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

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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 Pediatric 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 inattentive 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.

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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 \(^1^1\) (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 \(^1^2\) 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 meningoencephalitis had slower processing speed than those who did not carry a CDC-C diagnosis.

**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) \(^1^3\) 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-
HIV relationship to household members who were known to ily demographics and characteristics, including the participant’s rent or past exposure to efavirenz. Information regarding fam-

was an exclusion criterion and an IQ higher than 70 is mini-

sification and treatment data included CDC-C classification,

medication, behavioral therapies, and hospitalization).

obtains information about treatment history (eg, psychotropic

419 contains 34 items parallel to the Youth’s (Self-report) In-

ventory–417,18 is a 128-item self-report

Items parallel to the Youths (Self-report) Inventory–417,18 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’s (Self-report) Inventory–

contains 34 items parallel to the Child’s (Self-report) In-

ventory–4 but for young children (8-11 years) and does not ass-

essment. 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 pro-

vide 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 edu-

cational influences and response burden.

Additional measures were completed by caregivers. These in-

cluded assessment of the youth’s quality of life, including over-

all, physical, and emotional health and performance of daily ac-

tivities (scored 0-10, with 10 representing the best health); the

School Functioning Scale,21 which assesses academic perfor-

mance, special education, and grade retention (scored 0-10; a high

value indicates poor functioning); the Social Functioning Scale,

which assesses peer relations (scored 0-10; a high value indi-


cates 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 life-
time peak and current viral loads. Each participant’s HIV clas-

ification and treatment data included CDC-C classification,

current receipt of HAART (defined as ≥3 antiretroviral medica-
tions from ≥2 classes), years of HAART exposure, and cur-

rent or past exposure to efavirenz. Information regarding fam-

ily 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 condi-
tions within 4 broad psychiatric domains: attention-deficit/ hyperactivity disorder (ADHD), depression (major depressive episode or dysthymia), disruptive behavior disorder (opposi-
tional defiant disorder [ODD] or conduct disorder [CD]), and anxiety (generalized anxiety disorder or separation anxiety dis-

order). Outcomes included symptom severity scores (youth and
caregiver assessments) for psychiatric symptoms, WISC-IV sub-

scale scores, academic and social functioning, and QOL.

We explored the relationship between the child’s psychosomatic status and the child’s severity of HIV disease by using general esti-

mating equation linear regression models for continuous out-

comes and multiple logistic regression analyses for dichoto-

mous 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, 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 consid-

ered a potential confounder because an IQ of 70 or lower was an exclusion criterion and an IQ higher than 70 is mini-

mally correlated with psychiatric symptoms.

A separate analysis was conducted for each combination of a psychiatric condition and a group of HIV disease severity mark-

ers 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 ef-

fects 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 inhibi-
tor (NNRTI) considered to be associated with increased neu-
ropsychiatric complications, and psychiatric outcomes. In a sen-
sitivity analysis, we explored the independent effect of each of the HIV disease markers after controlling for personal and fam-

ily characteristics and efavirenz exposure. Finally, to under-

stand the ameliorating effects of treatment, we explored re-

gression 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 sta-

tistically significant. However, given the large number of mod-

els 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.

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 sev-

eral significant associations of HIV disease markers with
caregiver ratings of psychiatric symptom severity, but find-
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-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-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Youth or Caregiver Report</th>
<th>Youth Self-report</th>
<th>Caregiver Report</th>
</tr>
</thead>
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<td>Any condition</td>
<td>106/319 (33)</td>
<td>81/313 (26)</td>
<td>52/315 (17)</td>
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<td>ADHD</td>
<td>56/317 (18)</td>
<td>19/199 (10)</td>
<td>44/314 (14)</td>
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<td>Disruptive behavior</td>
<td>45/318 (14)</td>
<td>24/199 (12)</td>
<td>23/315 (7)</td>
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<td>Depression</td>
<td>46/319 (14)</td>
<td>45/313 (14)</td>
<td>4/315 (1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>33/319 (10)</td>
<td>32/313 (10)</td>
<td>3/315 (1)</td>
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**Table 2. Percentage of Youth Who Met Symptom Cutoffs for Targeted Psychiatric Conditions**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADHD-H</th>
<th>ADHD-I</th>
<th>CD</th>
<th>ODD</th>
<th>Depression&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Anxiety&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>aM</td>
<td>P Value</td>
<td>aM</td>
<td>P Value</td>
<td>aM</td>
<td>P Value</td>
</tr>
<tr>
<td>Disease History</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>CDC class&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5.9</td>
<td>.18</td>
<td>8.3</td>
<td>.04</td>
<td>1.6</td>
<td>.32</td>
</tr>
<tr>
<td>N, A, B</td>
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<td>9.8</td>
<td>1.9</td>
<td>.76</td>
<td>4.7</td>
<td>.51</td>
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<td>Peak RNA VL, copies/mL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 000</td>
<td>6.0</td>
<td>.27</td>
<td>8.8</td>
<td>.54</td>
<td>1.8</td>
<td>.79</td>
</tr>
<tr>
<td>0-100 000</td>
<td>6.8</td>
<td>9.3</td>
<td>1.7</td>
<td>.51</td>
<td></td>
<td></td>
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<td>Nadir CD4 percentage, %</td>
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<tr>
<td>0-14</td>
<td>6.6</td>
<td>.43</td>
<td>9.0</td>
<td>.82</td>
<td>1.9</td>
<td>.32</td>
</tr>
<tr>
<td>≥15</td>
<td>6.1</td>
<td>9.1</td>
<td>1.6</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at peak HIV RNA VL&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
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<td></td>
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<tr>
<td>-0.01</td>
<td>.90</td>
<td>0.09</td>
<td>.42</td>
<td>0.07</td>
<td>.13</td>
<td>0.00</td>
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<tr>
<td>Age at nadir CD4 percentage&lt;sup&gt;e&lt;/sup&gt;</td>
<td>.07</td>
<td>.38</td>
<td>0.96</td>
<td>0.08</td>
<td>.03</td>
<td>0.12</td>
</tr>
</tbody>
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**Table 3. Caregiver-Assessed CASI-4R Symptom Severity Scores**

<sup>a</sup>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).

<sup>b</sup>Older children assessed only for ADHD and disruptive behavior.

<sup>c</sup>Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-H, ADHD hyperactive-impulsive; ADHD-I, ADHD inattentive; aM, adjusted mean; CASI-4R, Child and Adolescent Symptom Inventory–4R; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; ODD, oppositional defiant disorder; VL, viral load.

<sup>d</sup>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.

<sup>e</sup>Includes dysthymia and major depressive disorder.

<sup>f</sup>Includes generalized anxiety and separation anxiety disorders.

<sup>g</sup>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).

<sup>h</sup>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.

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

<table>
<thead>
<tr>
<th></th>
<th>No (n = 261)</th>
<th>Yes (n = 56)</th>
<th>P Value</th>
<th>No (n = 273)</th>
<th>Yes (n = 46)</th>
<th>P Value</th>
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<tr>
<td>Mean (SD) score</td>
<td>8.24 (1.71)</td>
<td>7.39 (1.74)</td>
<td>&lt; .001c</td>
<td>8.18 (1.70)</td>
<td>7.63 (1.95)</td>
<td>.04c</td>
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<td>Problem, No. (%)</td>
<td>19 (7)</td>
<td>9 (16)</td>
<td>.06d</td>
<td>22 (8)</td>
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<tr>
<td>WISC-IV Coding Recallb</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean (SD) score</td>
<td>8.17 (3.04)</td>
<td>7.06 (3.05)</td>
<td>.007c</td>
<td>8.07 (3.13)</td>
<td>7.49 (2.62)</td>
<td>.21c</td>
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<td>Problem, No. (%)</td>
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<td>7 (13)</td>
<td>.08d</td>
<td>18 (7)</td>
<td>3 (7)</td>
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<td>23</td>
<td>2</td>
<td></td>
<td>22</td>
<td>3</td>
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<tr>
<td>Academic functioningc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) score</td>
<td>2.40 (2.03)</td>
<td>4.07 (2.54)</td>
<td>&lt; .001c</td>
<td>2.56 (2.12)</td>
<td>3.40 (2.60)</td>
<td>.05c</td>
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<tr>
<td>Problem, No. (%)</td>
<td>15 (6)</td>
<td>12 (23)</td>
<td>&lt; .001d</td>
<td>21 (8)</td>
<td>6 (13)</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD) score</td>
<td>1.74 (1.37)</td>
<td>2.54 (1.61)</td>
<td>&lt; .001c</td>
<td>1.82 (1.42)</td>
<td>2.17 (1.52)</td>
<td>.09c</td>
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<td>Problem, No. (%)</td>
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</table>

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 al22 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 colleagues24 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 colleagues25 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 parent 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.
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.

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