Early Viral Suppression Improves Neurocognitive Outcomes in HIV-infected Children

Abstract #851

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ABSTRACT

Background: Children and adolescents with perinatally-acquired HIV infection (PHIV+) are vulnerable to subtle to severe neurocognitive deficits during development. Early childhood represents a sensitive period of neurodevelopment and we hypothesized that both early virologic control and use of ART regimens with better central nervous system (CNS) penetration are associated with improved neurocognitive outcomes among school-aged PHIV+ children.

Methods: We analyzed data from PHIV+ children from two US-based prospective cohort studies, PHACS and IMPAACT 219C, who completed a neurocognitive assessment (WISC-III or WISC-IV) at 6 years of age or older, and who had ≥1 HIV-1 viral load measurement prior to or within 6 months after ART initiation. Multivariable general linear regression models were used to evaluate associations of viral suppression and CNS penetration effectiveness (CPE) scores with full scale IQ (FSIQ), adjusted for demographic and clinical covariates with p-value < 0.1 from univariable analyses.

Results: 396 PHIV+ children were included (mean age at time of WISC evaluation=9.6yrs); 54% were female, 66% Black, 27% Hispanic, and 83% spoke English as the primary language. The percent of children achieving viral suppression increased from 11% by 1 year of age to 41% by age 5. The estimated difference in mean FSIQ (comparing children who were virally suppressed vs. unsuppressed) by each age cutoff was 3.7 at age 1 (p=0.13), 2.2 at age 2 (p=0.29), 3.2 at age 3 (p=0.11), 4.4 at age 4 (p=0.02), and 3.9 at age 5 (p=0.03) after adjusting for age at neurocognitive assessment, birth cohort, WISC version, caregiver education, ethnicity, birth weight and child's primary language. CPE score of initial regimen and weighted average CPE score were not associated with higher FSIQ.

Conclusions: Virologic suppression during infancy or early childhood is associated with improved neurocognitive outcomes in school-aged PHIV+ children. Although the association attained statistical significance only at ages 4 and 5, the effect size was consistent across all age groups. In contrast, CPE scores showed no association with improved neurocognitive outcomes.

BACKGROUND

- Perinatal HIV infection is associated with subtle to severe neurocognitive deficits.[1,2]
- Initiation of antiretroviral therapy (ART) in infancy is associated with improved longevity and improved early childhood neurodevelopment.[3]
- There are conflicting adult data regarding the association between CPE score and neurocognitive function.[4,5]
- It is unclear if the neurodevelopmental benefits of early ART initiation persist later in childhood.
- It is also unclear if CNS penetrating ART regimens might be associated with better school-age neurocognitive outcomes.
- Because sensitive periods of neurodevelopment occur during the first few years of life, we hypothesized that virologic control and use of higher CPE scoring ART regimens during this time are associated with better school-age neurocognitive outcomes.

OBJECTIVES

- Estimate the association between age of viral suppression and school-age neurocognitive functioning among children with HIV infection.
- Determine the association between CPE score of initial ART regimen and weighted average CPE score and school-age neurocognitive functioning in children with HIV-infection.

METHODS

Study Population

- PHIV+ children from PHACS Adolescent Master Protocol (enrolled from 2007 – 2009) and IMPAACT 219C (enrolled from 2000 – 2006).
- Completed WISC-III or WISC-IV at ≥6 years.
- ≥1 HIV-1 viral load prior to or within 6 months after ART initiation.

Definitions and Statistical Methods

- Viral suppression: two consecutive viral loads ≤400 copies/mL obtained 1-6 months apart.
- Age of viral suppression: age at first viral load ≤400 copies/mL, among those meeting above criteria for viral suppression.
- CPE scores were calculated for initial ART regimen and a weighted average CPE score was calculated for each time period of interest using the 2011 ranking system developed by Letendre et al.[6]
- Multivariable general linear regression models were used to evaluate associations of viral suppression and CPE scores with FSIQ, adjusted for demographic and clinical covariates with p-value < 0.1 from univariable analyses, or based on an *a priori* specification.
- Results were stratified by birth cohort defined as prior to and after availability of HAART (1996) to evaluate presence of effect modification.

RESULTS

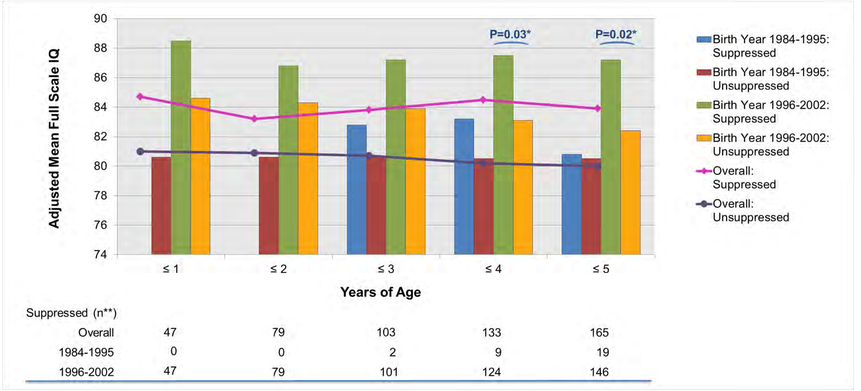
Table 1: Demographic Characteristics of PHIV+ Children (N=396)

Characteristics		N (%) / Mean (SD)
Female		213 (54%)
Age at WISC evaluation (years)		9.6 (2.6)
Version of WISC evaluation:	WISC-III	163 (41%)
	WISC-IV	233 (59%)
Black race		262 (66%)
Hispanic		108 (27%)
Primary language of child is English		328 (83%)
Birth weight < 2500g		83 (21%)
Baseline CDC classification: C		87 (22%)
Biological parent is baseline primary caregiver		201 (51%)
Nadir CD4% prior to ART initiation (N=256)		23.6 (13.2)
Peak logRNA prior to ART initiation (N=248)		5.2 (0.8)
Baseline primary caregiver education < High school		93 (23%)

Missing data: race (10%); Ethnicity (1%); birth weight (16%) ; nadir CD4% (35%); peak logRNA (37%); caregiver education (7%).

RESULTS

Figure: Adjusted Mean Full Scale IQ Score by Viral Suppression at each Age Cutoff, Overall and by Birth Cohort



Suppressed (n**)					
Overall	47	79	103	133	165
1984-1995	0	0	2	9	19
1996-2002	47	79	101	124	146

* Comparing adjusted means for suppressed and unsuppressed children among the 1996-2002 birth cohort.
** Cumulative number of children suppressed at each age cutoff.
Multivariable models were adjusted for: birth cohort, age at time of WISC evaluation, WISC version, caregiver education level, Hispanic ethnicity, low birth weight, child's primary language.

Table 2: Adjusted Associations Between Full Scale IQ Score and Continuous CPE Score, Overall and by Birth Cohort

	Overall (n=396)		1984 - 1995 (n=165)		1996 - 2002 (n=231)	
	Estimated Difference* (95% CI)	P-value	Estimated Difference* (95% CI)	P-value	Estimated Difference* (95% CI)	P-value
CPE score of the first ART regimen (with duration > 2 weeks) before age 5	0.0 (-0.5, 0.6)	0.88	-0.9 (-1.9, 0.1)	0.06	0.7 (-0.0, 1.5)	0.07
Weighted average CPE score by age 1	-0.6 (-1.2, 0.1)	0.10	-0.4 (-2.4, 1.6)	0.69	-0.6 (-1.3, 0.1)	0.09
Weighted average CPE score by age 2	-0.5 (-1.2, 0.1)	0.10	-0.1 (-1.8, 1.7)	0.94	-0.6 (-1.3, 0.1)	0.11
Weighted average CPE score by age 3	-0.3 (-1.0, 0.3)	0.31	0.2 (-1.4, 1.7)	0.84	-0.4 (-1.2, 0.4)	0.29
Weighted average CPE score by age 4	-0.2 (-0.9, 0.5)	0.52	0.2 (-1.3, 1.6)	0.84	-0.3 (-1.1, 0.5)	0.50
Weighted average CPE score by age 5	-0.2 (-0.9, 0.5)	0.58	0.1 (-1.3, 1.5)	0.92	-0.2 (-1.0, 0.6)	0.61

* Estimated difference in adjusted mean FSIQ for each one unit change in CPE score.
Multivariable models were adjusted for: birth cohort, age at time of WISC evaluation, WISC version, caregiver education level, Hispanic ethnicity, low birth weight, child's primary language.

SUMMARY

- Virologic suppression in early childhood was associated with a 2.2 – 4.4 point higher school-age WISC score, although this association reached statistical significance only for ages 4 and 5.
- The mean FSIQ was higher in the later birth cohort.
- The association between age of viral suppression and FSIQ was limited to PHIV+ children in the later cohort and may be due to the use of cART.
- CPE score of the initial ART regimen and the weighted average CPE score were negatively associated with FSIQ but did not reach statistical significance.

CONCLUSIONS

- Virologic suppression during infancy or early childhood is associated with improved school-age neurocognitive outcomes in PHIV+ children.
- Although the association attained statistical significance only at ages 4 and 5, the effect size was consistent across all age groups and may be due to low numbers in the younger age groups.
- CNS penetration effectiveness (CPE) scores showed no association with improved neurocognitive outcomes.
- Future studies will explore the relationships between virologic suppression, CPE scores and neurocognitive domains, including language, executive functions, memory, learning and processing speed.

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