



Language Impairment in 7-16 Year Old Perinatally HIV-Infected Children

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ORIGINAL ABSTRACT

Background: Children perinatally infected with HIV (P-HIV) are at risk for impairments in higher cognitive functions, including language impairment (LI). This study evaluated the prevalence of primary and secondary LI for P-HIV children, and examined associations with markers of HIV disease severity.

Methods: P-HIV children enrolled in PHACS were evaluated for language impairment (LI) using a comprehensive standardized language test (CELF-4). LI was defined as scoring > 1 SD below the reference mean (CELF-85). Children were classified as having primary LI (LI with monolingual English exposure and no cognitive or hearing impairment), secondary LI (LI with cognitive or hearing impairment and/or bi- or multi-lingual exposure), or no LI. Non-verbal cognitive abilities were evaluated with the WISC-IV. Hearing status was determined by audiological exam or parental report. Association of HIV disease markers with LI category was evaluated using chi-square tests and multinomial logit analysis.

Results: Of 141 children (48% male, 70% Black, 20% Hispanic) with language assessments, 50 (35%) had either primary LI (18, 13%) or secondary LI (31, 22%), compared to an overall expected 16%. Of those with secondary LI, 65% had accompanying low cognitive performance, 23% had abnormal hearing, and 39% reported bi- or multi-lingual exposure. Children with secondary LI were more likely to have CDC Class C diagnosis at study entry than those with primary LI or no LI (45% vs 11% and 29%, respectively, $\chi^2 p < 0.04$), and were more likely to initiate ART in the first 6 months of life than those with primary or no LI (61% vs 26% and 40%, respectively, $\chi^2 p = 0.03$). Other markers of increased HIV disease severity were also higher in children with secondary LI, but not significantly (see Table). After adjustment for age and other covariates, those enrolling as CDC Class C were marginally more likely to present with secondary LI and marginally less likely to have primary LI.

Conclusions: Language impairments in P-HIV children appear as part of the risk for higher cognitive abilities and are more common than expected. Secondary LI coexists with cognitive and/or hearing impairment and is more likely with more advanced HIV disease, while primary LI is less likely to be associated with advanced HIV disease. Thus, primary LI may escape detection as higher risk of cognitive impairment. This study reveals that HIV disease is one of the multiple factors that can contribute to LI.

* Data presented in abstract based on data available by August 16th, 2008

BACKGROUND

- Verbal functioning is among the cognitive domains at risk for impairment in HIV¹ children who experience Class C events (Smith, et al, 2006).
- ARV treatment for a duration over 24 months was accompanied by a decline in language abilities, although cognitive ability remained stable, suggesting differential effects of HIV on specific brain functions (Wolters, et al, 1997).
- The prevalence of language impairment in children with HIV has previously been estimated at 10% (Hopkins, et al, 1989).
- Updated prevalence estimates are needed which differentiate by type of language impairment, cognitive impairment, and hearing loss.
- Another critical need in this area is an investigation of whether pervasive effects on language acquisition are part of broader effects on cognitive abilities or represent differentiated effects on language acquisition related to specific brain functions.
- The role of environmental factors, such as caregiver education, also warrants investigation.

OBJECTIVES

To evaluate the prevalence of primary and secondary language impairment in perinatally HIV-infected children, and examine the association of HIV disease severity with language impairment.

METHODS

Study Population

The Adolescent Maste Protocol (AMP), which is part of Pediatric HIV/AIDS Cohort Study (PHACS), is a prospective cohort study conducted at 12 US sites designed to evaluate the impact of HIV infection and antiretroviral therapy on preadolescents and adolescents with perinatal HIV infection. Domains to be investigated include growth and sexual maturation, metabolic risk factors for cardiovascular disease, cardiac function, bone health, neurologic, neurodevelopment, language, hearing and behavioral function. Children aged 7 to 16 years born to HIV-infected mothers are eligible for enrollment into AMP. Enrollment began in March 2007. As of December 16, 2008, there were 319 HIV-infected children and 101 HIV-uninfected enrolled in AMP.

Our evaluation included 178 perinatally HIV-infected participants who completed the 6 month visit in AMP.

Definitions and Statistical Methods

- Language assessment:** Children were evaluated for language impairment using a comprehensive standardized language test (CELF-4).
- Language impairment (LI):** Defined as scoring > 1 S.D. below the reference mean on the CELF Core Language Standard Score (CELF score < 85)
 - Primary LI: Defined as LI with monolingual English exposure and no cognitive or hearing impairment,
 - Secondary LI: Defined as LI with cognitive or hearing impairment and/or non-English exposure
- Cognitive Assessment:** Verbal and Non-verbal cognitive abilities were evaluated with the WISC-IV.
- Hearing status:** Determined by audiologic exam or parental report.
- HIV Disease markers:** CD4% and viral load measurements were obtained as collected for routine clinical care. CDC Class was evaluated at study entry based on diagnosis history. ARV characteristics were based on lifetime history of medications and current regimen at AMP study entry.

- The prevalence of primary, secondary, and no LI was summarized overall and by demographic and HIV disease characteristics.
- Univariate and multivariate logistic regression models were used to evaluate the association of HIV disease characteristics and other factors on the risk of primary LI versus no impairment, secondary LI vs no impairment, and primary vs secondary LI. Final multivariable logistic regression models were reduced to only those covariates with $p < 0.10$.

* Data presented in poster based on data available by December 16th, 2008

RESULTS

178 children were evaluated for language impairment: median age=12.9 yrs (range=7.7 to 16.9), 48% male, 73% Black, and 18% Hispanic. The majority (76%) were on HAART with a protease inhibitor (PI) at entry, while 14% were receiving HAART without a PI.

Among these 178 P-HIV children, 63 (35%) had either primary LI (23, 13%) or secondary LI (40, 22%), compared to an overall expected 16% in the reference population.

Results of the evaluation of language impairment with HIV disease severity are summarized in the tables and figures.

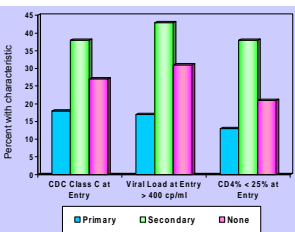
Table 1: Language Impairment (LI) by Antiretroviral (ARV) Therapy and Caregiver Education, along with Characteristics that Define Primary and Secondary LI

Characteristic	Language Impairment Category		
	CELF-4 < 85	CELF-4 ≥ 85	
	Primary (N=23)	Secondary (N=40)	None (N=115)
PI Use at Study Entry	21 (91%)	31 (78%)	83 (72%)
ARV Regimen at Study Entry			
HAART with PI	21 (91%)	31 (78%)	83 (72%)
HAART without PI	1 (4%)	3 (8%)	21 (18%)
Other ARV	0 (0%)	1 (3%)	3 (3%)
No ARV	1 (4%)	5 (13%)	8 (7%)
ARV initiated at ≤ 6 mos of age	8 (35%)	23 (58%)	46 (40%)
Caregiver is not HS Grad	5 (22%)	16 (40%)	26 (23%)
Abnormal Hearing ¹	0 (0%)	9 (23%)	5 (4%)
Non-English Exposure ²	0 (0%)	14 (36%)	14 (13%)
WISC Perceptual Reasoning Score < 80 ³	0 (0%)	26 (65%)	9 (8%)

1 = By definition, those with LI and one or more of these characteristics have secondary LI rather than primary LI.

Children with Secondary LI were more likely to have a caregiver who did not graduate high school (p=0.09) and were more likely to initiate ARV in the first 6 months of life (p=0.11) than those with Primary LI or no LI.

Figure 1: Percent with HIV Disease Severity Markers within each Language Impairment Category



Children with secondary LI were more likely to enroll with CDC Class C, high viral load, and low CD4% than those with primary LI or no impairment.

RESULTS

Table 2: Univariate Logistic Regression Models for Primary LI vs No Impairment

Variable	P Value	OR (95% CI)
HAART without PI vs. HAART with PI at Entry	0.11	10.19 (0.02-1.48)
Non-HAART no ARV vs. HAART with PI at Entry	0.34	0.36 (0.04-3.94)
PI Use at Entry (PI use vs. No PI use)	0.07	1.05 (0.90-18.26)
Age at ARV Initiation (≤ 6 months vs. > 6 months)	0.39	0.80 (0.31-2.04)
CDC Class at Entry (C vs. A, B, or N)	0.64	0.60 (0.19-1.92)
HIV-1 RNA at Entry (Detectable vs. Undetectable)	0.19	0.46 (0.15-1.42)
CD4 Percent at Entry (< 25% vs. >= 25%)	0.35	0.54 (0.15-1.97)
Caregivers Education (Not HS grad vs. HS grad)	0.93	0.95 (0.32-2.81)

In the final reduced multivariable logistic regression model, only protease inhibitor (PI) use at entry remained marginally significant (p=0.07), indicating a 4-fold higher odds of primary impairment for those on PIs as compared to those not on PIs.

Table 3: Univariate Logistic Regression Models for Secondary LI vs No Impairment

Variable	P Value	OR (95% CI)
HAART without PI vs. HAART with PI at Entry	0.14	0.38 (0.11-1.27)
Non-HAART no ARV vs. HAART with PI at Entry	0.49	1.46 (0.50-4.29)
PI Use at Entry (PI use vs. No PI use)	0.51	1.33 (0.57-3.10)
Age at ARV Initiation (≤ 6 months vs. > 6 months)	0.26	1.23 (0.84-2.11)
CDC Class at Entry (C vs. A, B, or N)	0.21	1.63 (0.76-3.48)
HIV-1 RNA at Entry (Detectable vs. Undetectable)	0.20	1.67 (0.77-3.40)
CD4 Percent at Entry (< 25% vs. >= 25%)	0.05	1.21 (0.69-2.11)
Caregivers Education (Not HS grad vs. HS grad)	0.04	1.28 (1.06-1.92)

In the final reduced multivariable logistic regression model, there remained a higher odds of secondary impairment for those with lower CD4% (OR=2.10, 95% CI: 0.94-4.69, p=0.07), those who initiated ARV at less than 6 months of age (OR=2.19, 95% CI: 1.03-4.66, p=0.04), and those whose caregivers had less than a high school education (2.36, 95% CI: 1.06-5.23, p=0.04).

Table 4: Univariate Logistic Regression Models for Primary LI vs Secondary LI

Variable	P Value	OR (95% CI)
HAART without PI vs. HAART with PI at Entry	0.55	0.49 (0.055-0.6)
Non-HAART no ARV vs. HAART with PI at Entry	0.21	0.25 (0.03-2.19)
PI Use at Entry (PI use vs. No PI use)	0.18	3.05 (0.60-15.55)
Age at ARV Initiation (≤ 6 months vs. > 6 months)	0.09	0.39 (0.14-1.14)
CDC Class at Entry (C vs. A, B, or N)	0.12	0.37 (0.11-1.30)
HIV-1 RNA at Entry (Detectable vs. Undetectable)	0.05	0.28 (0.08-0.99)
CD4 Percent at Entry (< 25% vs. >= 25%)	0.05	0.25 (0.06-0.99)
Caregivers Education (Not HS grad vs. HS grad)	0.14	0.42 (0.13-1.35)

In the final multivariable logistic regression model, only low CD4% at entry remained a significant predictor of Primary vs Secondary LI (p=0.05), indicating a 75% decrease in odds of primary impairment for those with low CD4%.

SUMMARY

- Of 178 children with language assessments (median age: 12.9 yrs, 48% male, 73% Black, 18% Hispanic), 63 (35%) had either primary LI (23, 13%) or secondary LI (40, 22%), compared to an overall expected 16% in the reference population.
- Children with Secondary LI had more advanced HIV disease than those with Primary or no LI (CDC Class C, detectable viral load, and CD4% < 25%), although these differences did not always attain statistical significance.
- Children with Secondary LI were more likely to initiate ARV in the first 6 months of life than those with Primary or no LI, while children with Primary LI were more likely to use PIs at entry than those with Secondary or no LI.
- Children with Secondary LI were more likely to have a caregiver who did not graduate high school than those with Primary or no LI.
- Sensitivity analyses excluding those defined as having Secondary LI solely based on non-English exposure (7 children) yielded very similar results.
- In addition, adjustment for age and gender had minimal effect on association of language impairment with HIV disease severity, and were not themselves associated with impairment.

CONCLUSIONS

- Language impairment in P-HIV children appears as part of the risk for impaired higher cognitive abilities and are more common than expected.
- Secondary LI coexists with cognitive and/or hearing impairment and is more likely with more advanced HIV disease, while primary LI is less likely to be associated with advanced HIV disease.
- About 13% of the P-HIV children met criteria for primary LI, a higher rate than the expected 7% (Tomblin, et al, 1997). These children may go undetected because they do not have nonverbal cognitive impairment and are less likely to show advanced HIV disease symptoms. PI use at entry warrants further investigation as a predictor.
- This study reveals that advanced HIV disease is one of multiple factors that can contribute to LI.

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