Longitudinal Evaluation of Language Impairment in Perinatally HIV Exposed Adolescents

Sean Redmond[1], Tzy-Jyun Yao[2], Jonathan S. Russell[2], Mabel L. Rice[3], Howard J. Hoffman[4], George Siberry[5], and Paige L. Williams[2]

for the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]Communication Science & Disorders, University of Utah, [2]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, [3]Child Language Doctoral Program, University of Kansas,
[4]Epidemiology and Statistics Program, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, [5]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health

Abstract # 814

Sean Redmond

390 South 1530 East Suite 1201
Salt Lake City, UT 84112

Tel: 801-585-6284
Fax: 801-581-7955
Email: sean.redmond@health.utah.edu

ABSTRACT*

Background: We previously documented a significantly higher prevalence (relative to comparable communities) of both primary language impairment (PLI) and language impairment concomitant with hearing/cognitive impairments (CLI) in perinatally HIV-infected (PHIV) and perinatally HIV-exposed uninfected (PHEU) participants (age range: 7-17y) from the Adolescent Master Protocol (AMP), a component of the Pediatric HIV/AIDS Cohort Study (PHACS). This analysis describes longitudinal outcomes of this cohort to determine the persistence of PLI and CLI and associations with antiretroviral (ARV) treatment, disease status, and other risk factors.

Methods: The Clinical Evaluation of Language Fundamental (CELF-4) was repeated on AMP participants 18 months after their baseline assessment. Different regression models were utilized to identify factors associated with change in standardized score (SC) and the resolution or development of LI.

Results: Complete language data at both time points were available on 319 participants (mean baseline age=12y, 80% black, 9% Hispanic). Among these, 112 (35%) had LI at baseline. Overall, SCs for the study population were highly stable and changes were similar in PHIV (n=212) and PHEU (n=107) participants. Family history of language delays/learning difficulties had a negative association with SC changes after controlling for demographic and socioeconomic factors and baseline LI status (coefficients = -3.35, 95% CI: -5.83, -0.88). Among PHIV, high CD4 count (> 350 cells/mm^3) (4.91, CI: -0.03, 9.86) and nadir CD4 < 200 cells/mm^3 (3.33, CI: 0.33, 6.34) at baseline, and being on combination antiretroviral (cART) (4.46, CI: 0.09, 8.83) were associated with a higher mean SC change. Over the follow-up period, initial LI status was persistent in the majority of cases (78%) and 21 new cases of LI occurred (10%). Family history was associated with higher odds of developing LI (adj. Odds Ratio (aOR) = 5.14, CI: 1.33, 19.9) and no significant risk factors for resolving LI were found among combined PHIV and PHEU after adjusting for demographics and baseline SC. Among PHIV, being on cART at baseline (aOR = 187, CI: 1.06, >999) was associated with greater odds, and higher percentage of detectable viral load up to baseline (aOR = 0.97, CI: 0.93, 1.00) was associated with lower odds of LI resolution after controlling for demographics and baseline SC.

Conclusions: Perinatally HIV exposed youth with LI are at risk for persistent LI, irrespective of infection status. Risk factors for declining scores included family history and – for PHIV – not receiving cART and low CD4 count.

BACKGROUND

- Previous studies indicate that children with HIV are at elevated risk for language impairments[1-3].
- Rice et al[4] documented further that this risk applies to PHEU children as well with similar occurrence between the PHIV and PHEU groups (34% vs. 37%) in AMP.
- Longitudinal data on perinatally HIV exposed study samples are needed to determine the persistence of language impairments and identify associations with HIV infection and other risk factors, and among PHIV adolescents, with ART and disease severity.

OBJECTIVES

1) To evaluate and compare changes in language scores and initial language status among PHIV and PHEU adolescents across two assessments 18 months apart
2) To identify predictors for change in participant's language scores or LI status
3) To evaluate association between change in SC or LI status with ARV exposure and disease severity in PHIV participants

METHODS

Study Population

- Participants of AMP from PHACS network at 22 sites in the United States who had baseline CELF-4 assessment (mean age = 12 years, range: 7-17) and then again 18 months later
- Monolingual as assessed at baseline
- Assessed in participant's primary language (English or Spanish)

Definitions and Statistical Methods

- **Language impairment (LI):** CELF-4 standardized score (SC) < 85
  - Resolution of LI: CELF-4 SC < 85 at baseline to ≥ 85 at follow-up
  - Development of LI: CELF-4 SC ≥ 85 at baseline to < 85 at follow-up
- **Concomitant Impairment:**
  - Non-verbal cognitive impairment: SC < 85 from age-appropriate Wechsler Intelligence Scale
  - Hearing impairment: worse ear pure tone average > 20 dB
- cART: at least 3 drugs from at least 2 different ARV drug classes
- Risk factors considered: concomitant impairment, socio-economic status measured by caregiver characteristics, family history
- General linear regression analysis (GLM) was used to model the change in SC (follow-up SC – baseline SC) on HIV infection status, demographics and risk factors
- Two logistic regression models were fit:
  - Including participants without LI at baseline to identify predictors for LI development
  - Including participants with LI at baseline to identify predictors for LI resolution
- Within PHIV cohort:
  - GLM and separate logistic regressions analyses were conducted to evaluate disease severity (historical, baseline, and during study CD4 counts and viral loads), adjusted for predictors identified above
  - Historical and baseline ARV exposures were also analyzed, adjusting for predictors and disease severity indicators

RESULTS

Table 1: Baseline demographics among PHIV and PHEU

	PHIV (n=212)	PHEU (n=107)	P-Value
Median Age (Years) (Q1, Q3)	12.85 (10.48, 14.88)	10.49 (8.69, 12.47)	<.01*
Female Sex	113 (53%)	53 (50%)	0.55**
Black Race	171 (81%)	85 (79%)	0.88**
Hispanic Ethnicity	16 (8%)	13 (12%)	0.22**
Caregiver Not HS Grad	167 (79%)	84 (79%)	0.89**
Caregiver Income <$20,001	78 (37%)	64 (60%)	<.01**
Caregiver Performance IQ <70	7 (3%)	9 (8%)	0.10**
Family History of Late Talking	43 (20%)	28 (26%)	0.26**

*Wilcoxon Test, **Fisher's Exact Test

Table 2: HIV disease characteristics among PHIV

	PHIV (n=212)
CD4 Nadir <200 cells/mm3 (Baseline)	56 (26%)
CD4 <350 cells/mm3 (Baseline)	26 (12%)
CD4 Nadir <350 cells/mm3 (Study Interval)	43 (20%)
Median % RNA Measures >400 copies/mL (Baseline) (Q1, Q3)	50.00 (24.83, 80.00)
RNA >400 copies/mL (Baseline)	64 (30%)
RNA Max >400 copies/mL (Study Interval)	97 (46%)

RESULTS

Table 3: ART regimens and duration among PHIV

	PHIV (n=212)
Median cART Duration (Years, Baseline) (Q1, Q3)	8.77 (5.80, 10.23)
Median NRTI Duration (Years, Baseline) (Q1, Q3)	10.79 (8.81, 12.86)
Median NNRTI Duration (Years, Baseline) (Q1, Q3)	1.69 (0.00, 4.86)
Median PI Duration (Years, Baseline) (Q1, Q3)	7.96 (4.50, 9.94)
cART (Baseline)	191 (90%)

Figure 1: Language scores at baseline and follow-up and Spearman correlation

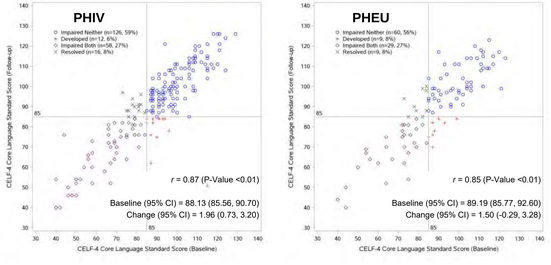


Table 4: Adjusted linear regression of change in language score

		Estimate	95%-CI Lower	95%-CI Upper	P-Value
Covars (n=318)	HIV Infected	0.52	-1.71	2.74	0.65
	Language Impaired (Baseline)	4.76	1.68	7.84	<.01
	Concomitant Impairment (Baseline)	2.20	-1.32	5.72	0.22
	Interaction: Lang*Conc Impairment	-3.29	-8.17	1.59	0.19
	Age (Years, Baseline)	-0.17	-0.56	0.23	0.41
	Female Sex	0.50	-1.51	2.50	0.63
	Black Race	3.62	0.76	6.48	0.01
	Hispanic Ethnicity	1.35	-2.55	5.26	0.50
	Family History of Late Talking	-3.35	-5.83	-0.88	<.01
PHIV Participants					
Disease Severity (n=211)	% RNA Measures >400 copies/mL (Baseline)	-0.02	-0.07	0.03	0.49
	CD4 Nadir <200 cells/mm^3 (Baseline)	3.33	0.33	6.34	0.03
	CD4 <350 cells/mm^3 (Baseline)	-4.91	-9.86	0.03	0.05
	CD4 Nadir <350 cells/mm^3 (Study Interval)	-0.86	-4.93	3.21	0.68
	RNA >400 copies/mL (Baseline)	0.27	-3.45	4.00	0.89
	RNA Max >400 copies/mL (Study Interval)	1.34	-1.88	4.56	0.41
ART (n=211 each)	cART Duration (Years)	0.40	0.01	0.79	0.04
	NRTI Duration (Years)	0.13	-0.48	0.75	0.67
	NNRTI Duration (Years)	0.07	-0.32	0.45	0.73
	PI Duration (Years)	0.32	-0.03	0.67	0.07
	cART (Baseline)	4.46	0.09	8.82	0.05

Table 5: Adjusted odds of LI development among youth without LI at baseline

		aOR Estimate	95%-CI Lower	95%-CI Upper	P-Value
Covars (n=176)	HIV Infected	0.83	0.25	2.77	0.76
	Core Lang Std Score (Baseline)	0.87	0.80	0.95	<.01
	Concomitant Impairment (Baseline)	0.60	0.10	3.48	0.57
	Age (Years, Baseline)	1.03	0.80	1.33	0.80
	Female Sex	0.96	0.30	3.03	0.94
	Black Race	0.23	0.05	0.95	0.04
	Hispanic Ethnicity	0.84	0.12	5.71	0.86
	Caregiver Performance IQ <70	7.73	0.94	63.72	0.06
	Family History of Late Talking	5.14	1.33	19.90	0.02
PHIV Participants					
Disease Severity (n=114)	% RNA Measures >400 copies/mL (Baseline)	1.03	0.97	1.08	0.37
	CD4 Nadir <200 cells/mm^3 (Baseline)	0.06	0.00	2.10	0.12
	CD4 <350 cells/mm^3 (Baseline)	16.32	0.24	1132.90	0.20
	CD4 Nadir <350 cells/mm^3 (Study Interval)	4.35	0.32	59.48	0.27
	RNA >400 copies/mL (Baseline)	4.70	0.26	84.82	0.29
	RNA Max >400 copies/mL (Study Interval)	0.08	0.00	2.54	0.15
ART (n=114 each)	cART Duration (Years)	0.83	0.59	1.17	0.29
	NRTI Duration (Years)	1.11	0.69	1.80	0.66
	NNRTI Duration (Years)	1.08	0.74	1.59	0.69
	PI Duration (Years)	0.90	0.67	1.21	0.50
	cART (Baseline)	0.41	0.02	10.42	0.59

Table 6: Adjusted odds of LI resolution among youth with LI at baseline

		aOR Estimate	95%-CI Lower	95%-CI Upper	P-Value
Covars (n=112)	HIV Infected	0.78	0.20	3.06	0.72
	Core Lang Std Score (Baseline)	1.36	1.16	1.59	<.01
	Concomitant Impairment (Baseline)	0.90	0.24	3.28	0.87
	Age (Years, Baseline)	1.14	0.89	1.46	0.31
	Female Sex	4.14	1.07	15.99	0.04
	Black Race	0.25	0.02	3.47	0.30
	Hispanic Ethnicity	1.58	0.09	26.90	0.75
PHIV Participants					
Disease Severity (N=74)	% RNA Measures >400 copies/mL (Baseline)	0.97	0.93	1.00	0.05
	CD4 <350 cells/mm^3 (Baseline)	0.14	0.00	4.49	0.26
ART (n=74 each)	cART Duration (Years)	1.37	0.98	1.91	0.06
	NRTI Duration (Years)	1.47	0.77	2.79	0.24
	NNRTI Duration (Years)	1.42	0.93	2.16	0.10
	PI Duration (Years)	1.16	0.90	1.50	0.24
	cART (Baseline)	186.72	1.06	>999	0.05

aOR = adjusted Odds Ratio, CI = confidence interval,
Study Interval = time between baseline and follow-up language assessments

SUMMARY

- Overall, language abilities for the AMP cohort were highly consistent across the two times of measurement and similar between PHIV and PHEU participants
- Within the context of overall stability at the group level however, large changes did take place for some participants
- Among demographic factors, female sex was associated with higher odds of LI resolving and black race was associated with improved language scores and with lower odds of LI developing
- After adjusting for demographics and baseline language scores, family history of language/learning disabilities was associated with decrements in participants' language scores and higher odds of LI developing
- No significant risk factors for resolving LI were found among combined PHIV and PHEU groups
- Cognitive or hearing impairment was not associated with change in language score or LI status.
- For PHIV group:
  - Being on cART at baseline and longer duration of cART was associated with improvements in language scores and with higher odds of LI resolving
  - Baseline CD4 > 350 and nadir CD4 < 200 were associated with improvements in language scores
  - Higher percentage of detectable viral load up to baseline was associated with lower odds of resolving LI

CONCLUSIONS

- Perinatally HIV exposed youth are at risk for persistent LI, irrespective of infection status
- For PHIV group, historical and baseline disease status and treatment were associated with changes in language scores and LI status
- Additional waves of data collection with the AMP cohort will specify further the roles of protective and risk factors and possibly uncover new ones
- Follow-up of adolescents into young adulthood is needed to establish the end-state of language associated with HIV exposure

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