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Co-Occurring Psychiatric Symptoms in Children Perinatally Infected With HIV and Peer Comparison Sample

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Abstract

Objective—To compare the rates of psychopathology in youths perinatally infected with HIV (N = 319) with a comparison sample of peers (N = 256) either HIV-exposed or living in households with HIV-infected family members.

Method—Participants were randomly recruited from 29 sites in the United States and Puerto Rico and completed an extensive battery of measures including standardized DSM-IV-referenced ratings scales.

Results—The HIV+ group was relatively healthy (73% with CD4% >25%), and 92% were actively receiving antiretroviral therapy. Youths with HIV (17%) met symptom and impairment criteria for the following disorders: attention-deficit/hyperactivity disorder (12%), oppositional defiant disorder (5%), conduct disorder (1%), generalized anxiety disorder (2%), separation anxiety disorder (1%), depressive disorder (2%), or manic episode (1%). Many youths with HIV (27%) and peers (26%) were rated (either self- or caregiver report) as having psychiatric problems that interfered with academic or social functioning. With the exception of somatization disorder, the HIV+ group did not evidence higher rates or severity of psychopathology than peers, although rates for both groups were higher than the general population. Nevertheless, self-awareness of HIV infection in younger children was associated with more severe symptomatology, and youths with HIV had higher lifetime rates of special education (44 vs 32%), psychopharmacological (23 vs 12%), or behavioral (27 vs 17%) interventions. Youth-caregiver agreement was modest, and youths reported more impairment.

Conclusion—HIV infection was not associated with differentially greater levels of current psychopathology; nevertheless, investigation of relations with developmental changes and specific illness parameters and treatments are ongoing.

Index terms

HIV; ADHD; psychopathology; children; Child and Adolescent Symptom Inventory-4R; Youth's Self-Report Inventory-4R; Child's Self-Report Inventory-4

With the advent of life-prolonging antiretrovirals, HIV infection has become a chronic disease and is no longer the certain death sentence in children that it was in the pre-antiretroviral era. However, HIV does not just affect the immune system, it is also neurotropic, suggesting its effects may be seen differently at different developmental stages. Often, the first manifestation of HIV before the widespread availability of highly active antiretrovirals (HAART) was progressive encephalopathy. In the post-HAART era, there is a growing literature suggesting that neuropsychiatric illnesses may also be a manifestation of HIV. Compounding the direct and indirect effects of HIV on these growing brains are perhaps the long-term effects of antiretroviral therapies and various stressors (biologic and societal) associated with presence of HIV in the family unit.

Several investigators have reported that many children and adolescents with HIV have or meet clinical criteria for psychiatric disorder, particularly attention-deficit/hyperactivity disorder (ADHD).^{1,2} For example, Pao et al³ reported that 85% of their sample of youths with HIV, who were infected as a result of risk-taking behavior ($n = 34$), met diagnostic criteria for at least one primary DSM-IV disorder, and 44% met criteria for current major depression. It has been suggested that various stressors (biological, societal, and viral) associated with HIV augment the psychosocial stigmata of HIV, thereby potentiating the adverse effects of the virus on brain processing and disease.^{4,5} In these studies, negative life events, such as a family member being hospitalized or dying (which is not uncommon in families with HIV) or loss of wages or housing, play a role in worsening immune suppression, further complicating the effect of virus on the central nervous system.^{5–8} Thus, children with HIV, who have grown up in disadvantaged households and have been exposed to medications potentially toxic to the central nervous system, may be at greater risk than other populations for co-occurring psychiatric symptoms.

Research involving children with and without chronic physical diseases,^{9–12} including HIV,^{1,13,14} generally indicate higher rates of adjustment problems (particularly anxiety and depression) in the former; however, the risk of psychopathology is multifactorial and depends in part on the type of illness^{15–17} and a host of biological and psychosocial variables. In the pre-HAART era, Bose et al¹⁸ compared HIV-infected children ($n = 36$) with seronegative peers and found higher rates of anxiety, social withdrawal, and academic underachievement in the former. Conversely, Havens et al¹⁹ reported no statistical significance when comparing the psychopathology in a sample of children ($n = 26$) with HIV and perinatal drug exposure and a non-HIV sample with perinatal drug exposure. Similarly, Mellins et al²⁰ evaluated a sample of 3- to 8-year-old children with HIV ($n = 96$) and peer comparisons ($n = 211$) at 6-month intervals and failed to show a relationship between HIV status or prenatal illicit drug use and behavior problems. Others, however, in the post-HAART era have reported differentially higher rates of psychiatric hospitalization and psychotropic drug prescribing for youths with HIV versus the general pediatric population and HIV-exposed but uninfected children, but conclusions pertaining to the latter must be qualified owing to the age differential in study samples.²¹

For a variety of reasons, research about psychopathology in children and adolescents with HIV must be qualified owing to insufficient sample size, geographically restricted samples, inadequate comparison groups, or retrospective data collection. In addition, the failure to use DSM-IV²²-referenced assessment instruments or document impairment has limited, to some extent, the generalization of findings to clinical management concerns. Finally, when the time data collection commenced, few investigations had fully evaluated HIV-related psychopathology in the post-HAART era samples. Since then, several relevant investigations^{23–25} and literature reviews^{13,14} have been published, and their findings in relation to our results are described later in this report. The present study seeks to address these concerns, and estimate and compare the prevalence and severity of psychiatric problems in a large, diverse group of youths with HIV relative to youths from similar HIV-positive family backgrounds. On the basis of the extant literature for individuals with HIV and more generally for children with chronic diseases, we expected that youths with HIV would evidence more psychopathology than peer comparisons. Exploratory analyses were conducted to examine whether (a) youths with HIV who were aware of their clinical status had differentially more mental health issues and as to whether (b) exposure to the virus was associated with increased risk of psychiatric symptoms in uninfected youths. Owing to the well-documented disparity between caregiver and youth self-report²⁶ and the likelihood this incongruence may reflect different pathogenic processes,^{27,28} analyses of caregiver, and youth ratings were conducted separately.

Method

Participants

Potential participants were recruited from the Pediatric AIDS Clinical Trials Group (PACTG), an ongoing National Institute of Health-funded, multi-center, research initiative to study children and adolescents with HIV. This initial assessment phase of this particular protocol (PACTG 1055) was conducted from June 2005 to September 2006, with a 24-month follow-up that continued through December 2008 as part of what is now referred to as the International Maternal Pediatric Adolescent AIDS Clinical Trials Group. Participants were two groups of 6- to 17-year-old youths, perinatally infected with HIV (N = 323) and peer comparisons (N = 259), all of whom were recruited from 29 PACTG clinics. Participants were stratified by age (ages 6 to <12 and ages 12 to <18 years) and by gender into four subgroups. The study was designed to enroll the same number of subjects within each of the subgroups. To be eligible, youths in both groups were required to be living with the same caregiver for at least 12 months before screening, and the youths were excluded if their IQ was known to be <70 or mental retardation had been previously established (e.g., individual education plan indicated mental retardation).

This study was approved by an institutional review board at each PACTG site, and appropriate measures were taken to protect the identity of the participants. Written informed consent was obtained from the primary caregiver and written assent from youths 12 years. Owing to concerns about inadvertent HIV disclosure for youths who were required to provide written assent (i.e., might ask why they were being asked to participate), institutional review boards generally required that older HIV youths signing assents be aware of their clinical status as a precondition for eligibility. Disclosure information was obtained from study staff and based on information reported in a caregiver-completed questionnaire as well as youth and caregiver interactions with clinical management team.

HIV+Participants—Required measures were completed for 319 of the 323 HIV+ youths enrolled at study entry. Of youths with HIV, 59% had undetectable HIV ribonucleic acid viral load (<400 copies per mL); 73% had 25% or more CD4 cell counts; and the median

CD4 cell count was 690 (Table 1). Only 23% were considered to have ever been in Centers for Disease Control (CDC) clinical class C. About two thirds (66%) were receiving highly active antiretroviral treatment (HAART) with protease inhibitors, and an additional 15% were receiving HAART without protease inhibitors. The median duration of HAART therapy was 6.5 years.

Peer Comparison Sample—Required measures were completed for 256 of the 259 comparison youths enrolled at study entry. These included youths who were either HIV-exposed (perinatally HIV-exposed; $n = 174$) or living in households with HIV-infected family members (HIV-affected; $n = 82$).

Procedure

To obtain a representative sample balanced for age and gender, lists of all eligible HIV patients and peer comparisons within the designated age range were generated by the study team for each of the 29 participating sites. Lists were sorted into blocks of eight youths, balanced for age (older vs younger) and gender. Sites were required to contact each patient in a block before moving onto the next block and continued enrollment until 400 participants in each group were entered or enrollment was closed. Recruitment at each site was monitored by the research team, and sites that were significantly below average recruitment rate were contacted and procedures for increasing enrollment were discussed.

Of the 1,162 youths ($\pm$ HIV) who were included in the initial randomization schedule and were both contacted about the study and not ineligible, $\sim 50\%$ participated. Considering the overall level of economic disadvantage, family stressors, medical visits, number of sites, and solicitations for involvement in research, the participation rate was both encouraging and comparable to or better than other similar studies with this patient population.²⁹ When our study began, there were approximately 8,500 youths aged younger than 19 years living with HIV in the United States, almost 6,200 of whom were perinatally infected.³⁰ Therefore, the initial recruitment randomization sample represented approximately 20% of youths with HIV.

Study Visits

At study entry, youths and their caregivers completed an extensive battery of questionnaires and rating scales as part of their involvement in this study that included information about demographics (e.g., caregiver education, marital status, family composition, and self-identified ethnicity); child's medical, mental health, and academic history; quality of life; past and current mental health treatments; social functioning; home environment and possible psychosocial stressors; and lifetime history of psychiatric medications. Caregiver mental health was also assessed. For youths with HIV, we obtained lifetime history of antiretroviral medications and major HIV-related diagnoses. All measures were administered in a hospital outpatient clinic. Participants were given the option of returning to complete the measures within 90 days of initiation if they were too burdensome to complete in one sitting. All participants and caregivers were encouraged to complete their own answers on self-report instruments with staff available to read the questions to subjects and caregivers as needed.

Measures

The Child and Adolescent Symptom Inventory-4R (CASI-4R)³¹ is a 147-item caregiver-completed pencil and paper rating scale for evaluating youths 5 to 18 years and combines the symptom modules from the Child Symptom Inventory-4^{32,33} and the Adolescent Symptom Inventory-4.³⁴ Individual items bear one-to-one correspondence with DSM-IV symptoms (i.e., high content validity). The present study focused on relatively more

prevalent and more impairing disorders and included ADHD- inattentive, ADHD-inattentive type, ADHD- combined type, oppositional defiant disorder (ODD), conduct disorder (CD), generalized anxiety disorder, separation anxiety disorder, social phobia, major depressive episode, dysthymic disorder, manic episode, somatization disorder, and disturbing events. There are three scoring procedures for the CASI-4R: Screening Cutoff (categorical), Symptom Severity (dimensional), and Clinical Cutoff (includes impairment). When the Symptom Count score (number of symptoms necessary to meet DSM-IV threshold criteria) is equal to, or greater than, the number of symptoms specified by DSM-IV as being necessary for a diagnosis, the child receives a Screening Cutoff score of “yes” for the disorder. Symptom Severity scores are the sum of the item scores for all the symptoms of a specific disorder. Items are rated on a 4-point scale: Never = 0, Very often = 3. For most disorders, the informant is asked whether symptoms impair social or academic performance. Impairment is defined as frequency ratings of “often” or “very often.” The Screening Cutoff score can be combined with the Impairment score to generate a Clinical Cutoff score. The findings of numerous studies indicate that the CASI-4R is a reliable and valid screening tool³⁵ and has been used in studies of many pediatric disorders such as autism,³⁶ epilepsy,³⁷ leukemia,³⁸ low birth weight,³⁹ multiple sclerosis,⁴⁰ and spina bifida.⁴¹

The Youth's (Self-Report) Inventory-4R (YI-4R)⁴² is a 128-item, self-report rating scale for children and adolescents, ages 12 to 18 years, with items parallel to those in the CASI-4R. Research indicates that the Youth's (Self-Report) Inventory-4R demonstrates satisfactory internal consistency ($\alpha = 0.66\text{--}0.87$), test-retest reliability ($r = .54\text{--}.92$), and convergent and discriminant validity with corresponding scales of other child self-report measures.^{42,43} As with the CASI-4R, there are impairment questions for all symptom categories except somatization and social phobia. The Child (Self-Report) Inventory-4⁴⁴ contains 34 items and is a parallel version of the Youth's (Self-Report) Inventory-4R for children between the ages of 8 and 11 years. Symptom categories include generalized anxiety, separation anxiety, social phobia, somatization, major depressive episode, and dysthymia. Two items pertain to experiencing an “extremely upsetting event” and continuing to be bothered by it or having memories or dreams about such an event. Younger children were not asked to assess impairment.

Additional measures assessed child and family characteristics. The caregiver-completed Social and Academic Functioning Questionnaire⁴⁵ obtains information about mean performance in all academic subjects, school attendance, suspensions (and other disciplinary actions), grade retentions, failed courses, and special and remedial education services. The School Functioning subscale (0–10; high value indicates poor function) is based on behavior problems, special education, grade retention, and average academic performance.

Two subscales (Letter-Number Sequencing and Coding Recall) of the Wechsler Intelligence Scale for Children-IV Fourth Edition Integrated⁴⁶ were administered to provide an indication of the subject's attention span, memory, and processing speed. These subscales are designed to minimize cultural or educational influences.

The Parent Questionnaire⁴⁵ obtains information about treatment history (e.g., psychotropic medication, behavioral therapies such as group, family and individual counseling, behavior modification, after-school tutoring, hospitalization, and diet). Laboratory data collected included lifetime nadir and current CD4 count, CD4%, and lifetime peak and current viral load documented within 90 days of study entry.

Analyses

Differences in child, family, and home environment characteristics between HIV+ and comparison groups were assessed using Student's *t* tests, Wilcoxon rank sum tests, Fisher's

exact test, and chi-square tests, as appropriate. Both unadjusted and adjusted (i.e., controlling for covariates) general linear regression models were used to evaluate differences in psychiatric symptoms between groups. The covariates in the adjusted models were demographic (age, gender) and family characteristics (caregiver education, household income, presence of caregiver-reported symptoms, life stressors in prior year, and caregiver relationship to participant). Group comparisons were conducted for the entire sample and within age-grouping and gender strata when relevant. Multivariate models included all main effects and confounders and also interactions among HIV status, age, and gender for those effects meeting the model-building criterion of $p < .20$. Final models used caregiver education to represent socioeconomic status, due to improved data completeness as compared to household income. For outcomes in which interactions between HIV-status and either age or gender were suggested, adjusted means were computed within relevant age or gender strata. For impairment and prevalence data, odds ratios were computed adjusting for demographic and family environment variables using multiple logistic regression methods. Owing to concerns about Type 2 error (i.e., falsely concluding that neither the virus or its attendant therapies or psychosocial sequelae may have contributed to mental health problems), no adjustments were made for multiple comparisons. Unadjusted effect sizes (ES) were calculated as the difference in means divided by the pooled standard deviation, the magnitude of which are classified as small (0.2), medium (0.5), and large (0.8).⁴⁷ Adjusted ESs were calculated as the difference between least squares (adjusted) means divided by the root mean square error from the general linear model results. Agreement between the child-self-reported and child-caregiver-reported cutoff scores was assessed using Kappa statistics for agreement and McNemar's test. For symptom severity, we estimated the Spearman rank correlation coefficients between the child and the caregiver reported symptom severity. The significance criterion was $p < .05$.

Results

In keeping with the explicit objectives of the study (i.e., estimate and compare mental health problems) findings are described for both unadjusted analyses, when the primary objective is to describe clinical service needs in youths with HIV, and adjusted analyses (controlling for covariates) when the primary goal is to test a possible link between HIV status and mental health problems.

Participant Characteristics

HIV+ and comparison groups were similar with regard to gender, age, and percentage of caregivers who self-reported at least one of the targeted psychiatric conditions (Table 1). However, the HIV+ group was slightly older (effective size [ES] = 0.50), had lower Wechsler Intelligence Scale for Children processing speed scores (ES = 0.46), and less likely to be living in financially impoverished environment. There were more self-identified African-American and fewer Hispanic-American youths in the HIV+ than comparison group. Youths with HIV were less likely to be living with a biological parent than peer comparisons, and within the comparison group, more youths who were perinatally exposed to HIV lived with biological parents than those who were not exposed (80 vs 70%, $p = .05$). Almost two thirds of youths in each group (HIV±) had experienced at least one life stressor during the previous year. The HIV+ group was more likely to have received interventions for academic and mental health problems.

Prevalence

Screening Cutoff Scores—For most disorders, screening prevalence rates based on caregiver report were comparable for both groups (HIV+ and comparison), and this was true for both unadjusted (Table 2) and adjusted models. The exceptions (adjusted model with

both age groupings combined) were lower rates ($p = .02$) of conduct disorder (CD) in the HIV+ (4.8%) versus comparison (9.3%) group and higher rates ($p = .02$) of somatization disorder in the HIV+ (10.5%) versus comparison (6.9%) group. However, both groups (HIV $\pm$) evidenced higher rates of many disorders compared with the CASI-4R norm samples^{33,34} but much lower rates for all disorders compared with youths referred to a child psychiatry outpatient service^{33,48} (Table 2).

Adjusted analyses of youth self-reports with both age groupings combined indicated differentially higher rates of oppositional defiant disorder (ODD) ($p < .04$) in adolescent peers (18.1%) versus adolescents with HIV (9%). The only other group differences were marginally significant higher rates of disturbing events (all ages combined; 7.3 vs 5.8%, $p = .05$), CD (8.6 vs 5.0%, $p = .07$), and attention-deficit/hyperactivity disorder (ADHD) inattentive (5.7 vs 5.5%, $p = .07$) in comparison versus HIV group.

As previously noted, almost twice as many comparison as HIV+ youths were living with at least one biological parent. Exploratory analyses (unadjusted model) comparing HIV+ ($n = 134$) and peer comparisons ($n = 192$) who were living with biological parents yielded no statistically significant group differences for caregiver-assessed symptoms. However, adolescent peer comparisons self-reported higher rates of ADHD (13.2 vs 2.7%, $p = .03$) than adolescents with HIV.

Clinical Cutoff Scores—There was only one group difference (unadjusted model) for the percentage of youths who met Clinical Cutoff (i.e., Screening Cutoff plus Impairment) for the more prevalent DSM-IV disorders according to either caregiver or self-report (Table 3). In the older age group, peer comparisons had a higher rate of CD than the HIV+ group (6 vs 1%, $p = .02$). The adjusted analyses (results not shown) indicated that the odds of meeting criteria for a depressive disorder was lower for youths with HIV than peer comparisons (2 vs 3.5%, $p = .04$). A separate subgroup adjusted analysis for older youths showed that those with HIV evidenced lower rates of mood (depression, manic episodes) disorders than peer comparisons (4 vs 9%, $p = .05$). Exploratory analyses (unadjusted analyses) comparing HIV+ ($n = 134$) and comparison ($n = 192$) groups who were living with biological parents yielded no statistically significant group differences.

Awareness of HIV Status

As previously noted, almost all the older youths were aware of their HIV status; however, this was true for only 36% of the younger cohort. Unadjusted analyses indicated that HIV-aware children ($n = 43$) were rated by their caregiver as having more severe oppositional-defiant ($p = .015$; ES = 0.47), generalized anxiety ($p = .0$; ES = 0.39), separation anxiety ($p = .011$; ES = 0.49), dysthymia ($p = .035$; ES = 0.47), and disturbing event ($p = .037$; ES = 0.40) symptoms than children reported as being unaware ($n = 76$). For the adjusted analyses (Fig. 1), only dysthymia remained significant, but several symptom dimensions were marginally significant. When the children rated their own behavior, there was one marginally significant ($p = .05$; ES = 0.38) finding for generalized anxiety (aware > unaware).

Caregiver-Reported Symptom Severity (Dimensional) Scores

There was one statistically significant main effect of group status (adjusted model) for caregiver ratings of symptom severity: youths with HIV had more severe somatization scores than peer comparisons ($p < .001$; ES = 0.38). Exploratory adjusted analyses comparing HIV+ ($n = 132$) and comparison ($n = 189$) groups who were living with biological parents found more severe CD ($p = .04$; ES = 0.24) and somatization ($p < .001$; ES = 0.42) in youths with HIV.

Youths Self-Reported Symptom Severity (Dimensional) Scores

There were two significant main effects of group (adjusted model). Youths with HIV reported less severe CD ($p = .03$; ES = 0.29) and ODD ($p = .04$; ES = 0.27) symptoms than peer comparisons.

Impairment

We compared HIV status groups for caregiver (both age groups) and self-reported (older youths only) perceptions of impairment, because it is not uncommon for an individual to be impaired and yet not meet criteria for the requisite number of symptoms for a specific disorder. Unadjusted analyses for caregiver reports (Table 4) indicated comparable rates of overall (HIV+ = 15%; comparison = 14%) and specific impairments; but for the adjusted (data not shown) analyses, there were higher rates of impairing depression symptoms in peer comparisons versus the HIV+ group (2.8 vs 1%, $p = .04$).

In the older cohort (Table 4), unadjusted analyses of self-perceptions of impairment indicated the overall rate of impairment was seemingly high in both HIV+ and peer comparisons (24 vs 33%, $p = .08$), but peer comparisons had higher rates of CD than HIV+ group (8.6 vs 0.5%, $p < .001$). The adjusted analyses (data not shown) showed a larger percentage of peer comparisons self-reported impairment due to at least one disorder than the HIV+ group ($p = .02$). Specifically, peer comparisons self-reported higher rates of impairment for ADHD (17.3 vs 10.1%, $p = .007$) and CD ($p = .011$) symptoms and marginally significant greater impairment for manic episode symptoms (8.6 vs 4%, $p = .058$) than the HIV+ group.

Informant Agreement

Agreement between caregiver and youth Symptom Severity scores was modest: younger cohort ($r = .10-.27$) and older cohort ($r = .16-.35$). Similarly, Kappas for Screening Cutoff scores were generally very low: younger cohort ($\kappa = 0.00-0.10$) and older cohort ($\kappa = 0.00-0.26$). Findings for youths with HIV and peer comparisons were comparable.

HIV-Exposed Versus HIV-Affected Peers

Exploratory adjusted analyses (controlling for caregiver education, life stressors, caregiver symptom, relation to caregiver, age group, and gender) were conducted to determine if peers who were perinatally exposed to the virus ($n = 172$) had more severe symptoms than peers living in a household with an HIV+ person ($n = 84$), and whether the HIV+ group was more impaired than either of the comparison subgroups. There were only two significant pairwise differences for caregiver ratings; somatization scores were higher for the HIV+ group compared with either exposed ($p = .002$) or affected ($p < .001$) peers. Analyses of self-report ratings (adolescents) indicated that the exposed peers had more severe CD ($p = .005$) and ODD ($p = .014$) symptoms than youths with HIV.

Family Characteristics

There were several noteworthy relations between covariates and caregiver Symptom Severity scores. Caregivers who were also biological parents rated their youths as having less severe ADHD ($p < .05$), CD ($p = .02$), ODD ($p = .04$), and generalized anxiety ($p = .04$) symptoms than nonbiological parents. For every group of psychiatric symptoms, caregivers who self-reported at least one targeted psychiatric condition also rated their youths as having more severe symptoms ($p = .01- < .001$) than caregivers who did not indicate a mental health problem. Caregivers with at least a high school diploma (vs those without) rated their youths as having more severe ADHD inattentive ($p = .04$) but less severe separation anxiety ($p < .001$), somatization ($p = .04$), and manic episode ($p < .01$) symptom scores. Caregivers who

reported a stressful life experience (vs those who did not) rated their youths as having higher depression ($p = .004$), manic episode ($p = .01$), social phobia ($p = .03$), somatization ($p < .001$), and disturbing event ($p = .01$) scores.

Child self-reported child Symptom Severity scores were generally not associated with any of the four covariates included in our models to represent social and family circumstances. Only in the case of disturbing events was there a significant positive association with life stressors ($p = .04$).

Discussion

The primary objective of this study was to determine if youths with HIV are at differentially greater risk for mental health problems than peers from similar environmental backgrounds. Such concern seems warranted owing to potential biological risk factors associated with a virus that crosses the blood-brain barrier as well as exposure in-utero and prophylactically to potentially neurotoxic antiretroviral medications. Moreover, it is not unusual for caregivers to express concerns and apprehensions about their children some day having to cope with social stigmatization and imagined limitations in personal, social, and professional development. However, contrary to research prior to the era of highly active antiretrovirals suggesting a possible link between HIV infection and mental health issues, our findings generally indicated youths with HIV were not at differentially greater risk for current psychiatric problems (i.e., point prevalence) than peers living in similar environmental settings. This was true whether the comparison group was comprised of uninfected youths who were perinatally exposed to HIV or who were living in a household with an HIV-infected person. Moreover, both caregiver and youth self-reports (which evidenced only modest convergence) suggested that if anything the peer comparisons were generally at greater risk of psychiatric symptoms, particularly aggressive and antisocial behavior and self-perceptions of impairment. This was unexpected given the extensive literature supporting the risk for mental health problems in children with chronic illness.^{9–12,15} The resiliency of the human spirit is also evident in our impairment data. Specifically, 73% of youths with HIV were not rated, either by themselves or their caregivers, as currently having psychiatric problems that interfered with academic or social functioning, a rate that was comparable to our peer comparison sample (74%). The notion that many children with chronic disease adjust satisfactorily to their life situation is also supported by findings from the juvenile cancer literature.^{16,17} It is also likely that youths with HIV benefitted from access to medical specialists with demonstrated excellence in HIV management, including referral to relevant mental health care professionals. In its own curious way this disease and its clinical management may have interacted with family environment variables to protect these particular youths with HIV from even greater psychological adversity.

This does not mean, however, that living with HIV was necessarily easy for everyone. The HIV+ group did report higher rates and greater severity of somatization symptoms than the peer comparison sample. In addition, caregiver-reported lifetime rates of intervention indicated that 37% of our youths with HIV had received either a behavioral or pharmacological intervention for an emotional or behavioral problem (vs 22% for peer comparisons) and 44% had been evaluated for special education (vs 32% for peer comparisons).⁴⁹ These treatment findings suggest that lifetime rates of mental health problems may actually be higher in youths with HIV versus peer comparisons. Moreover, compared with normative data samples, both HIV+ and peer comparison samples manifested greater frequency and severity of co-occurring symptoms, which is consistent with an extensive literature associating environmental and economic disadvantage with differentially higher rates of mental health problems. For example, the most commonly reported disorder in our study sample was attention-deficit/hyperactivity disorder (ADHD),

with a prevalence rate of 11% to 12% in both groups of youths according to Clinical Cutoff scores. In a nationally representative study of 3,082 youths aged 8 to 15 years, Froehlich et al⁵⁰ reported a parent-assessed ADHD prevalence rate of 8.7% for the entire sample, but a higher rate (11%) for the poorest youths.

The substantial percentage of youths in both samples, particularly peer comparisons, who were impaired by their symptoms but not receiving intervention, speaks to the special needs of poor families who may be less well equipped to negotiate the legion of hurdles in obtaining adequate health care. Many children with HIV infection have family histories of substance abuse and/or psychiatric illness and also experience significant loss, family disruptions, and other negative life events, due at least in part to the impact of HIV disease and its sequelae on their families.^{13,14,51–53} Moreover, simply living in a household with a parent or sibling with HIV may be associated with psychosocial stressors such as the fear of losing a parent, limited or inconsistent social support, not receiving the same amount of attention as an HIV+ sibling (whether imagined or real), or conflicted feelings about escaping infection.^{54–59} In other words, these variables, either individually or in combination with other environmental factors, may have contributed in some way to psychopathology and the relatively higher rates and severity of symptomatology when compared with normative data samples.

The perfect comparison group in pediatric HIV infection is for many reasons an unattainable goal owing to a legion of socio-cultural, disease, and treatment variables. Although we statistically adjusted for relevant background characteristics potentially associated with outcome variables and conducted secondary analyses, it is not possible to prove the null hypothesis. For these and other reasons, convergence of findings across studies with differing methodologies is probably the best strategy for resolving critical issues in HIV infection. In this regard, Mellins et al²⁰ who also used a behavior rating scale to evaluate behavioral and emotional symptoms, also found that 3- to 8-year-old children with HIV (n = 96) and HIV-exposed but uninfected peers (n = 211) did not differ in symptom severity, including ADHD. More recently, however, this same research team reported on rates of psychiatric disorder in the past year ascertained with structured interview in youths (aged 9–16 years) with HIV (n = 206) versus perinatally exposed but uninfected peers (n = 134) recruited from four medical centers.²⁵ They found significantly higher overall rates of psychiatric disorder in youths with HIV (61%) versus peer comparisons (49%), but group differences were not significant for specific disorders with the exception of ADHD: HIV+ (18%) and comparison (8%) groups.

The fact that younger youths in our study who were aware of their HIV status were rated as having more symptomatology than peers who were not aware also appears to support the notion that HIV creates adjustment problems for some individuals. However, other investigators have reported that disclosure may actually contribute in some way to psychological well-being,⁶⁰ but findings are mixed and study samples are small.⁶¹ One of the few studies that actually compared youths' pre- and post-exposure status found that disclosure did not have an adverse effect on quality of life,²³ and another investigation reported disclosure did not impact adherence to treatment.²⁴

Limitations

The findings of this study are subject to several qualifications. Although we designed our study to be representative of the population of youths with HIV served by the Pediatric AIDS Clinical Trials Group (PACTG) network, the participants in this study had well-controlled HIV disease. The majority (59%) had undetectable viral loads, excellent CD4% (73%–25% CD4 cells), and only 23% had current or past events of AIDS-defining illnesses. Therefore, our results may not apply to patients who are more adversely affected, not being

treated at National Institute of Health or National Institute of Health and Human Development sites funded for clinic HIV research, or to the estimated 3 million children worldwide with HIV living in other countries. Moreover, we limited our sample to youths who had been living with the same caregiver for at least 1 year, which we considered necessary to support the validity of caregivers' reports of child psychiatric symptoms.

The comparison group was comprised of both perinatally HIV-exposed and HIV-affected youths, and it is possible that exposure to the therapies that prevent transmission of the virus could have impacted rates of mental health problems. Exploratory analyses found the two subgroups of peer comparison youths exhibited similar rates, severity, and impairment scores, with the exception of conduct disorder (CD), which was clearly more of an issue for the HIV-exposed but uninfected youths. A satisfactory explanation for this finding is wanting and remains a topic for future study.

Finally, the youths and their caregivers enrolled in this study represented 463 families, of which 371 families (80%) enrolled only a single individual, and the remaining 92 families enrolled two or more subjects. To examine whether this impacted our reported findings, we conducted additional analyses adjusting for within-family correlations in reported symptom severity and symptom cutoffs, obtaining results that were similar to those already presented here.

Clinical Implications

Youths perinatally infected with HIV do not appear to be at differentially greater risk of mental health problems than peers from similar community and home environments. Lest this somewhat reassuring conclusion be misunderstood, we hasten to emphasize the following facts: our HIV+ group received higher lifetime rates of intervention for mental health problems than the comparison sample, and our prevalence estimates of the later were based solely on one point in time. Therefore, it is possible that the lifetime rates of mental health problems are actually higher in our HIV sample than comparison youths. Moreover, youths with HIV are more likely to come from impoverished backgrounds, and rates of mental health problems are in general higher for individuals living in such environments. Therefore, both youths with HIV and their community-based peers constitute high risk populations. For example, twice as many adolescents in each of the study samples were reported to have experienced an upsetting life event that continued to bother him/her compared with norm samples. Pediatricians and adolescent care providers involved in the management of HIV will inevitably be called on to identify, diagnose, and treat mental health issues and address their implications for intervention, adherence to treatment regimens, and even disease transmission. Moving forward, we emphasize the potentially complex relationship of biological and environmental exposures with psychiatric outcome and the need for continued research. In summary, this is but one in a series of reports that will address various aspects of mental health issues in youths with HIV to include a longitudinal analysis of the role of specific biologic and environmental variables in pathogenesis of mental distress in this at-risk clinical population of largely poor, minority youth.

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Figure 1.

Caregiver-rated symptoms in younger children (<12 years) aware and unaware of their HIV status: analyses adjusted for gender, caregiver education, caregiver-reported symptoms, life stressors, and caregiver relationship to youth. ODD, oppositional defiant disorder.

Table 1
Demographic, Treatment, and Family Characteristics of Youths Perinatally Infected
With HIV and a Peer Comparison Sample

Characteristics	HIV+ (N = 319)	Comparison (N = 256)	<i>p</i>
Child			
Gender (male)	163 (51%)	122 (48%)	.45 ^a
Ethnicity			
European-American non-Hispanic	40 (13%)	34 (13%)	.06 ^b
African-American non-Hispanic	173 (54%)	111 (43%)	
All Hispanic-American	102 (32%)	106 (41%)	
Other-American	4 (1%)	5 (2%)	
Age, yr (median)	13.1	11.3	<.001 ^c
<12	120 (38%)	148 (58%)	
12	199 (62%)	108 (42%)	
IQ (M, SD)			
Working memory subtest	8.5 (3.2)	8.9 (3.0)	.14 ^d
Processing speed subtest	8.0 (3.1)	9.4 (3.1)	<.001 ^d
Social functioning (M, SD)	1.9 (1.4)	1.9 (1.5)	.87
Academic functioning (M, SD)	2.7 (2.2)	2.0 (2.1)	<.001 ^d
Treatment, n (%)			
Psychotropic meds (ever)	74 (23)	30 (12)	<.001 ^a
Psychotropic meds (current)	43 (13)	25 (10)	.19 ^a
Behavioral therapy (ever)	84 (27)	43 (17)	.01 ^a
Any therapy (ever)	116 (37)	54 (22)	<.001 ^a
Special education (ever evaluated for)	136 (44)	79 (32)	.004 ^a
Family			
Biological caregiver (yes)	134 (43%)	192 (76%)	<.001 ^a
Life stressors (median)	1.0	1.0	.05 ^c
No stressors	114 (36%)	77 (31%)	
1 or more stressor	199 (64%)	173 (69%)	
Caregiver psychiatric symptoms			
None	275 (88%)	209 (85%)	.26 ^a
One or more	37 (12%)	38 (15%)	
Income			
\$20,000	133 (48%)	155 (66%)	<.001 ^a
>\$20,000	145 (52%)	81 (34%)	
Caregiver education			
<High school graduate	93 (30%)	99 (39%)	.02 ^a
High school graduate	219 (70%)	152 (61%)	

Missing observations: biological caregiver (four HIV+, five comparison), life stressors (six in each group), caregiver symptoms (seven HIV+, nine comparison), income (41 HIV+, 20 comparison), and caregiver education (seven HIV+, five comparison).

^aFisher's exact test.

^bPearson's χ^2 test.

^cWilcoxon rank sum test.

^dStudent's *t* test.

Table 2

Specific Disorders (Unadjusted Model) in Study

Disorder	HIV+	Comparison	Norm ^a	Clinic Males ^a	Clinic Females ^a
Younger Cohort	N = 119	N = 143	N = 551	N = 441	N = 149
ADHD-inattentive	5.9	2.8	3.6	32.7	32.9
ADHD-hyperactive-impulsive	5.9	4.9	2.0	7.5	4.7
ADHD-combined	5.1	4.9	1.6	23.4	18.1
Any ADHD	17.0	12.6	7.2	63.6	55.7
Oppositional defiant disorder	5.0	7.7	5.3	39.9	35.6
Conduct disorder	5.0	9.8	2.9	22.2	19.5
Generalized anxiety disorder	1.7	0.0	1.6	8.4	8.1
Separation anxiety disorder	8.4	6.3	2.2	7.0	10.1
Social phobia	4.2	0.7	1.3	NA	NA
Somatization	8.4	5.6	NA	NA	NA
Major depressive episode	0.8	0.7	0.0	0.9	4.6
Dysthymia	1.7	0.7	0.7	4.1	6.0
Manic episode	0.0	0.0	NA	NA	NA
Disturbing event	28.6	18.9	NA	NA	NA
Any study disorder	43.7	35.0	NA	NA	NA
Older Cohort	N = 196	N = 105	N = 761	N = 102	N = 42
ADHD-inattentive	9.7	9.5	4.6	NA	NA
ADHD-hyperactive-impulsive	1.5	1.0	0.4	NA	NA
ADHD-combined	1.0	1.9	0.4	NA	NA
Any ADHD	12.2	12.5	5.4	62.3	33.3
Oppositional defiant disorder	4.1	6.7	5.3	23.5	16.7
Conduct disorder	4.6	8.6	3.0	12.7	14.3
Generalized anxiety disorder	0.5	1.0	0.7	10.8	16.7
Separation anxiety disorder	1.0	5.7	0.1	NA	NA
Social phobia	0.5	1.0	1.3	7.8	9.5
Somatization	11.7	8.6	4.9	NA	NA

Disorder	HIV+	Comparison	Norm ^a	Clinic Males ^a	Clinic Females ^a
Younger Cohort	N = 119	N = 143	N = 551	N = 441	N = 149
Major depressive episode	0.5	1.9	0.8	18.6	50.0 ^b
Dysthymia	0.0	1.9	0.4	NA	NA
Manic episode	0.0	0.0	0.9	5.5 ^c	5.5 ^c
Disturbing event	24.0	25.7	12.5	NA	NA
Any disorder	39.3	39.1	NA	NA	NA

For the older cohort, separation anxiety *p* value is .02 for HIV+ vs comparison. All other *p* values are >.12 for older cohort and >.07 for younger cohort.

^aDescriptions of and procedures for the norm samples and the outpatient clinic-referred child psychiatry samples are presented in the manuals for the Children Symptom Inventory-4³³ and Adolescent Symptom Inventory-4.^{34,48}

^bEither major depressive episode or dysthymia.

^cRate for males and females combined. CASI-4R, Child and Adolescent Symptom Inventory-4R; HIV, perinatal HIV infection; NA, not available.

Table 3
Number (%) of Youths Who Met Clinical Cutoff (Screening Cutoff Score Plus Impairment) for Specific DSM-IV-Defined Psychiatric Disorders (Unadjusted Model), Overall, and by Age Cohort

Disorder	Total	<i>p</i> ^a	Younger (6–11 yr)	<i>p</i> ^a	Older (12–17 yr)	<i>p</i> ^a
Number of participants						
HIV	319		120		199	
Comparison	256		148		108	
ADHD		.90		.44		.57
HIV	37 (12)		16 (14)		21 (11)	
Comparison	28 (11)		14 (10)		14 (13)	
Conduct disorder		.14		1.00		.02
HIV	4 (1)		2 (2)		2 (1)	
Comparison	8 (3)		2 (1)		6 (6)	
Oppositional defiant disorder		.36		1.00		.16
HIV	15 (5)		4 (3)		11 (6)	
Comparison	17 (7)		6 (4)		11 (10)	
Generalized anxiety disorder		.79		.66		.29
HIV	7 (2)		3 (3)		4 (2)	
Comparison	7 (3)		2 (1)		5 (5)	
Separation anxiety disorder		.19		.63		.35
HIV	3 (1)		1 (1)		2 (1)	
Comparison	6 (2)		3 (2)		3 (3)	
Depressive disorder		.29		1.00		.09
HIV	6 (2)		0 (0)		6 (3)	
Comparison	9 (4)		1 (1)		8 (7)	
Manic episode		1.00		—		.43
HIV	3 (1)		0 (0)		3 (2)	
Comparison	3 (1)		0 (0)		3 (3)	
Any study disorder		0.91		.36		.24
HIV	55 (17)		18 (15)		37 (19)	
Comparison	42 (17)		16 (11)		26 (24)	

Missing observations per condition: all comparison (2–6); all HIV+ (0–2); younger comparison (1–5); younger HIV+ (0–2); older comparison (1); and older HIV+ (0).

^aFisher's exact test. OR, odds ratio; HIV, perinatal HIV infection; depressive disorder, major depressive episode or dysthymia.

Table 4

HIV Status and Informant (Unadjusted Model)

	Youth Self-Report (12–17 yr)		Caregiver Report (6–17 yr)	
	Total	N (%)	Total	N (%)
Any disorder				
HIV	200	47 (24)	314	46 (15)
Comparison	105	35 (33)	248	35 (14)
ADHD				
HIV	200	20 (10)	313	38 (12)
Comparison	104	18 (17)	247	28 (11)
Oppositional defiant				
HIV	199	17 (9)	314	14 (4)
Comparison	105	10 (10)	248	17 (7)
Conduct disorder				
HIV	200	1 (1)	314	10 (3)
Comparison	105	9 (9)	248	7 (3)
Generalized anxiety				
HIV	200	19 (10)	313	11 (4)
Comparison	105	13 (12)	248	7 (3)
Separation anxiety				
HIV	200	8 (4)	313	5 (2)
Comparison	105	5 (5)	248	6 (2)
Depression				
HIV	200	13 (7)	311	3 (1)
Comparison	105	11 (10)	248	7 (3)
Manic episode				
HIV	200	8 (4)	314	2 (1)
Comparison	105	9 (9)	248	2 (1)

^aFisher's exact test.