be related to a high risk of reading impairment in children with early LIs, with later diagnosis of reading impairments.[22] The diagnosis of LI 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, although the LIs are likely to persist.[23] Children exposed to or living with HIV who have LIs may be at risk for poor or delayed academic achievement.[3]

Understanding the sources of low performance on language assessments in children with HIV or receiving HAART for HIV requires differentiation of LIs associated with cognitive impairments or as a consequence of hearing impairment. Here we adopt the terminology of primary language impairment (Pri-LI) for children with LIs with no other known impairments,[24] versus concurrent language impairment (Con-LI, sometimes referred to as "secondary LI"[24]) for children with LI along with possible hearing or cognitive impairment or both.[25] 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 when compared with those who are perinatally HIV-exposed but HIV-uninfected can clarify whether an increased risk of LI is attributable to HIV infection.

Evaluation of risk factors for LI, 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.[26] 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 with HIV-exposed and uninfected (HEU) children, and the relationships of HIV disease characteristics along with environmental risk factors on LI.

METHODS

Study Population

This investigation used data collected in the Adolescent Master Protocol (AMP), a component of the Pediatric HIV/AIDS Cohort Study. 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 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 institutional review board. Written assent was obtained as appropriate. The study opened to enrollment in March 2007.

Children aged 7 to 16 years born to women with HIV infection were eligible. The study design included both children infected with HIV (HIV+) and HEU children. At each semiannual 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 6-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),[27] and LI was defined as scoring more than 1 SD below the reference mean (CELF-4 Core Language Standard Score less than 85, equivalent to the 16th 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 1 SD below the mean is commonly used in studies of children with specific LI (SLI), allowing comparison across studies.[28]

The age range of the AMP study crosses 2 versions of the CELF-4 protocol. Children aged 7 and 8 years completed the following subtests: Concepts and Following Directions, Word Structure, Recalling Sentences, and Formulated Sentences. Children aged 9 years and older completed the following 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.

Language impairment (LI) was classified as primary LI (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 examination, 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 previous audiometric examinations. Nonverbal cognitive impairment was defined as a standard score less than 85, 1 SD below the mean (less than −1 SD), on the Perceptual Reasoning Index of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV).[29] 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 details in the Results section.

Assessment of Other Risk Factors for LI

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 2 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, 2 widely used indicators of HIV disease severity (see guidelines at http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.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 Centers for Disease Control and Prevention (CDC) Clinical Classification, determined by pediatric surveillance definitions for participants younger than 13 years (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,[30] although environmental prediction of LIs has yielded mixed outcomes in large population samples.[31] These variables were obtained by caregiver self-report at study entry. Maternal ARV drug use during pregnancy was obtained at entry in Pediatric HIV/AIDS Cohort Study or from previous studies in which the child or mother or both participated. Caregiver's performance IQ 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.[32]

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 analyses of variance and Fisher's exact tests were used to compare characteristics between HIV+ and HEU groups and

across LI 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 $p < .20$ in univariate models. To be as inclusive as possible, final adjusted models retained all covariates with $p < .15$. 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+ with 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 HIV-exposed and uninfected [HEU]) had a valid and complete language assessment, at a median age of 12 years (range 7–16 y); 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 primary language impairment (Pri-LI), Con-LI, and no LI could be distinguished (excluding 8 children due to missing Wechsler Intelligence Scale for Children-Fourth Edition [WISC-IV] Perceptual Reasoning Index 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. Although 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, when compared with 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 1 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 9 (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 LI category by HIV infection status and demographic factors is summarized in Table 2. The prevalence of Pri-LI and Con-LI was similar in the HIV+ and HEU groups, with 10% versus 12% for Pri-LI and 24% versus 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 when compared with 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 LI (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 2 groups of children with LI.

A summary of HIV disease severity by the LI 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 and to have a previous Centers for CDC Class C diagnosis, a detectable viral load, and CD4% <25%. Most children were on HAART with protease inhibitor at the 6-month visit (72%) with no differences in ART regimen by LI group.

Table 4 summarizes the results of univariate and final adjusted multivariable logistic regression models for Pri-LI versus 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 versus no LI for HIV+ when compared with HEU groups of children; however, children who were black had over twice the odds of primary LI versus no LI (adjusted odds ratio [aOR] = 2.43, $p = .03$).

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

Table 1. 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

Characteristic[a]	HIV Status		Total (N = 437)	p[b]
	HIV+ (N = 284)	HEU (N = 153)		
CELF score				
Mean (SD)	88.5 (18.4)	87.5 (17.9)	88.1 (18.2)	.57
Language impairment				
Primary	29 (10%)	19 (12%)	48 (11%)	.71
Concurrent	67 (24%)	38 (25%)	105 (24%)	
None	188 (66%)	96 (63%)	284 (65%)	
Age (y)				
Mean (SD)	12.6 (2.6)	11.0 (2.5)	12.0 (2.7)	<.001
7–8	31 (11%)	43 (28%)	74 (17%)	<.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%)	<.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%)	.06
Race				
White or other	56 (20%)	53 (35%)	109 (25%)	.002
Black or African-American	214 (75%)	97 (63%)	311 (71%)	
Hispanic or Latino ethnicity	54 (19%)	49 (32%)	103 (24%)	.003
Caregiver not high school graduate	66 (23%)	39 (25%)	105 (24%)	.64
Annual household income ≤20,000	121 (43%)	97 (63%)	218 (50%)	<.001
Caregiver married	111 (39%)	51 (33%)	162 (37%)	.25
Caregiver is biological parent	119 (42%)	124 (81%)	243 (56%)	<.001
Caregiver's WASI performance IQ				
N	219	112	331	
Mean (SD)	92.9 (14.9)	90.9 (14.3)	92.2 (14.7)	.25
Impairment (IQ <70)	7 (2%)	8 (5%)	15 (3%)	.16
Maternal ARV use in pregnancy	50 (18%)	130 (85%)	180 (41%)	<.001

CELF, Clinical Evaluation of Language Functioning; WASI, Wechsler Adult Scales of Intelligence; IQ, intelligence quotient; ARV, antiretrovirals; HEU, HIV-exposed and uninfected. [a]Seventeen 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; antiretroviral treatment (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. [b]p value calculated by Fisher's exact test for categorical variables and by t test for continuous variables.

panel). Univariate logistic models for Con-LI versus no LI among HIV + and HEU revealed a significant effect of caregiver education ($p = .01$) and a marginal effect of low caregiver nonverbal IQ ($p = .06$) 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, $p = .003$) or Hispanic (aOR = 3.2, $p = .01$), who had a less educated caregiver (aOR = 1.8, $p = .04$) or a caregiver with low cognitive score (aOR = 3.3, $p = .05$), or had a caregiver who was not the biological parent (aOR = 1.9, $p = .02$). There was no significant effect of HIV infection status on the odds of Con-LI versus 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+ versus HEU (mean difference = 0.44, 95% confidence interval: −3.20 to 4.08, $p = .81$). However, participants of black race had an adjusted mean CELF-4 score which was 6.3 points lower than those of non-black race ($p = .002$), and those of lower socioeconomic status had lower mean scores, as reflected by having a caregiver without high school education (4.9 points lower, $p = .02$) and an annual household income less than $20,000 (3.4 points lower, $p = .06$). In addition, low caregiver cognitive score based on performance IQ <70 was associated with significantly lower adjusted

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[a]	Language Impairment Classification			Total (N = 437)	p[b]
	Primary (N = 48)	Concurrent (N = 105)	None (N = 284)		
CELF score					
Mean (SD)	74.2 (9.6)	65.8 (12.7)	98.7 (10.3)	88.1 (18.2)	<.001
HIV status					
HIV-infected	29 (10%)	67 (24%)	188 (66%)	284	.71
HIV-exposed, uninfected	19 (12%)	38 (25%)	96 (63%)	153	
Age (y)					
Mean (SD)	11.8 (2.7)	11.8 (2.8)	12.2 (2.6)	12.0 (2.7)	.33
7–8	11 (15%)	23 (31%)	40 (54%)	74	.25
9–12	19 (10%)	48 (24%)	133 (67%)	200	
13–16	18 (11%)	34 (21%)	111 (68%)	163	
Birth year					
Before 1995	14 (11%)	25 (19%)	92 (70%)	131	.27
1995–1999	23 (10%)	57 (25%)	149 (65%)	229	
2000 and later	11 (14%)	23 (30%)	43 (56%)	77	
Sex					
Male	27 (12%)	48 (22%)	146 (66%)	221	.45
Female	21 (10%)	57 (26%)	138 (64%)	216	
Race					
White or other	8 (7%)	20 (18%)	81 (74%)	109	.06
Black or African-American	40 (13%)	79 (25%)	192 (62%)	311	
Ethnicity					
Hispanic or Latino	6 (6%)	32 (31%)	65 (63%)	103	.04
Not Hispanic or Latino	42 (13%)	73 (22%)	216 (65%)	331	
Caregiver education					
Not a HS graduate	10 (10%)	36 (34%)	59 (56%)	105	.02
At least a HS graduate	38 (11%)	69 (21%)	225 (68%)	332	
Annual household income					
≤20,000	26 (12%)	57 (26%)	135 (62%)	218	.37
>20,000	21 (10%)	44 (21%)	141 (68%)	206	
Caregiver marital status					
Married	14 (9%)	36 (22%)	112 (69%)	162	.33
Not married	34 (12%)	69 (25%)	172 (63%)	275	
Caregiver is biological parent					
Yes	25 (10%)	52 (21%)	166 (68%)	243	.25
No	23 (12%)	53 (27%)	118 (61%)	194	
Caregiver's WASI performance IQ					
N	40	68	223	331	
Mean (SD)	89.8 (13.1)	87.7 (14.2)	94.0 (14.9)	92.2 (14.7)	.004
Impairment (IQ <70)	2 (13%)	6 (40%)	7 (47%)	15	.12
No impairment	38 (12%)	62 (20%)	216 (68%)	316	
Maternal ARV use in pregnancy					
Yes	17 (9%)	49 (27%)	114 (63%)	180	.39
No	26 (13%)	45 (23%)	129 (65%)	200	

CELF, Clinical Evaluation of Language Functioning; WASI, Wechsler Adult Scales of Intelligence; IQ, intelligence quotient; ARV, antiretrovirals; HS, high school.
[a]Seventeen 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; antiretroviral treatment (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 primary language impairment, concurrent language impairment, and no language impairment within each characteristic. [b]p value calculated using Fisher's exact test for categorical variables and by analysis of variance for comparison of means for continuous variables.

Table 3. HIV Disease Markers, Current 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

Characteristic[a]	Language Impairment			Total (N = 284)	p[b]
	Primary (N = 29)	Concurrent (N = 67)	None (N = 188)		
HIV viral load >400 copies/mL	3 (10%)	31 (46%)	46 (24%)	80 (28%)	<.001
CD4% <25%	3 (10%)	22 (33%)	35 (18%)	60 (21%)	.02
CDC Class C	3 (10%)	29 (43%)	45 (24%)	77 (27%)	.001
Nadir CD4% ≥25%	10 (34%)	14 (21%)	51 (27%)	75 (26%)	.36
Peak $\log_{10}$ HIV RNA (copies/mL)					
Mean (SD)	5.2 (1.1)	5.6 (0.7)	5.3 (0.8)	5.4 (0.8)	.004
Duration on HAART					
Mean (SD)	9.5 (2.6)	9.4 (2.8)	8.7 (2.9)	9.0 (2.9)	.12
≤5 y	2 (7%)	8 (12%)	29 (15%)	39 (14%)	.47
Age at ART initiation					
Mean (SD)	2.1 (2.0)	1.0 (1.6)	1.7 (2.0)	1.6 (1.9)	.01
Before 6 mo	6 (21%)	37 (55%)	71 (38%)	114 (40%)	.004
ART regimen					.83
HAART with PI	23 (79%)	46 (69%)	136 (72%)	205 (72%)	
HAART without PI	4 (14%)	11 (16%)	32 (17%)	47 (17%)	
Non-HAART ART	0 (0%)	4 (6%)	9 (5%)	13 (5%)	

ART, antiretroviral treatment; HAART, highly active antiretroviral therapy, defined as at least 2 antiretroviral drugs from at least 2 drug classes, PI, protease inhibitor; CDC, Centers for Disease Control and Prevention. [a]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. [b]p value calculated by Fisher's exact test for categorical variables and by analysis of variance for comparison of means for continuous variables.

mean scores (10.0 points lower, $p = .04$). 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 nonsignificant (mean difference = 0.8, $p = .62$).

Within the HIV+ group, univariate and adjusted logistic regression models investigating disease severity measures are summarized in Table 4 (bottom panel) for Pri-LI versus no LI and Table 5 (bottom panel) for Con-LI versus no LI. In univariate models, none of the disease measures reached statistical significance for predicting the odds of Pri-LI versus no LI. In the multivariate model, only age at ART initiation reached significance indicating a 2-fold increase in odds of Pri-LI for those with later ART initiation. In contrast, those with detectable viral load, previous CDC Class C diagnosis, or earlier ART initiation had 2- to 3-fold higher odds of Con-LI versus 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). Although 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 score (Table 6).

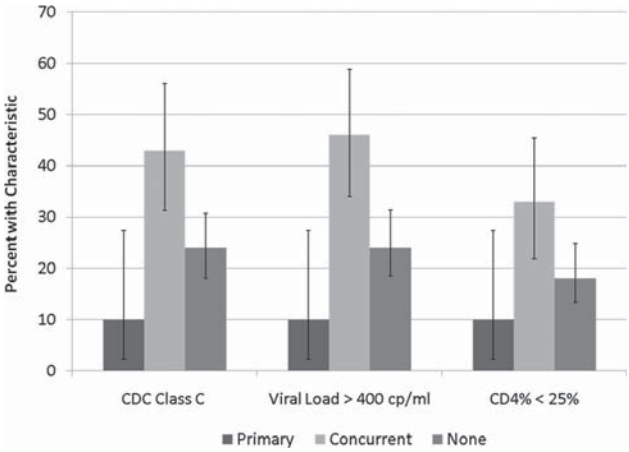

Figure 1. Percent with certain indicators of HIV disease severity among perinatally HIV-infected children within each language impairment category with 95% confidence intervals.

Table 4. Logistic Regression Models of Primary Language Impairment vs No Language Impairment Among All Children and Within HIV-Infected Children

		Univariate Logistic Regression Models			Final Adjusted Logistic Regression Models		
	N	Odds Ratio	95% Confidence Interval	*p*	Adjusted Odds Ratio	95% Confidence Interval	*p*
Overall Sample (HIV+ and HEU)							
HIV status (HIV+ vs HEU)	332	0.78	(0.42, 1.46)	.44	0.75	(0.40, 1.41)	.37
Black race	332	2.40	(1.08, 5.32)	.03	2.43	(1.09, 5.43)	.03
Age ≥13 y	332	0.94	(0.50, 1.76)	.84	—		
Birth year (vs 1995–1999)	332			.41			
Before 1995		0.99	(0.48, 2.01)	.97	—		
2000 and later		1.66	(0.75, 3.67)	.21	—		
Male	332	1.22	(0.66, 2.25)	.54	—		
Hispanic ethnicity	329	0.47	(0.19, 1.17)	.10	—		
Caregiver not HS graduate	332	1.00	(0.47, 2.13)	.99	—		
Household income ≤20,000	323	1.29	(0.69, 2.41)	.42	—		
Caregiver married	332	0.63	(0.32, 1.23)	.18	—		
Caregiver is biological parent	332	0.77	(0.42, 1.43)	.41	—		
Caregiver PIQ <70[a]	332	1.62	(0.33, 8.12)	.56	—		
ARVs during pregnancy[a]	332	0.74	(0.38, 1.43)	.37	—		
HIV+ youth[b]							
HIV viral load >400 copies/mL	217	0.36	(0.10, 1.23)	.10	0.36	(0.10, 1.25)	.11
CDC Class C	217	0.37	(0.11, 1.27)	.11	0.37	(0.11, 1.30)	.12
Age at ART initiation ≤6 mo	215	0.42	(0.16, 1.09)	.07	0.38	(0.15, 0.99)	.05
CD4% <25%	217	0.50	(0.14, 1.76)	.28	—		
Peak viral load >750,000 copies/mL	217	1.04	(0.34, 3.25)	.94	—		
Nadir CD4% ≥25%	217	1.41	(0.62, 3.24)	.41	—		
Duration on HAART ≤5 y	206	0.41	(0.09, 1.84)	.25	—		
Regimen (vs HAART with PI)	216			.75			
HAART without PI		0.74	(0.24, 2.29)	.60	—		
Non-HAART or no ART		0.62	(0.14, 2.85)	.54	—		

HEU, HIV-exposed and uninfected; PIQ, performance intelligent quotient; ARV, antiretrovirals; PI, protease inhibitor; CDC, Centers for Disease Control and Prevention; ART, antiretroviral treatment; HAART, highly active antiretroviral therapy. [a]Missing data indicator method used in this model. [b]Final adjusted model was not adjusted for any demographic factors.

DISCUSSION

In this cohort, LI was common among children in both HIV+ and HEU groups, with impairment observed among almost 40% of participants when compared with an expected rate of 16% in the US population.[27] The elevated risk is especially noteworthy given that recent studies note that the practice of including children with LIs in the norming data of tests such as CELF-4 reduces test sensitivity for identifying children with LIs.[33] The rate of LI was similar for children in HIV+ and HEU groups, both overall and within subclassifications of primary LI (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 specific LI (SLI), psychometrically defined similar to Pri-LI, was 7.4% in a study of healthy 5- to 6-year-old children.[18] Prevalence of SLI for urban African-American children and for primarily urban Hispanic children (both groups were primarily low socioeconomic status) in that study was 11% and 8%, respectively. An additional 5% of the cohort demonstrated low nonverbal cognitive functioning accompanied by LI, while 12% performed at low nonverbal cognitive levels (70–87 IQ) without LI.[19] 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 LI 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 the 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.

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 Models (N = 386)		
	N	OR	95% Confidence Interval	*p*	aOR	95% Confidence Interval	*p*
Overall Sample (HIV+ and HEU)							
HIV status (HIV+ vs HEU)	389	0.90	(0.56, 1.44)	.66	0.86	(0.50, 1.50)	.60
Age ≥13 y	389	0.75	(0.46, 1.20)	.23	—		
Birth year (vs 1995–1999)	389			.14			.11
Before 1995		0.71	(0.42, 1.22)	.21	0.65	(0.36, 1.15)	.14
2000 and later		1.40	(0.77, 2.53)	.27	1.42	(0.75, 2.67)	.28
Male	389	0.80	(0.51, 1.25)	.32	—		
Black race	389	1.46	(0.88, 2.42)	.15	3.66	(1.57, 8.55)	.003
Hispanic ethnicity	386	1.46	(0.88, 2.40)	.14	3.16	(1.35, 7.37)	.01
Caregiver not HS graduate	389	1.99	(1.21, 3.26)	.01	1.77	(1.03, 3.02)	.04
Household income ≤20,000	377	1.35	(0.86, 2.14)	.20	—		
Caregiver married	389	0.80	(0.50, 1.28)	.35	—		
Caregiver is biological parent	389	0.70	(0.44, 1.09)	.12	0.54	(0.32, 0.92)	.02
Caregiver PIQ <70[a]	389	2.99	(0.97, 9.21)	.06	3.25	(0.99, 10.66)	.05
ARVs during pregnancy[a]	389	1.23	(0.76, 1.98)	.39	—		
HIV+ youth[b]							
HIV viral load >400 cp/mL	255	2.66	(1.48, 4.77)	.001	3.04	(1.57, 5.87)	<.001
CDC Class C	255	2.43	(1.35, 4.37)	.003	2.19	(1.14, 4.22)	.02
Age at ART initiation ≤6 mo	253	2.00	(1.14, 3.52)	.02	2.12	(1.13, 3.97)	.02
CD4% <25%	255	2.14	(1.14, 4.01)	.02	—		
Peak viral load >750,000 cp/mL	255	1.72	(0.84, 3.55)	.14	—		
Nadir CD4% ≥25%	255	0.71	(0.36, 1.39)	.32	—		
Duration on HAART ≤5 y	244	0.73	(0.31, 1.68)	.46	—		
Regimen (vs HAART with)	254			.58			
HAART without PI		1.02	(0.47, 2.18)	.97	—		
Non-HAART or no ART		1.56	(0.67, 3.59)	.30	—		

OR, odds ratio; aOR, adjusted odds ratio; HEU, HIV-exposed uninfected; HS, high school; ART, antiretroviral treatment; HAART, highly active antiretroviral therapy; PI, protease inhibitor; CDC, Centers for Disease Control and Prevention; PIQ, performance intelligent quotient. [a]Missing data indicator method used in this model. [b]Final adjusted model was also adjusted for males vs females (aOR = 0.52, $p = .05$), black race (aOR = 3.0, $p = .02$), low caregiver's education (aOR = 2.2, $p = .03$), and biological parent as caregiver (aOR = 0.53, $p = .06$).

Other studies report genetic linkage and association for SLI,[28,34,35] 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 LI in isolation. It is notable that 25 of the 59 children with CDC Class C diagnoses had previously reported diagnoses of encephalopathy.[36,37] It is also possible that the smaller number of children with Pri-LI reduced the 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

Table 6. Linear Regression Models for the Continuous CELF Score, Adjusted for Other Covariates as Needed, for All Subjects and Restricted to HIV+ Subjects

	N	Adjusted Linear Regression Models, Without Child's Cognitive Impairment			Adjusted Linear Regression Models, With Child's Cognitive Impairment		
		Adjusted Mean Difference	95% CI	*p*	Adjusted Mean Difference	95% CI	*p*
Overall sample (HIV+ and HEU)							
HIV status (HIV+ vs HEU)	437	0.44	(−3.20, 4.08)	.81	0.79	(−2.33, 3.91)	.62
Black race	437	−6.29	(−10.14, −2.43)	.002	−4.14	(−7.45, −0.83)	.01
Caregiver not HS graduate	437	−4.86	(−8.97, −0.72)	.02	−4.28	(−7.79, −0.77)	.02
Household income ≤20,000	424	−3.39	(−6.94, 0.15)	.06	−1.63	(−4.67, 1.41)	.29
Caregiver PIQ <70[a]	437	−10.01	(−19.31, −0.71)	.04	−6.85	(−14.72, 1.01)	.09
Child's cognitive impairment	413	—	—	—	−20.02	(−23.16, −16.89)	<.001
HIV+ youth							
HIV viral load >400 cp/mL	284	−5.76	(−10.36, −1.15)	.02	−4.80	(−8.82, −0.78)	.02
CDC Class C	284	−4.30	(−10.36, −1.15)	.07	−1.30	(−5.41, 2.80)	.53
Black race	284	−8.71	(−13.52, −3.90)	<.001	−4.77	(−9.00, −0.43)	.03
Caregiver not HS graduate	284	−6.92	(−11.86, −1.98)	.01	−5.53	(−9.79, −1.27)	.01
Child's cognitive impairment	277	—	—	—	−19.14	(−23.08, −15.20)	<.001

CELF, Clinical Evaluation of Language Functioning; CI, confidence interval; HEU, HIV-exposed uninfected; HS, high school; CDC, Centers for Disease Control and Prevention; PIQ, performance intelligent quotient score from the Wechsler Adult Scales of Intelligence. [a]Missing data indicator method used in this model.

Con-LI but significantly lower odds of Pri-LI. The negative effects of HIV infection on the central nervous system can occur before birth and during infancy,[38] before many of the participants in this study initiated ART. Although 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 such as Pri-LI, while later initiation of ART ensured survival but may have permitted a longer pretreatment 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 was 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 y 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 LI 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. Although 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 examinations on all children with hearing impairment. Nevertheless, to our knowledge, this is the first study that specifically addresses hearing impairment in evaluation of language functioning among children with HIV. The major strengths of this study include the focus on LI, 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 ARV 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 LI.

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