ARV Risk for Speech and Language Impairments in HEU Children at 3 and 5 Years

Abstract #813

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ABSTRACT*

Background: Perinatally HIV-exposed but uninfected (PHEU) children have elevated risk of late language emergence at age 1 year, with possible links to *in utero* antiretroviral (ARV) exposure. This study investigated possible risks, including ARV exposure, for speech (SI) and language impairments (LI) in monolingual PHEU children in the important preschool period. This is the first study of SI in PHEU children and the first of LI among PHEU children in this age range.

Methods: Speech and Language assessments were conducted as part of the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring of ART Toxicities (SMARTT) study at ages 3 (N= 208) and 5 (N = 429). Domains of speech, overall language, vocabulary and grammar were assessed. SI/LI was subdivided into primary (PSI /PLI) versus concomitant (CSI / CLI). Logistic regression models were used to estimate adjusted odds of SI and LI for different ARV exposures, controlling for confounding variables.

Results: Elevated risk for language impairments was found at 3 and 5 years, but no elevated risk for speech impairments. Risk factors included male sex, black race, and other socioeconomic measures, although these varied by age group, primary vs. concomitant group, and by the particular speech or language measure. Adjusted logistic regression models revealed possible protective effects as well as increased risk for specific ARVs. Tenofovir at age 3 was associated with increased risk for speech impairments yet was protective for language, vocabulary, and grammar at age 5.

Conclusions: Elevated risk for language impairments persist into preschool age in HEU children. Intrauterine exposure to specific ARVs can be protective or increase risk for such delays, and this varies by age. Health care providers should screen HEU children for language delays at preventive care visits and intervene in order to optimize school performance.

*Data presented in abstract based on data available by May 1, 2014

BACKGROUND

- During this period speech and language develops rapidly and the two dimensions develop independently, requiring separate measurements[3]. Brain development is very active at this age.
- Studies of PHEU children at 1 and 2 years and elementary-school aged children show elevated risk for language impairments[1, 2]. Studies of possible risk in the preschool period have not been available.
- Safety studies are needed for possible combination ARV (cARV) and/or individual drug effects during this age period.
- An earlier study of school-aged children found that predictors of language impairments for perinatally HIV infected and PHEU children differed based on whether they also had concomitant disorders of cognitive and/or hearing impairment (CLI) as compared to children without these concomitant disorders (PLI)[2].
- Differences in predictors between CLI and PLI groups of HEU children suggest that the causal pathways for language impairment may involve language-selective pathways or more general pathways that also affect hearing or cognitive development.
- Consideration of such possible differences could add precision to evaluation of potential drug effects over the full developmental course of children's speech and language development.

OBJECTIVES

In 3- and 5-year-old PHEU children, determine:
1) The prevalence of PSI and/or PLI;
2) The prevalence of SI/LI concomitant with intellectual or hearing impairment (CSI/CLI);
3) Whether risks for speech and/or language impairment are associated with *in utero* cARV exposure.

METHODS

Study Population

This investigation used data collected in the SMARTT study, a prospective cohort study conducted by the PHACS network at 22 sites in the United States. This study included SMARTT participants with speech/language assessments at 3 and/or 5 years-of-age.

Definitions and Statistical Methods

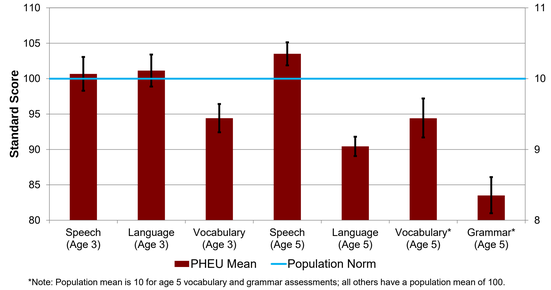
- Age 3 Outcomes
  - Speech: Goldman Fristoe Test of Articulation (GFTA-2) percentile score
  - Language: Test of Early Language Development (TELD-3) Spoken Language Quotient (SLQ)
  - Vocabulary: Peabody Picture Vocabulary Test (PPVT-3) standard score
- Age 5 Outcomes
  - Speech: GFTA-2 percentile score
  - Language: Test of Language Development (TOLD-P:3) SLQ
  - Vocabulary: TOLD-P:3 Picture Vocabulary standard score
  - Grammar: TOLD-P:3 Grammatic Completion standard score
- SI/LI: standardized score (SC) below the 15th percentile
- Intellectual Delay
  - Age 3: Bayley Screener Cognitive domain as "at risk"
  - Age 5: Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) Perf. IQ<85
- Hearing Loss: worse ear pure tone average ≥ 20 dB
- Primary Impairment: SI/LI with nonverbal IQ ≥85, no hearing loss
- Concomitant Impairment: SI/LI with intellectual delay or with hearing loss
- Maternal ARV history during pregnancy was collected through medical record review and from prior studies (classes studied: NNRTIs and PIs)
- cARV: at least 3 drugs from at least 2 different ARV drug classes
- Possible confounders: child demographic characteristics, maternal substance use during pregnancy, maternal CD4 count and viral load during pregnancy, and caregiver characteristics.
- Prevalence in each impairment category for each outcome measure was estimated with 95% confidence intervals. The mean SC was compared to population means using one-sample t-test. Separate logistic regressions modeled Primary vs No Impairment and then Concomitant vs No Impairment for each speech or language outcome, and for each ARV exposure, unadjusted and adjusted for potential confounders.

Table 1: Demographics of monolingual PHEU participants, by age

	Age 3 (n=208)	Age 5 (n=429)	Age 3 or 5 Total (n=492)
Median age (min, max)	3.1 (2.8, 3.9)	5.1 (4.8, 5.9)	--
Female sex	118 (57%)	229 (53%)	262 (53%)
Black race	152 (73%)	361 (84%)	398 (81%)
Hispanic ethnicity	34 (16%)	26 (6%)	51 (10%)
Primary language English	189 (91%)	429 (100%)	--
Spanish	19 (9%)	0 (0%)	--
Maternal alcohol use during pregnancy	11 (5%)	31 (7%)	36 (7%)
Maternal tobacco use during pregnancy	46 (22%)	98 (23%)	109 (22%)
Latest maternal CD4% <25	62 (30%)	117 (27%)	141 (29%)
Caregiver lacks high school degree	72 (35%)	128 (30%)	152 (31%)
Household income <= 20,000	134 (64%)	266 (62%)	310 (63%)
Median number in household (Q1, Q3)	4 (3, 5)	4 (3, 5)	4 (3, 5)
Caregiver Verbal IQ <85	81 (39%)	180 (42%)	194 (39%)
Caregiver health problems	187 (90%)	369 (86%)	426 (87%)
Caregiver difficulty caring for child	30 (14%)	74 (17%)	80 (16%)

RESULTS

Figure 1: Speech and language average standard scores (and 95% confidence intervals) among monolingual PHEU participants



*Note: Population mean is 10 for age 5 vocabulary and grammar assessments; all others have a population mean of 100.

Table 2: Covariates of each speech/language Primary Impairment at age 3

	Speech (n=164)		Language (n=168)		Vocabulary (n=151)	
	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age (years)	2.26 (0.05, 82.32)	0.70	2.58 (0.17, 40.30)	0.50	4.52 (0.43, 47.87)	0.21
Female sex	1.03 (0.23, 4.90)	1.00	0.41 (0.15, 1.09)	0.07	0.42 (0.17, 1.03)	0.06
Black race	2.32 (0.44, Infinity)	0.44	2.85 (0.46, 17.48)	0.26	3.86 (0.62, 24.23)	0.15
Hispanic ethnicity	11.98 (<0.01, 112.73)	1.00	0.52 (0.04, 6.13)	0.60	2.36 (0.30, 18.74)	0.42
Maternal alcohol use during pregnancy			4.97 (1.16, 21.35)	0.03		
CG lacks high school degree			3.56 (1.32, 9.65)	0.01		
CG Verbal IQ <85					3.43 (1.35, 8.68)	0.009
CG health problems	0.14 (0.03, 0.70)	0.02				
CG difficulty caring for child	5.00 (1.10, 23.70)	0.04				

aOR=adjusted odds ratio from logistic regression model; CI=confidence interval; CG=caregiver.

Figure 2: Study prevalence of PSI/CSI and PLI/CLI

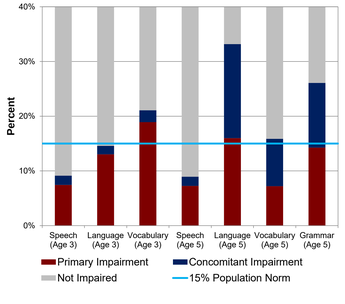


Table 4: Covariates of each speech/language Primary Impairment at age 5

	Speech (n=158)		Language (n=281)		Vocabulary (n=357)		Grammar (n=310)	
	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age (years)	0.32 (<0.01, 13.80)	0.55	1.64 (0.20, 13.21)	0.64	3.04 (0.24, 38.24)	0.39	2.52 (0.31, 20.61)	0.39
Female sex	3.10 (0.76, 12.63)	0.11	0.91 (0.49, 1.71)	0.77	1.57 (0.68, 3.60)	0.29	0.79 (0.41, 1.51)	0.48
Black race	4.82 (0.16, 149.39)	0.37	2.57 (0.72, 9.23)	0.15	2.39 (0.54, 10.58)	0.25	3.20 (0.72, 14.13)	0.13
Hispanic ethnicity	6.24 (0.18, 212.49)	0.31	2.21 (0.49, 9.89)	0.30	2.53 (0.41, 15.83)	0.32	1.86 (0.28, 12.39)	0.52
Maternal alcohol use during pregnancy							4.11 (1.39, 12.21)	0.01
Maternal tobacco use during pregnancy							0.40 (0.15, 1.08)	0.07
Latest maternal CD4% <25			1.82 (0.95, 3.51)	0.07				
Household income <= 20,000			2.01 (0.97, 4.15)	0.06				
Number in household			1.31 (1.07, 1.60)	0.008				

aOR=adjusted odds ratio from logistic regression model; CI=confidence interval; CG=caregiver.

Table 5: Adjusted* association between *in utero* ARV exposure and speech or language impairment

	ARV	Age / Group	Impairment	Adjusted OR (95% CI)	P-Value
Protective Effects	cARV vs 3NRTI	5 / PSI	Speech	0.24 (0.05, 1.10)	0.07
	Didanosine	5 / CLI	Language	0.16 (0.02, 1.27)	0.08
		5 / CLI	Grammar	0.17 (<0.01, 0.81)	0.05
	Tenofovir	5 / CLI	Language	0.53 (0.27, 1.04)	0.06
		5 / CLI	Vocabulary	0.42 (0.16, 1.12)	0.08
		5 / CLI	Grammar	0.32 (0.13, 0.77)	0.01
	Nelfinavir	5 / CLI	Language	0.52 (0.27, 1.00)	0.05
Increased Risk	cARV vs 3NRTI	3 / PLI	Language	5.17 (1.02, Infinity)	0.09
	Didanosine	5 / PLI	Vocabulary	3.46 (1.18, 10.21)	0.02
	Lamivudine	5 / CLI	Language	2.10 (0.90, 4.93)	0.09
	Tenofovir	3 / PSI	Speech	5.28 (1.09, 30.39)	0.04
	Zidovudine	5 / CLI	Language	2.35 (1.00, 5.50)	0.05
		5 / CLI	Grammar	2.50 (0.84, 7.43)	0.10

*adjusted with covariates of the corresponding Age/Group/Impairment models; aOR=adjusted odds ratio from logistic regression model; CI=confidence interval; cARV=combination antretrovirals.

Table 3: Covariates of each speech/language Concomitant Impairment at age 5

	Language (n=327)		Vocabulary (n=364)		Grammar (n=332)	
	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value	aOR (95% CI)	P-Value
Age (years)	0.38(0.05, 2.75)	0.34	0.60(0.05, 7.04)	0.68	0.21(0.02, 2.27)	0.20
Female sex	0.54(0.31, 0.94)	0.03	1.20(0.58, 2.49)	0.63	0.39(0.20, 0.78)	0.007
Black race	2.93(1.03, 8.34)	0.04	5.22(0.93, 29.27)	0.06	8.94(1.57, 50.99)	0.01
Hispanic ethnicity	1.50(0.33, 6.79)	0.60	2.99(0.48, 18.60)	0.24	6.86(1.18, 39.96)	0.03
CG health problems					0.40(0.18, 0.90)	0.03

aOR=adjusted odds ratio from logistic regression model; CI=confidence interval; CG=caregiver.

SUMMARY

- Results show elevated risk for LI for HEU children at 3 and more so at 5 years when compared to population norms, although there was no elevated risk for SI.
- There were insufficient numbers of children at 3 years who met criterion for low levels of nonverbal cognitive abilities on the Bailey-III Screener to form a CLI group. There may be under-identification of children with low nonverbal cognitive abilities on this assessment.
- Protective effects as well as increased risk were evident, varying between speech and language impairments, Primary vs. Concomitant groups, and age differences.
- Relative to triple NRTI, cARV was associated with increased risk for PLI at 3 years of age and was protective for PSI at 5 years. Individual drug effects differ by age and by outcomes (speech vs. language).
- Tenofovir was associated with increased risk for PSI at 3 years yet was protective for all three measures of language at 5 years for the CLI group.
- Recent evidence[4] suggests that tenofovir was detectable in brain tissue collected from adults dying with HIV disease, raising the possibility that the differential effects of tenofovir on speech and language outcomes at 3 and 5 could be related to pathways and timing of drug effects on brain development needed for speech and language.

CONCLUSIONS

These findings provide additional support for the developmental evidence of increased risk for language impairments in HEU children with perinatal ARV exposure, by adding evidence from the preschool period. Further, the results reveal the need to consider speech and language impairments separately, and the dynamic changes in the 3 to 5 year period. There was no consistently strong evidence of a relationship between ARV exposure and SI/LI, but some signals bear evaluation in other cohorts. Further exploration of the relationship between ARV exposure and speech/language impairment at ages 3 and 5 is warranted to confirm the observed associations.

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