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Neurocognition Following Antiretroviral Initiation in Behaviorally HIV-infected Youth

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Introduction

- Since antiretroviral therapy (ART) became available, HIV dementia is rare, but subtle neurocognitive impairment remains according to some studies. Prevention of central nervous system sequelae is one rationale for current guidelines to initiate ART upon diagnosis.
- Modest positive effects of ART on HIV-associated cognitive dysfunction have been demonstrated in adults.
- Effects of ART in early infection are less well known; it is hypothesized that it could prevent establishment of a chronic inflammatory state thought to contribute to neurocognitive dysfunction. No studies have reported impact of ART initiation on cognition in youth despite being a population at high risk for HIV. Reservations regarding ART initiation in youth include poor adherence, with emergence of drug resistant virus, and potential toxicity due to the prospect of longer term therapy and ongoing brain development.
- Baseline findings from ATN 071 demonstrated a high rate of neurocognitive impairment in youth age 18-24 with behaviorally acquired HIV. Despite associations of some cognitive measures with CD4 count, the role of HIV in the impairments and their potential for improvement with ART were unclear.
- **Objective:** To describe positive or negative change in neurocognitive functioning following ART initiation in treatment-naïve youth with behaviorally acquired HIV compared to untreated youth, and whether change is affected by degree of immune suppression at the time of ART initiation (CD4 > or < 350).

Methods

Design

Longitudinal study of treatment initiation and neurocognitive functioning in youth with behaviorally acquired HIV. Three groups: 1. Baseline CD4 > 350, HIV RNA ≥ 1,000 copies/mL, initiating treatment; 2. CD4 > 350, not initiating treatment (standard of care at the time of study opening); 3. CD4 ≤ 350, initiating treatment (standard of care at the time of study opening). Study was conducted at 15 ATN sites and 5 IMPAACT sites across the U.S. Group 1 participants were co-enrolled in ATN 061 study of T-cell subset impact of early ART initiation and were de-intensified to atazanavir monotherapy after 24 weeks sustained viral suppression.

Participants

181 behaviorally HIV-infected youth age 18-24. Exclusion criteria were: ART other than for prevention of mother-to-child transmission, cumulative treatment during pregnancy greater than 6 months; not fluent in English or Spanish; current pregnancy; substance use judged severe enough to interfere with meeting study requirements; psychosis; significant non-HIV-related cognitive or motor impairment.

Measures

Psychiatric Functioning and Substance Use:
- Beck Depression Inventory-II (BDI-II); Behavioral Symptom Inventory (BSI); Alcohol, Smoking and Substance Involvement Screening Test (ASSIST); 7-day self report of medication adherence for youth on ART; self-report of substances used on day of testing rated for psychoactive effect

Medical Record Abstraction:
- CD4 T cell count and %; plasma HIV-1 RNA viral load; date of first positive HIV test; current and past comorbid conditions, rated according to potential impact on cognition according to Frascati guidelines

Neurocognitive Functioning (scaled/z-scores):
- Global/Adaptive functioning: Wechsler Adult Intelligence Scale-III (WAIS-III); baseline only
- Monitoring battery: administered at weeks 0, 24, 48, 96, 144. Age-normed, with other demographic corrections where available; scores converted to z-scores and averaged within domain

Domain of functioning	Test Name	What it measures
Attention/Working Memory Scale	Digit Span (WAIS-III)	Attention
	Letter-Number Sequencing (WAIS-III)	Working Memory
Motor/Psychomotor Scale	Digit Symbol (WAIS-III)	Psychomotor Speed
	Grooved Pegboard	Fine Motor
	Timed Gait	Gross Motor
Complex Executive Scale	Trailmaking Test (Part B)	Executive Function
	Controlled Oral Word Association (F, A, S; Animals)	Executive Function
	Stroop Test (Interference trial)	Impulse Control

Analyses

Hierarchical linear modeling (HLM) using software HLM v 7.0 to analyze the longitudinal neurocognitive scales. Growth curve modeling investigated nonlinear change in attention, motor, or complex executive indices over time. Both linear and quadratic time measures were included in the model (weeks and weeks^2, respectively). The growth curve models allowed for testing of group effects, demographic characteristics, and clinical covariates both as factors affecting overall neurocognitive performance and as interactions affecting changes over time in neurocognitive performance. Included person-level baseline characteristics were group, gender, age, race/ethnicity, language spoken, education risk (special education class or repeated grade), education level, income earned in past 30 days, CD4 count, time since HIV diagnosis, viral load. Time-varying covariates included diagnoses with potential impact on test performance, BDI-II score, BSI score, medications with psychotropic effects, use of alcohol, cannabis, tobacco, or other drugs, and medication adherence (7-day self-report of missed doses). Finally, the model also included terms for status of antiretroviral treatment (including early ART initiation) and ART de-intensification. Exploratory analyses examined effect over time of baseline IQ and inclusion of efavirenz in ART regimen.

Results

Table 1. Enrollment and attrition

Time Point	Group 1 > 350; starting ART		Group 2 > 350; ART monitored per SOC		Group 3 < 350; starting ART per SOC	
	Count	Percent	Count	Percent	Count	Percent
Baseline	56	100.0	66	100.0	59	100.0
Week 24	52	92.9	63	95.5	56	94.9
Week 48	48	85.7	53	80.3	50	84.7
Week 96	48	85.7	45	68.2	46	78.0
Week 144	47	83.9	44	66.7	46	78.0

Figure 1. Change in VL and CD4 by group

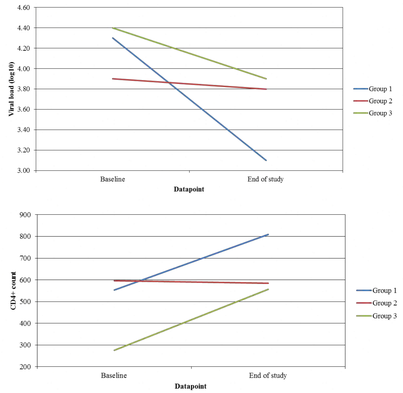
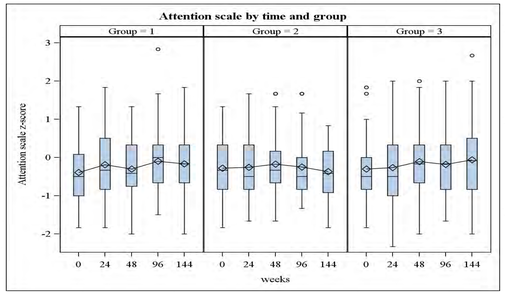
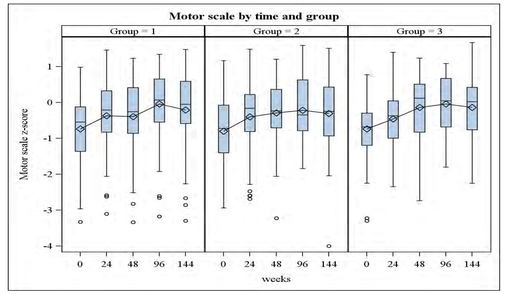


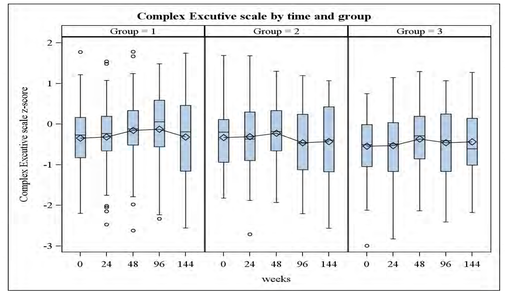
Table 3. Demographic characteristics

	Count/ Mean	Percent/ Std. Dev.
Age (years)	21.0	21.0
Male gender	146	80.7
Race/Ethnicity		
Hispanic	41	22.7
Non-Hispanic White	13	7.2
Non-Hispanic Black/African American	118	65.2
Asian/Pacific Islander	4	2.2
Other or Mixed Race	5	2.8
Language at home		
English	172	95.0
Spanish	7	3.9
Other	2	1.1
Level of education		
Eighth grade or less	5	2.8
Not completed high school	45	24.9
High school graduate	51	28.2
Some education after high school	70	38.7
College graduate	10	5.5
Repeated a grade	39	21.5
Special class or education	41	22.7
Past year income		
< $6,000	121	66.9
$6,000 - $35,999	55	30.4
Refused to answer	2	1.1
Unknown	3	1.7
Potential impact of comorbid diagnoses at baseline		
Severe	10	5.5
Moderate	59	33.7
Mild	16	10.0
None	89	50.8

Results







- All three index scores increased from baseline and peaked at week 96, then leveled or decreased slightly (Fig. 2-4). Significantly lower attention index functioning at baseline was seen in youth who were Hispanic, had education risk, or diagnoses with potentially severe impact. Lower motor index scores at baseline were associated with female gender, and diagnoses with severe or moderate potential impact. Lower complex executive index was seen for youth who were older, non-Hispanic Black, or Hispanic, had education risk, or severe potential impact of diagnoses.
- There were no significant differences between treatment groups at baseline or in change over time. No differences were associated with ART de-intensification (n=36) or efavirenz (n=37).
- Higher Full-scale IQ at baseline was associated with higher index scores at baseline and greater improvement in motor/psychomotor index scores over time.
- Follow-up analysis compared change over time for youth who never initiated ART (N=36), youth on ART with sustained viral suppression over all time points (N=56), and youth with inconsistent or no viral suppression (N=83). Groups did not differ in neurocognitive change.

Conclusions

- Treatment-naïve youth with behaviorally acquired HIV followed for three years showed improvement over time in neurocognitive functioning that was independent of ART initiation or timing of initiation (CD4 above or below 350). Improvement could be related to practice effects or nonspecific effects of engagement in care.
- Sustained viral suppression over three years was not associated with greater improvement; neither was there evidence of neurotoxicity.
- ART de-intensification was not associated with change over time; thus, there is no evidence of more or less improvement with de-intensification.
- The measures selected for the study have been shown to be sensitive to change in HIV disease severity in adults and showed expected associations with demographic and other factors, suggesting poor sensitivity is not a likely explanation for the lack of association between HIV disease indicators and change in neurocognitive measures.
- Analyses accounted for other risks to neurocognitive functioning such as substance use, premorbid educational risk, depression and distress, and demographic factors associated with poverty and educational disadvantage. Adherence was measured. Lower global functioning at baseline appears to be associated with less motor/psychomotor improvement over time.
- Relationships with study covariates suggest some observed impairments may be at least partly due to preventable or modifiable factors. Exploration of other effective pharmacologic, cognitive, and behavioral interventions for management of cognitive impairments in youth with HIV may be warranted.
- Adolescents with behaviorally acquired HIV may be at heightened risk for impairments resulting from early subclinical neuroimmune events such as immune activation and inflammation that are not ameliorated by ART. Regimens used in this study had little variability in CNS penetrance and further research is needed to assess its role in neurocognitive impact of treatment in youth.

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