ONLINE FIRST

Human Immunodeficiency Virus Disease Severity, Psychiatric Symptoms, and Functional Outcomes in Perinatally Infected Youth

Sharon Nachman, MD; Miriam Chernoff, PhD; Paige Williams, PhD; Janice Hodge, RN, BS; Jerry Heston, MD; Kenneth D. Gadow, PhD

Objective: To evaluate associations between human immunodeficiency virus (HIV) disease severity and psychiatric and functional outcomes in youth with perinatal HIV infection.

Design: Cross-sectional analysis of entry data from an observational, prospective 2-year study. Logistic and linear regression models adjusted for potential confounders were used.

Setting: Twenty-nine sites of the International Maternal Pediatrics Adolescent AIDS Clinical Trials Group study in the United States and Puerto Rico.

Participants: Youth aged 6 to 17 years who had HIV infection (N=319).

Main Exposures: Antiretroviral treatment and perinatal HIV infection.

Main Outcome Measures: Youth and primary caregivers were administered an extensive battery of measures that assessed psychiatric symptoms; cognitive, social, and academic functioning; and quality of life.

Results: Characteristics of HIV were a current CD4 percentage of 25% or greater (74% of participants), HIV RNA levels of less than 400 copies/mL (59%), and current highly active antiretroviral therapy (81%). Analyses indicated associations of past and current Centers for Disease Control and Prevention class C designation with less severe attention-deficit/hyperactivity disorder inattention symptoms, older age at nadir CD4 percentage and lower CD4 percentage at study entry with more severe conduct disorder symptoms, higher RNA viral load at study entry with more severe depression symptoms, and lower CD4 percentage at study entry with less severe symptoms of depression. There was little evidence of an association between specific antiretroviral therapy and severity of psychiatric symptoms. A lower nadir CD4 percentage was associated with lower quality of life, worse Wechsler Intelligence Scale for Children Coding Recall scores, and worse social functioning.

Conclusion: Human immunodeficiency virus illness severity markers are associated with the severity of some psychiatric symptoms and, notably, with cognitive, academic, and social functioning, all of which warrant additional study.

Trial Registration: clinicaltrials.gov Identifier: NCT00100542

Arch Pediatr Adolesc Med. 2012;166(6):528-535.
Published online February 6, 2012.
doi:10.1001/archpediatrics.2011.1785

Author Affiliations: Departments of Pediatrics (Dr Nachman) and Psychiatry and Behavioral Science (Dr Gadow), Stony Brook University, Stony Brook, New York; Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts (Drs Chernoff and Williams); Frontier Science and Technology Research Foundation, Amherst, New York (Ms Hodge); and Child and Adolescent Psychiatry Associates, PLLC, Cordova, Tennessee, and St Jude Children's Research Hospital, Memphis, Tennessee (Dr Heston).

SINCE THE ADVENT OF HIGHLY active antiretroviral therapy (HAART), perinatally human immunodeficiency virus–infected (HIV+) youth are surviving childhood in increasing numbers. We recently reported on a large sample of HIV+ youth (aged 6-18 years) and a comparison sample of control youth (exposed but not infected or living in a household with an HIV+ individual) in which we observed comparable rates of youth self-report of psychiatric symptoms (among HIV+ youth 12-17 years old, 24%; among controls, 33%).[1] Compared with controls, HIV+ youth received significantly higher rates of behavioral, educational, and pharmacological intervention (23% vs 12%), suggesting the possibility of a link between the virus or its pharmacological treatments and behavioral disturbance.[2] Unfortunately, few studies have examined this possibility in HIV+ youth, and there is little information about the short- and long-term effects of HIV illness severity or different forms of HAART on the development of neuropsychiatric symptoms.[3-8]

Mellins et al[9] examined 47 HIV+ youth aged 9 to 16 years who were recruited from a New York City HIV clinic population and did not find a significant association between HIV illness severity and development of psychiatric illnesses. In contrast, Wood and colleagues[10] found an association between a past Centers for Disease Control and Prevention (CDC) AIDS-defining illness (class C [CDC-C]) and an

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

increased risk of psychiatric impairment in a sample of 81 HIV+ adolescents. In that retrospective study, behavioral problems were assessed using the Conners Rating Scale[11] (completed by the teacher and caregiver), and psychiatric illnesses were reported by clinic physicians on the basis of symptoms. The authors did not find any significant associations with IQ. Smith et al[12] also examined the relation of HIV disease severity with psychiatric and cognitive outcomes and found that youth with past CDC-C diagnoses, especially those with encephalopathy, had slower processing speed than those who did not carry a CDC-C diagnosis.

Owing to the well-documented role of behavioral disturbance and cognitive impairment on social and academic difficulties, as well as risky sexual behavior in adolescents (and their implications for disease transmission), it is critical to better understand the true relation of HIV disease severity measures and attendant therapies with the severity of psychiatric symptoms in HIV+ youth as they age. The present study examines these issues in a large, geographically representative, well-characterized sample of HIV+ youth who were evaluated prospectively with well-validated measures of *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) symptoms.

METHODS

International Maternal Pediatrics Adolescent AIDS Clinical Trials Group (IMPAACT) study P1055 is a prospective, multisite, 2-year observational study designed to enroll similar numbers of HIV+ and control participants within each of 4 age (<12 or ≥12 years) and sex subgroups across the 29 research sites. Youth must have lived with the same primary caregiver for at least 12 months prior to study entry; youth with known mental retardation (IQ <70 or special education evaluations) were excluded. This report focuses on the HIV+ participants, who are described in detail in **Table 1**.

Information about study participants and their families was gathered through interviews and self-completed instruments.[1,2] Participants could return to complete interviews within 90 days of the study visit if more time was needed. Staff members were available to read the questions (both English and Spanish) to informants as needed. This study was approved by an institutional review board at each IMPAACT site. Written informed consent was obtained from primary caregivers, and assents were obtained from youth as allowed by local institutional review boards. Each participating site submitted a site implementation plan regarding psychiatric referrals and unintended HIV disclosure, recruitment and retention, incentives, and quality control.

MEASURES

Youth and primary caregivers completed *DSM-IV*–referenced rating scales. The Child and Adolescent Symptom Inventory–4R (CASI-4R)[13-15] is a validated 147-item, caregiver-completed scale for evaluating children and adolescents aged 5 to 18 years; individual items correspond to *DSM-IV* symptoms and are rated on a 4-point Likert scale (0 indicates never; 3, very often). Items are summed to generate a symptom severity score for each disorder. Items rated "often" and "very often" are used to determine whether an individual meets *DSM-IV* symptom criteria for a specific disorder (ie, symptom criteria). Finally, for each disorder, informants are asked whether symptoms interfere with social or academic functioning (rat-

Table 1. Participant Characteristics

Characteristic	HIV-Infected, No. (%) (N = 319)
Male sex	163 (51)
Age at entry, mean (SD), y	12.9 (3.1)
≥12 y	199 (62)
Ethnicity	
White, non-Hispanic	40 (13)
Black, non-Hispanic	173 (54)
Hispanic, all ethnicities	102 (32)
Other	4 (1)
HIV Treatment	
ARV group at study entry	
HAART with PI only	180 (56)
HAART with NNRTI only	47 (15)
HAART with PI + NNRTI	32 (10)
1-2 NRTIs	12 (4)
≥3 NRTIs	13 (4)
Other combination therapy	8 (3)
Not receiving ARVs	27 (8)
Receiving efavirenz at study entry[a]	61 (19)
Duration of HAART at study entry, y	
Mean (SD) [range]	5.44 (2.89) [0.0-11.3]
Median (Q1-Q3)	6.5 (3.3-7.7)
Receiving HAART for ≥5 y	204 (64)
Receiving PI for ≥5 y	186 (58)
HIV Disease at Study Entry	
HIV RNA VL, copies/mL[a]	
0-400	189 (59)
401-10 000	64 (20)
10 001-100 000	49 (15)
>100 000	16 (5)
CD4 percentage, %	
0-14	22 (7)
15-24	62 (19)
≥25	235 (74)
CD4 count, cells/μL	
0-199	19 (6)
200-499	70 (22)
500-749	97 (30)
750-999	63 (20)
≥1000	70 (22)
HIV Disease History	
CDC class C	73 (23)
Peak HIV RNA VL, copies/mL	
0-400	6 (2)
401-10 000	23 (7)
10 001-100 000	104 (33)
>100 000	178 (56)
Missing	8 (3)
Nadir CD4 percentage, %	
0-14	130 (41)
15-24	102 (32)
≥25	79 (25)
Missing	8 (3)
Age at nadir CD4 percentage, mean (SD), y	7.6 (4.6)
Age at peak HIV VL, mean (SD), y	6.9 (4.8)

Abbreviations: ARV, antiretrovirals; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q, quartile; VL, viral load.

[a] One missing value.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

ings of "often" or "very often" indicate functional impairment). Individuals who have the prerequisite number of *DSM-IV* symptoms (symptom criteria) plus functional impairment meet clinical criteria for a specific disorder. Primary caregivers also completed a validated parallel self-assessment tool, the Adult Self-report Inventory–4.[16]

Youth self-reports of psychiatric symptoms were collected by 2 instruments according to prespecified age groups. The Youth's (Self-report) Inventory–4[17,18] is a 128-item self-report rating scale for youth aged 12 to 18 years, with items parallel to those in the CASI-4R. The Child (Self-report) Inventory–4[19] contains 34 items parallel to the Youth's (Self-report) Inventory–4 but for young children (8-11 years) and does not assess impairment. All screening tools used were available in validated Spanish translations.

Two subscales of the Wechsler Intelligence Scale for Children–Fourth Edition Integrated (WISC-IV)[20] were administered to provide an indication of the participant's working memory (Letter-Number Sequencing) and processing speed (Coding Recall). These subscales were selected to minimize language, cultural, or educational influences and response burden.

Additional measures were completed by caregivers. These included assessment of the youth's quality of life, including overall, physical, and emotional health and performance of daily activities (scored 0-10, with 10 representing the best health); the School Functioning Scale,[21] which assesses academic performance, special education, and grade retention (scored 0-10; a high value indicates poor functioning); the Social Functioning Scale,[21] which assesses peer relations (scored 0-10; a high value indicates poor functioning); and the Parent Questionnaire,[21] which obtains information about treatment history (eg, psychotropic medication, behavioral therapies, and hospitalization).

Laboratory data related to HIV infection included lifetime nadir and current CD4 counts and CD4 percentages and lifetime peak and current viral loads. Each participant's HIV classification and treatment data included CDC-C classification, current receipt of HAART (defined as ≥3 antiretroviral medications from ≥2 classes), years of HAART exposure, and current or past exposure to efavirenz. Information regarding family demographics and characteristics, including the participant's relationship to household members who were known to be HIV+, was also recorded.

STATISTICAL ANALYSIS

We assessed the presence and severity of 7 psychiatric conditions within 4 broad psychiatric domains: attention-deficit/hyperactivity disorder (ADHD), depression (major depressive episode or dysthymia), disruptive behavior disorder (oppositional defiant disorder [ODD] or conduct disorder [CD]), and anxiety (generalized anxiety disorder or separation anxiety disorder). Outcomes included symptom severity scores (youth and caregiver assessments) for psychiatric symptoms, WISC-IV subscale scores, academic and social functioning, and QOL.

We explored the relationship between the child's psychiatric status and the child's severity of HIV disease by using general estimating equation linear regression models for continuous outcomes and multiple logistic regression analyses for dichotomous outcomes, controlling for a priori potential confounders: age group (<12 vs ≥12 years), sex, relation to caregiver (whether the caregiver was a biological parent), caregiver educational level, life stressors in the preceding year (≥1 vs none), and caregiver psychiatric symptoms (ie, whether the caregiver met symptom criteria for ≥1 targeted disorder vs none). Participant IQ was not considered a potential confounder because an IQ of 70 or lower was an exclusion criterion and an IQ higher than 70 is minimally correlated with psychiatric symptoms.

A separate analysis was conducted for each combination of a psychiatric condition and a group of HIV disease severity markers reflecting past HIV disease (peak HIV RNA VL, nadir CD4 percentage, age [in years] at peak RNA VL, and nadir CD4 percentage) and current HIV disease (HIV RNA VL and CD4 percentage at study entry). For all analyses, we controlled for the absence or presence of CDC-C; therefore, the estimated effects of the other markers are over and above any effects of that variable. All models also evaluated possible links between prior use of efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI) considered to be associated with increased neuropsychiatric complications, and psychiatric outcomes. In a sensitivity analysis, we explored the independent effect of each of the HIV disease markers after controlling for personal and family characteristics and efavirenz exposure. Finally, to understand the ameliorating effects of treatment, we explored regression models based on current HIV treatment: HAART with a protease inhibitor (PI) only, HAART with an NNRTI only, HAART with a PI and an NNRTI, and past HIV treatment (≥5 years of HAART or ≥5 years of treatment with a PI).

In hypothesis testing, 2-sided $P<.05$ was considered statistically significant. However, given the large number of models fitted and predictors evaluated, the results are considered exploratory, and particular attention in interpretation was paid to consistency across analyses. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Inc), and are based on data submitted as of October 2007.

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS AND CAREGIVERS

Of the 319 HIV+ youths aged 6 to 17 years enrolled in IMPAACT P1055, 51% were male and 62% were 12 years or older at study entry. Most (81%) were receiving HAART at study entry, with 8% not receiving therapy. About one-quarter (23%) were classified as CDC-C, 74% had a current CD4 percentage of 25% or greater, and 59% had HIV RNA levels of less than 400 copies/mL at study entry (Table 1).

Half the participants (52%) lived with their HIV+ biological mother, with only 43% identified as the primary caregiver. Most (70%) had 1 or more additional HIV+ persons in the home, and 17% of the participants had an HIV+ sibling in the home.

Among the 37 primary caregivers who met *DSM-IV* symptom criteria for at least 1 psychiatric condition, 20 of their 37 children (54%) met symptom criteria for at least 1 of the 7 target disorders compared with 84 of 275 youth (31%) whose caregivers did not meet symptom criteria ($P=.01$)

One-third of HIV+ youth met *DSM-IV* symptom cutoff criteria for at least 1 of 7 targeted psychiatric illnesses as assessed by the caregiver or youth self-report (**Table 2**).

HIV DISEASE AND PSYCHIATRIC SYMPTOM SEVERITY (ADJUSTED ANALYSES)

Adjusted multivariate analysis (**Table 3**) revealed several significant associations of HIV disease markers with caregiver ratings of psychiatric symptom severity, but find-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

Table 2. Percentage of Youth Who Met Symptom Cutoffs for Targeted Psychiatric Conditions[a]

Condition	No./Total No. (%)		
	Youth or Caregiver Report	Youth Self-report[b]	Caregiver Report
Any condition	106/319 (33)	81/313 (26)	52/315 (17)
ADHD	56/317 (18)	19/199 (10)	44/314 (14)
Disruptive behavior	45/318 (14)	24/199 (12)	23/315 (7)
Depression	46/319 (14)	45/313 (14)	4/315 (1)
Anxiety	33/319 (10)	32/313 (10)	3/315 (1)

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.
[a] Targeted conditions include ADHD, disruptive behavior disorder (oppositional defiant disorder or conduct disorder), depression (dysthymia or major depressive episode), and anxiety (generalized anxiety or separation anxiety disorder).
[b] Older children assessed only for ADHD and disruptive behavior.

Table 3. Caregiver-Assessed CASI-4R Symptom Severity Scores[a]

Characteristic	ADHD-H		ADHD-I		CD		ODD		Depression[b]		Anxiety[c]	
	aM	*P* Value	aM	*P* Value	aM	*P* Value	aM	*P* Value	aM	*P* Value	aM	*P* Value
Disease History												
CDC class[d]												
C	5.9	.18	8.3	.04	1.6	.32	4.7	.24	8.5	.49	4.5	.93
N, A, B	6.8		9.8		1.9		5.3		8.0		4.4	
Peak RNA VL, copies/mL												
>100 000	6.0	.27	8.8	.54	1.8	.79	4.8	.66	8.3	.84	4.3	.31
0-100 000	6.8		9.3		1.7		5.1		8.2		4.6	
Nadir CD4 percentage, %												
0-14	6.6	.43	9.0	.82	1.9	.32	5.4	.09	8.2	.79	4.5	.60
≥15	6.1		9.1		1.6		4.5		8.3		4.4	
Age at peak HIV RNA VL[e]	−0.01	.90	0.09	.42	0.07	.13	0.00	.96	0.02	.82	0.02	.70
Age at nadir CD4 percentage[e]	0.07	.38	−0.01	.96	0.08	.03	0.12	.10	0.10	.22	0.02	.68
Current Status												
CDC class												
C	5.6	.18	7.9	.04	1.8	.76	4.7	.51	8.8	.40	4.4	.92
N, A, B	6.4		9.4		1.9		5.1		8.2		4.3	
Entry CD4 percentage, %												
0-24	6.4	.25	8.9	.49	2.2	.04	5.3	.19	7.7	.02	4.5	.48
≥25	5.6		8.4		1.5		4.5		9.2		4.2	
Entry HIV RNA VL, copies/mL												
>10 000	5.3	.19	7.3	.05	1.7	.85	4.5	.68	9.2	.01	4.0	.48
401-10 000	5.9		9.1		1.9		5.2		9.1		4.7	
0-400	6.7		9.5		1.8		5.0		7.1		4.4	

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADHD-H, ADHD hyperactive-impulsive; ADHD-I, ADHD inattention; aM, adjusted mean; CASI-4R, child and adolescent symptom inventory-4R; CASI-4R, Child and Adolescent Symptom Inventory–4R; CD, conduct disorder; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; ODD, oppositional defiant disorder; VL, viral load.
[a] Adjusted means and beta estimates are based on multiple regression analysis with HIV disease characteristics as predictors. Linear regression model also adjusted for age group, sex, use of efavirenz at study entry, caregiver's biological relationship, caregiver's educational level, life stressors during the preceding year, and caregiver's psychiatric status.
[b] Includes dysthymia and major depressive disorder.
[c] Includes generalized anxiety and separation anxiety disorders.
[d] Class N indicates no symptoms; A, mild symptoms; C, AIDS defined; and B, not A and not C (http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm).
[e] Data represent regression parameter estimates.

ings were mixed. Specifically, a lower CD4 percentage at study entry was associated with more severe CD symptoms but with less severe depression symptoms. A higher entry RNA VL was associated with more severe depression symptoms but also with less severe ADHD inattention (ADHD-I) symptoms. Being classified as CDC-C was associated with less severe ADHD-I symptoms. Older age at the nadir CD4 percentage was associated with more severe CD and total severity for both ODD and CD. In similar analyses for youth self-reported psychiatric symptom severity (data not shown), a lower CD4 percentage at study entry was associated with more severe CD symptoms, and a lower nadir CD4 percentage (0%-14% vs >14%) was associated with less severe ADHD-I symptoms. Sensitivity analyses corroborated these results (data not shown).

SPECIFIC HIV TREATMENT AND PSYCHIATRIC SYMPTOM SEVERITY

Evaluations investigating HAART regimens did not show any consistent associations between specific current or past HAART regimens and severity of the 7 targeted psy-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

Table 4. Quality of Life and Cognitive, Academic, and Social Functioning Scores[a]

Characteristic	QOL/Health[b] aM	QOL/Health[b] *P* Value	Letter-Number Sequencing[b] aM	Letter-Number Sequencing[b] *P* Value	Coding Recall[b] aM	Coding Recall[b] *P* Value	Academic Functioning[c] aM	Academic Functioning[c] *P* Value	Social Functioning[c] aM	Social Functioning[c] *P* Value
Disease History										
CDC class[d]										
C, severely symptomatic	7.6	.30	7.8	.29	7.9	.99	3.0	.38	2.1	.72
N, A, B	7.9		8.3		7.9		2.7		2.1	
Exposure to efavirenz										
Yes	7.9	.10	7.5	.01	7.7	.44	2.6	.04	1.9	.18
No	7.5		8.6		8.0		3.2		2.2	
Peak RNA VL, copies/mL										
>100 000	7.9	.05	7.9	.37	7.5	.04	2.8	.56	2.0	.20
0-100 000	7.5		8.2		8.2		3.0		2.2	
Nadir CD4 percentage, %										
0-14	7.4	<.001	8.1	.71	7.5	.04	3.1	.21	2.3	.03
≥15	8.1		8.0		8.2		2.7		1.9	
Age at peak HIV RNA VL[e]	0.07	.03	−0.02	.79	0.03	.63	0.02	.65	−0.01	.69
Age at nadir CD4 percentage[e]	−0.09	<.001	−0.04	.49	−0.08	.09	0.02	.53	0.00	.99
Current Status										
CDC class										
C, severely symptomatic	7.6	.16	7.6	.21	7.7	.56	3.1	.27	2.1	.97
Entry CD4 percentage, %										
0-24	7.7	.34	7.2	.01	7.4	.08	3.3	.07	2.2	.23
≥25	7.9		8.4		8.2		2.7		1.9	
Entry HIV RNA VL, copies/mL										
>10 000	8.0	.16	8.4	.13	7.9	.84	2.7	.31	1.8	.23
401-10 000	7.4		7.2		7.8		3.3		2.1	
0-400	7.9		7.8		7.7		2.9		2.2	

Abbreviations: aM, adjusted mean; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; QOL, quality of life; VL, viral load.
[a] Adjusted means and beta estimates based on multiple regression analyses with HIV disease characteristics as predictors. Linear regression model also adjusted for age group, sex, caregiver's biological relationship, caregiver education, life stressors during the preceding year, and caregiver's psychiatric status.
[b] Higher score indicates better functioning.
[c] Higher score indicates poorer functioning.
[d] Class N indicates no symptoms; A, mild symptoms; C, AIDS defined; and B, not A and not C (http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm).
[e] Data represent regression parameter estimates.

chiatric disorders (data not shown). No efavirenz effects were found in the multivariate models. Although the findings were mixed, there was some evidence that treatment with a HAART regimen containing a PI or an NNRTI was associated with less severe (youth self-reported) ADHD-I symptoms ($P=.05$ for each), and treatment with a regimen of HAART and a PI was associated with less severe ADHD-I symptoms according to the caregiver's evaluation ($P=.04$).

HIV DISEASE SEVERITY AND TREATMENT AND SOCIAL AND ACADEMIC FUNCTIONING

Relatively few associations between HIV illness characteristics and functional outcomes were significant (**Table 4**). Youth with a lower nadir CD4 percentage, older age at the nadir CD4 percentage, and younger age at the peak VL had lower QOL. Youth with a higher peak VL (>100 000 copies/mL) and a lower nadir CD4 percentage (<15%) had lower Coding Recall scores. A lower nadir CD4 percentage was also associated with worse social functioning.

Experience with efavirenz was associated with lower Letter-Number Sequencing scores but with better academic functioning (Table 4). Youth who were following a HAART regimen with a PI only at study entry had higher QOL ($P=.03$) (data not shown). Youth with 5 or more years of HAART had better social functioning ($P=.02$) but lower Coding Recall scores ($P=.01$). However, there were subtle differences depending on the HAART regimen. Youth with 5 or more years of PI exposure had worse social functioning ($P=.05$) and lower WISC-IV Letter-Number Sequencing scores ($P=.03$).

COGNITIVE, SOCIAL, AND ACADEMIC FUNCTIONING

Youth who met *DSM-IV* symptom criteria for ADHD had lower health ratings, lower Coding Recall scores, and worse academic and social functioning than did youth without symptoms of ADHD (**Table 5**). Children who met symptom criteria for depression had poorer academic functioning and lower overall health ratings (composite score for all QOL items) than did those without depression.

COMMENT

A major concern for health professionals is the possibility that severity of HIV illness or specific HAART regimens may be associated with increased risk for mental health prob-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

Table 5. Group Differences for Youth Who Did and Did Not Meet *DSM-IV* Symptom Criteria for ADHD or Depression

	ADHD			Depression		
	No (n = 261)	Yes (n = 56)	*P* Value	No (n = 273)	Yes (n = 46)	*P* Value
Health rating[a,b]						
Mean (SD) score	8.24 (1.71)	7.39 (1.74)	<.001[c]	8.18 (1.70)	7.63 (1.95)	.04[c]
Problem, No. (%)	19 (7)	9 (16)	.06[d]	22 (8)	6 (13)	.27[d]
Missing	5	1		6	0	
WISC-IV Coding Recall[b]						
Mean (SD) score	8.17 (3.04)	7.06 (3.05)	.007[c]	8.07 (3.13)	7.49 (2.62)	.21[c]
Problem, No. (%)	14 (6)	7 (13)	.08[d]	18 (7)	3 (7)	1.00[d]
Missing	23	2		22	3	
Academic functioning[e]						
Mean (SD) score	2.40 (2.03)	4.07 (2.54)	<.001[c]	2.56 (2.12)	3.40 (2.60)	.05[c]
Problem, No. (%)	15 (6)	12 (23)	<.001[d]	21 (8)	6 (13)	.27[d]
Missing	10	4		14	0	
Social functioning[e]						
Mean (SD) score	1.74 (1.37)	2.54 (1.61)	<.001[c]	1.82 (1.42)	2.17 (1.52)	.09[c]
Problem, No. (%)	11 (4)	6 (11)	.09[d]	14 (5)	3 (7)	.73[d]
Missing	6	2		8	0	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition Integrated.

[a] Composite score for all quality of life questions.

[b] A higher score indicates better functioning; a problem is represented by a score less than the 10th percentile.

[c] By Wilcoxon rank sum test.

[d] By Fisher exact test.

[e] A higher score indicates poorer functioning; a problem is represented by a score greater than the 90th percentile.

lems. A third of youth in our study met *DSM-IV* symptom cutoff criteria for at least 1 targeted psychiatric disorder. Analyses of HIV disease variables and severity of psychiatric symptoms revealed few specific associations, and we feel compelled to emphasize that findings were variable, mixed, and at times counterintuitive. For example, a lower entry CD4 percentage was associated with less severe depression, but a higher entry RNA VL was associated with more severe depression.

There was some evidence of an association of HIV variables with QOL and cognitive, social, and academic functioning. Specifically, a younger age at peak VL was associated with lower QOL scores, whereas a lower nadir CD4 percentage was associated with poorer QOL, social performance, and Coding Recall scores, suggesting that a higher viral load at a younger age or severe immune suppression may influence these functions. In fact, participants who were older at their nadir CD4 percentage had worse QOL. A higher peak VL was associated with slower WISC-IV processing speed (Coding Recall). Perhaps poorer immunologic or virologic control at different ages affects different brain functions. This is consistent with the finding by Smith et al[12] that a prior CDC-C diagnosis was related to more deficits in cognitive functioning than in adaptive functioning. We found that more severe HIV disease (indicated by the nadir CD4 percentage) was associated with worse cognitive functioning and social skills, but our analyses do not allow us to make causal inferences about these associations. Our data, in conjunction with findings from other groups, suggest that receptive language, word recognition, and educational problems are common in youth with perinatal HIV infection regardless of virologic suppression.[22,23] The significance of our results is that it extends previous research findings to a large age-stratified, geographically representative, HAART-treated population.

Whereas 81% of study youth were receiving HAART, only 59% had virologic success (defined as an undetectable viral load), suggesting that resistance and nonadherence to a treatment regimen may be independent HIV disease severity issues for some individuals. The relation of treatment adherence (or lack thereof) with current CD4 percentage and control of viral replication cannot be ignored, suggesting that using current HIV laboratory values as assessment tools for measuring current overall central nervous system functioning may not be possible.

Similar to our study, Piazza-Waggoner and colleagues[24] reported on a cohort of children with primary immunodeficiencies and found significant behavioral issues; youth with the most severe immunity issues had the worst behavioral problems. Smith and colleagues[25] reported that parents' depressive symptoms were positively associated with their children's psychological symptoms (odds ratio, 1.6-2.4) and psychosocial functioning (odds ratio, 1.6 according to parental report). Although our study did not support a clear association between severe immune suppression and significant behavioral issues, the concern that HIV infection in the family environment may affect the entire family, producing higher levels of anxiety and depression in all members at risk for these psychiatric comorbidities, is a consideration. Although primary care providers may or may not have immunodeficiencies, their mental health and coping issues likely influence their parenting ability, perhaps affecting treatment adherence and virologic outcomes in their children. Future analyses will need to address these issues.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

Our results are subject to several qualifications. One major limitation of a cross-sectional study is the inability to draw causal inferences about obtained associations. For example, it is possible that youth who were the sickest at a younger age (represented by the nadir CD4 percentage) experienced specific neurotoxic sequelae leading to long-term issues with social functioning. It is also possible, for example, that ODD/CD symptoms contributed to disease severity mediated by poor adherence to treatment. In our study, age at nadir CD4 percentage did not associate consistently with a specific psychiatric symptom. Those who were older at their nadir CD4 percentage had only more severe disruptive behaviors, suggesting the multifactorial effect that the virus, treatment, and immune function (as measured by CD4 percentage) had on brain functioning. This study was not developed to tease apart the differential impact of the virus, immune function, HIV therapies, and their interactions on the developing brain of children treated for HIV infection since early infancy. Finally, our primary objective was to determine whether HIV illness variables are associated with the severity of symptoms and with functioning separate from other variables (eg, substance use) known to be associated with these outcomes. Future studies will need to address their combined and interactive effects.

Accepted for Publication: December 7, 2011.
Published Online: February 6, 2012. doi:10.1001/archpediatrics.2011.1785
Correspondence: Sharon Nachman, MD, Department of Pediatrics, Stony Brook University, Health Sciences Center T-11, Room 031, Stony Brook, NY 11794 (sharon.nachman@stonybrook.edu).
Author Contributions: *Study concept and design:* Nachman, Williams, Hodge, Heston, and Gadow. *Acquisition of data:* Nachman and Hodge. *Analysis and interpretation of data:* Nachman, Chernoff, Williams, and Gadow. *Drafting of the manuscript:* Nachman, Chernoff, Hodge, and Gadow. *Critical revision of the manuscript for important intellectual content:* Nachman, Chernoff, Williams, Heston, and Gadow. *Statistical analysis:* Nachman, Chernoff, and Williams. *Obtained funding:* Nachman, Williams, and Gadow. *Administrative, technical, and material support:* Nachman, Hodge, and Gadow. *Study supervision:* Nachman, Williams, and Gadow. *Data management:* Hodge.
Financial Disclosure: None reported.
Funding/Support: Overall support for IMPAACT was provided by grant U01 AI068632 from the National Institute of Allergy and Infectious Diseases (NIAID), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and grant AI068632 from the National Institute of Mental Health (NIMH). This work was supported by the Statistical and Data Analysis Center at Harvard School of Public Health under the National Institute of Allergy and Infectious Diseases cooperative agreements #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group. Support of the sites was provided by NIAID and the NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network funded by NICHD (contract number N01-DK-9-001/HHSN267200800001C).
Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Additional Information: The following institutions and individuals participated in IMPAACT P1055: 2901 (IMPAACT site code)—Division of Infectious Diseases, Harvard Medical School, Children's Hospital Boston, Boston, Massachusetts: Sandra Burchett; 3601—University of California, Los Angeles (UCLA)/Brazil AIDS Consortium Clinical Research Site (CRS): Karin Nielsen, Nicole Falgout, Joseph Geffen, and Jaime G. Deville; 3606—Miller Children's Hospital Long Beach, Long Beach Memorial Medical Center, Long Beach, California: Audra Deveikis; 3609—Division of Infectious Diseases, Department of Pediatrics, Harbor UCLA Medical Center: Margaret Keller; 3702—Division of Pediatrics, Immunology & Rheumatology, University of Maryland Medical Center, Baltimore: Vicki Tepper; 4001—Chicago Children's CRS, Chicago, Illinois: Ram Yogev; 4501—Pediatric AIDS CRS, University of California, San Francisco, San Francisco, California: Diane Wara; 4601—Maternal, Child, and Adolescent HIV CRS, University of California, San Diego: Stephen A. Spector, Lisa Stangl, Mary Caffery, and Rolando Viani; 4701—Pediatrics CRS, Duke University Medical Center, Durham, North Carolina: Kareema Whitfield, Sunita Patil, Joan Wilson, and Mary Jo Hassett; 5012—NICHD CRS, New York University, New York, New York: Sandra Deygoo, William Borkowsky, Sulachni Chandwani, and Mona Rigaud; 5013—NICHD CRS, Jacobi Medical Center, Bronx, New York: Andrew Wiznia; 5017—NICHD CRS, University of Washington, Seattle Children's Hospital, Seattle: Lisa Frenkel; 5018—NICHD CRS, University of South Florida, Tampa: Patricia Emmanuel, Jorge Lujan Zilberman, Carina Rodriguez, and Carolyn Graisbery; 5026—Mount Sinai School of Medicine, New York: Roberto Posada and Mary S. Dolan; 5031—NICHD CRS, San Juan City Hospital, San Juan, Puerto Rico: Midnela Acevedo-Flores, Lourdes Angeli, Milagros Gonzalez, and Dalila Guzman; 5038—Division of Infectious Diseases, Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut: Warren A. Andiman, Leslie Hurst, and Anne Murphy; 5039—Department of Pediatrics, State University of New York (SUNY) Upstate Medical University, Syracuse: Leonard Weiner; 5040—NICHD CRS, SUNY Stony Brook, Stony Brook: Denise Ferraro, Michele Kelly, and Lorraine Rubino; 5044—NICHD CRS, Howard University, Washington, DC: Sohail Ranal; 5048—NICHD CRS, University of Southern California, Los Angeles: Suad Kapetanovic; 5051—NICHD CRS, University of Florida, Jacksonville: Mobeen H. Rathore, Ayesha Mirza, Kathleen Thoma, and Chas Griggs; 5052—NICHD CRS, University of Colorado, Denver: Robin McEvoy, Emily Barr, Suzanne Paul, and Patricia Michalek; 5055—NICHD CRS, South Florida CDC, Ft Lauderdale: Ana Puga; 6501—St Jude/University of Tennessee Health Science Center CRS: Patricia Garvie; 6701—IMPAACT CRS, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania: Richard Rutstein; 6704—Saint Christopher's Hospital for Children, Philadelphia: Roberta LaGuerre; 6901—IMPAACT CRS, Bronx-Lebanon Hospital Center, Bronx: Murli Purswani; 6905—Metropolitan Hos-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 06/19/2013

pital Center, New York: Mahrukh Bamji; and 7301—Western New England Maternal Pediatric Adolescent AIDS CRS: Katherine Luzuriaga.

Additional Contributions: We acknowledge the helpful comments of anonymous reviewers. Kimberly Hudgens, MSHCA, MBA, provided operational support of this study.

REFERENCES

1. Gadow K, Chernoff M, Williams PL, et al. Co-occurring psychiatric symptoms in children perinatally infected with HIV and peer comparison sample. *J Dev Behav Pediatr*. 2010;31(2):116-128.
2. Chernoff M, Nachman S, Williams P, et al; IMPAACT P1055 Study Team. Mental health treatment patterns in perinatally HIV-infected youth and controls. *Pediatrics*. 2009;124(2):627-636.
3. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. *Annu Rev Med*. 2010;61:169-185.
4. Havens JF, Whitaker AH, Feldman JF, Ehrhardt AA. Psychiatric morbidity in school-age children with congenital human immunodeficiency virus infection: a pilot study. *J Dev Behav Pediatr*. 1994;15(3)(suppl):S18-S25.
5. Misdrahi D, Vila G, Funk-Brentano I, Tardieu M, Blanche S, Mouren-Simeoni MC. *DSM-IV* mental disorders and neurological complications in children and adolescents with human immunodeficiency virus type 1 infection (HIV-1). *Eur Psychiatry*. 2004;19(3):182-184.
6. Pao M, Lyon M, D'Angelo LJ, Schuman WB, Tipnis T, Mrazek DA. Psychiatric diagnoses in adolescents seropositive for the human immunodeficiency virus. *Arch Pediatr Adolesc Med*. 2000;154(3):240-244.
7. Scharko AM. *DSM* psychiatric disorders in the context of pediatric HIV/AIDS. *AIDS Care*. 2006;18(5):441-445.
8. Shanbhag MC, Rutstein RM, Zaoutis T, Zhao H, Chao D, Radcliffe J. Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy. *Arch Pediatr Adolesc Med*. 2005;159(7):651-656.
9. Mellins CA, Brackis-Cott E, Dolezal C, Abrams EJ. Psychiatric disorders in youth with perinatally acquired human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2006;25(5):432-437.
10. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. The impact of AIDS diagnoses on long-term neurocognitive and psychiatric outcomes of surviving adolescents with perinatally acquired HIV. *AIDS*. 2009;23(14):1859-1865.
11. Conners CK. *Conners' Rating Scales: Revised Technical Manual*. North Towanda, NY: Multi-Health Systems; 1997.
12. Smith R, Chernoff M, Rutstein R, et al; Pediatric HIV/AIDS Cohort Study. The long-term impact of HIV disease severity on cognitive and adaptive functioning during childhood and adolescence [abstract 861]. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 17, 2010; San Francisco, California.
13. Gadow KD, Sprafkin J. *Child and Adolescent Symptom Inventory–4R*. Stony Brook, NY: Checkmate Plus; 2005.
14. Gadow KD, Sprafkin J. *Stony Brook Child Psychiatric Checklist–3*. Stony Brook: Dept of Psychiatry, State University of New York, Stony Brook; 1986.
15. Gadow KD, Sprafkin J. The symptom inventories: an annotated bibliography. Checkmate Plus. Revised: February 15, 2011. http://www.checkmateplus.com. Accessed July 5, 2011.
16. Gadow KD, Sprafkin J. *Adult Self-report Inventory–4 Manual*. Stony Brook, NY: Checkmate Plus; 2004.
17. Gadow KD, Sprafkin J. *Youth's Inventory–4 Manual*. Stony Brook, NY: Checkmate Plus; 1999.
18. Gadow KD, Sprafkin J, Carlson GA, et al. A *DSM-IV*–referenced, adolescent self-report rating scale. *J Am Acad Child Adolesc Psychiatry*. 2002;41(6):671-679.
19. Gadow KD, Sprafkin J. *Child Self Report Inventory–4*. Stony Brook, NY: Checkmate Plus; 2004.
20. Kaplan E, Fein D, Maerlander A, Morris R, Kramer J. *Wechsler Intelligence Scale for Children (4th Edition Integrated)*. San Antonio, TX: Psychological Corp; 2004.
21. Gadow KD, Devincent C, Schneider J. Predictors of psychiatric symptoms in children with an autism spectrum disorder. *J Autism Dev Disord*. 2008;38(9):1710-1720.
22. Souza E, Santos N, Valentini S, Silva G, Falbo A. Long-term follow-up outcomes of perinatally HIV-infected adolescents: infection control but school failure. *J Trop Pediatr*. 2010;56(6):421-426.
23. Brackis-Cott E, Kang E, Dolezal C, Abrams EJ, Mellins CA. The impact of perinatal HIV infection on older school-aged children's and adolescents' receptive language and word recognition skills. *AIDS Patient Care STDS*. 2009;23(6):415-421.
24. Piazza-Waggoner C, Adams CD, Cottrell L, Taylor BK, Wilson NW, Hogan MB. Child and caregiver psychosocial functioning in pediatric immunodeficiency disorders. *Ann Allergy Asthma Immunol*. 2006;96(2):298-303.
25. Smith Fawzi MC, Eustache E, Oswald C, et al. Psychosocial functioning among HIV-affected youth and their caregivers in Haiti: implications for family-focused service provision in high HIV burden settings. *AIDS Patient Care STDS*. 2010;24(3):147-158.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013