Published in final edited form as:

AIDS Care. 2010 May ; 22(5): 640–648. doi:10.1080/09540120903280919.

Prevalence of pain and association with psychiatric symptom severity in perinatally HIV-infected children as compared to controls living in HIV-affected households

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Abstract

This cross-sectional study evaluated the prevalence of pain and psychiatric symptoms in perinatally HIV-infected children at entry into P1055, a multicenter investigation of the prevalence and severity of psychiatric symptoms in HIV-infected children. Subjects 6–17 years of age and their primary caregivers were recruited from 29 International Maternal Pediatric Adolescent AIDS Clinical Trials sites in the USA and Puerto Rico. A total of 576 children (320 HIV+ and 256 HIV – children) were enrolled from June 2005 to September 2006. Subject self-reports of pain were measured by the Wong–Baker visual analog scale and Short-Form McGill Pain Questionnaire. Symptomatology for anxiety, depression, and dysthymia was assessed through Symptom Inventory instruments. Caregiver's assessment of their child's pain and psychiatric symptomatology was similarly measured. Logistic regression models were used to evaluate predictors of pain. We found that a higher proportion of HIV-infected than uninfected subjects reported pain in the last two months (41% vs 32%, $p=0.04$), last two weeks (28% vs 19%, $p=0.02$), and lasting more than one week (20% vs 11%, $p=0.03$). Among HIV-infected youth, females (OR=1.53, $p=0.09$), White race (OR=2.15, $p=0.04$), and Centers for Disease Control (CDC) Class C (OR=1.83, $p=0.04$) were significantly more likely to report pain. For all subjects, only 52% of caregivers recognized their child's pain and just 22% were aware that pain affected their child's daily activities. The odds of reported pain in HIV+ increased with higher symptom severity for generalized anxiety (OR=1.14, $p=0.03$), major depression (OR=1.15, $p=0.03$), and dysthymia (OR=1.18, $p=0.01$). This study underscores the importance of queries concerning pain and emotional stressors in the care of HIV+ and uninfected children exposed to HIV+ individuals. The discordance between patient and caregiver reports of pain and its impact on activities of daily living highlights that pain in children is under-recognized and therefore potentially under-treated.

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Keywords

pain; HIV; children

Introduction

Multiple immunological and neurological pathways are involved in pain and psychiatric symptoms in HIV-infected children and adolescents. Sources of chronic pain in HIV-1 infected children include neural inflammation, systemic manifestations of AIDS, adverse drug reactions, invasive infections, and recurrent abdominal pain. Nucleoside reverse transcriptase inhibitors (NRTIs) may be neurotoxic, and thus add to pain in HIV-infected children (Van Dyke, Wang, & Williams, 2008).

A relationship between anxiety, depression, and catastrophizing coping strategies in children and adolescents with multiple chronic, painful conditions has been described (Anie, Steptoe, Ball, Dick, & Smalling, 2002; Carter et al., 1999; Crombez, Eccleston, Van den Broeck, Goubert, & Van Houdenhove, 2004; Kashikar-Zuck, Vaught, Goldschneider, Graham, & Miller, 2002; LeBovidge, Lavigne, Donenberg, & Miller, 2003; Schanberg, Keefe, Lefebvre, Kredich, & Gil, 1996; Vervoort, Goubert, Eccleston, Bijttebier, & Crombez, 2006). Anxiety, depression, social, and behavioral disorders occur in 12–70% of young children and adolescents with perinatally acquired HIV infection (Bose, Moss, Brouwers, Pizzo, & Lorion, 1994; Havens, Whitaker, Feldman, & Ehrhardt, 1994; Mellins, Brackis-Cott, Dolezal, & Abrams, 2006).

P1055, a multicenter, prospective observational study conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group, was designed to examine the impact of HIV on the development of psychiatric symptomatology in a cohort of perinatally HIV-infected children and adolescents. Given the potential confounding relationship between pain, stress, immune status, and psychiatric symptomatology, a secondary objective of P1055 was to evaluate the presence and correlates of pain in HIV-infected subjects as compared to a control group of HIV-uninfected children living in a household with an HIV-infected person.

Design and methods

Design

The P1055 study was designed to evaluate the prevalence and severity of psychiatric symptoms in HIV-infected children aged 6–17 years as compared to a control group of HIV-uninfected controls who were either perinatally HIV-exposed or living in a household with an HIV-infected person. HIV-infected and control subjects were recruited into P1055 from 29 IMPAACT sites in the USA and Puerto Rico after review and approval of the research protocol by the Institutional Review Boards of participating institutions. Written informed consent to enroll was obtained from the participants' legal guardians prior to participation. Written assent was obtained from older children when appropriate.

Subjects

HIV-infected subjects aged 6–17 years who acquired infection through maternal-to-child-transmission (MTCT) (HIV+) and similarly aged perinatally HIV-exposed children or uninfected children living in a household with an HIV-infected person (control) were enrolled. In order to increase the representativeness of the study population, children were selected to participate in the study based on random selection in sequential blocks of size

eight from all eligible subjects known to the site. The study opened for accrual in June 2005 and closed to new enrollees in September 2006. All participants were required to have been living with the same parent or primary caregiver for at least 12 months prior to evaluation, and cognitively capable of responding to the study questionnaires. Specific exclusion criteria were known mental retardation ($IQ \leq 70$) or an individualized education profile (IEP) signaling mental retardation, and HIV infection acquired through adult risk behavior.

Study measurements

Demographic and household characteristics were collected on all subjects. Race attribution was by self-report of the participants for the purpose of demographics. For HIV-infected subjects, health characteristics (CD4%, HIV-1 plasma viral load, CDC Clinical Classification) and a lifetime history of antiretroviral treatment were obtained. Historical data for major medical and psychiatric diagnoses and the use of psychotropic medications were collected. Screening tools and pain assessments were administered in the language native to the subject and their family by staff at each site. Subjects who could not read the questions were assisted by staff, but the subject was responsible for marking all answers. Study staff recorded pain results on subject case report forms interpreted as per literature or guidelines. Our analysis considered pain data collected at study entry as a single point-in-time assessment.

Pain measurement tools

Age appropriate approaches for assessing self-reported pain were utilized. All caregivers completed the assessments of perceived pain in their child. The prevalence of any perceived pain occurring in the last two months, the last two weeks, and at the enrollment visit was obtained by separate interview of both the caregiver and each subject. Subject and caregiver also reported the duration of pain and whether it interfered with activities of daily living (ADL).

All subjects and caregivers assessed pain for the child participants using an ordinal Wong–Baker FACES visual analog scale (VAS) (Wong & Baker, 1988) validated for non-verbal assessment. In addition, subjects 12 years and older completed the Short-Form McGill Pain Questionnaire (SF-MPQ) which included a VAS, total pain intensity score, a total pain rating index (PRI), and its components of affective PRI, and sensory PRI (Melzack, 1987). SF-MPQ is validated for age of 12 years and higher.

Psychiatric measures

Psychiatric assessments were based on youth and caregiver-completed Symptom Inventory (SI-4) instruments that evaluated the symptoms of generalized anxiety disorder (GAD), major depressive disorder (MDD), and dysthymic disorder (DD), along with other symptoms not considered in this analysis. The SI-4 symptoms were evaluated by computing a total severity score within each domain, and by evaluating whether each subject scored positively on enough symptoms within the subscale to be classified as exceeding the cutoff for that particular symptom subscale; in this analysis, we focus on the symptom severity scores.

Statistical analyses

Prevalence of pain as reported at the study entry visit was compared between HIV-infected and control subjects using Fisher's exact tests. Comparisons of demographic characteristics between groups were performed using Pearson's chi-square test for multi-category characteristics, and using a Kruskal–Wallis test for continuous outcomes. Since pain has been reported to vary by gender and age group, separate analyses of pain prevalence were

repeated within each gender and age group for all the subjects. Analyses of pain intensity were conducted by gender for older children who completed the McGill Pain Questionnaire. Multiple logistic regression models were fit to evaluate the effect of generalized anxiety, major depression, and dysthymia symptom severity on the presence of pain adjusting for age, gender, and other potential confounders. Sensitivity analyses accounting for clustering of responses within families were conducted using generalized estimating equation (GEE) models. In summarizing the results, p -values <0.05 were considered to be statistically significant. All analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC).

Results

Demographics

A total of 320 HIV-infected and 256 uninfected control subjects enrolled and completed the baseline visit including the pain evaluation. Psychiatric symptom inventory severity scores for MDD, GAD, and DD were available for 311 HIV-infected (97%) and 247 control (96%) subjects. Characteristics of the study population are summarized in Table 1. Control subjects tended to be younger and were significantly more likely to have at least one of their biological parents as primary caregiver (78% vs 43%), while HIV-infected subjects were more likely to have another relative or adoptive parent as their primary caregiver. Controls tended to have caregivers with lower education level and lower household income. Among the 320 HIV-infected subjects, 23% had an AIDS diagnosis (CDC Clinical Class C). The median CD4 value was 31%, with over half the group having less than 400 copies/mL HIV-1 RNA. Use of Highly Active Antiretroviral Treatment (HAART) with or without a protease inhibitor was reported by 81% of HIV-infected youth.

Assessment of pain by HIV study group

Among all subjects, 37% reported having pain within the two months prior to study. There was no difference between the two groups in the proportion reporting current pain; however, a significantly higher percentage of HIV-infected subjects reported pain in the past two weeks and two months compared to controls (Table 2). Additionally, HIV+ youth were more likely to report pain lasting over one week. There were no group differences for the Wong-Baker FACES scale. Moreover, there were no group differences (youth 12–17 years) for the SF-MPQ VAS, total PRI, or sensory PRI. However, older controls had a marginally higher affective PRI scores (mean=0.79 vs 0.55, $p=0.06$).

Comparisons between HIV-infected and control subjects varied by both gender and age group. Among males, there was a higher prevalence of pain during the last two weeks for HIV-infected than controls (25% vs 14%, $p=0.03$), but no differences were observed in current pain, longer-term pain, duration of pain, or pain intensity as measured by the Wong-Baker FACES scale. In contrast, HIV-infected females had significantly higher rates of pain compared to control females during the last two months (46% vs 33%, $p=0.01$), and a higher proportion with pain of more than one-week duration (26% more vs 11%, $p=0.01$).

In the younger-aged cohort, there was significantly higher prevalence of pain in HIV-infected than control subjects within the last two months (46% vs 28%, $p=0.003$), within the last two weeks (34% vs 15%, $p<0.001$), and at enrollment (14% vs 7%, $p=0.09$). In addition, 29% reported duration of pain lasting more than one week compared to 7% of controls ($p<0.001$).

A multiple logistic regression model for pain in the last two months (Figure 1) indicated that, among controls, older children tended to report more pain than younger children, while among HIV-infected, younger girls and boys tended to report more pain than older HIV-infected youth. In a model restricted to HIV-infected children, notable predictors of pain

during the last two months included female sex (OR=1.53, $p=0.09$), White race (OR=2.15, $p=0.04$), and CDC class C (OR=1.83, $p=0.04$). After adjustment for these factors, entry CD4%, nadir CD4%, entry HIV-1 plasma viral load, and maximum past HIV-1 plasma RNA values were not predictive of pain.

Association of antiretroviral therapies with pain

There was no significant difference in rates of child-reported pain between those who had received specific antiretroviral medications versus those who had not received them (didanosine: 45% reporting pain vs 39% without pain, $p=0.38$; stavudine: 39% vs 42%, $p=0.72$; saquinavir: 38% vs 41%, $p=1.00$; and lopinavir/ritonavir: 38% vs 42%, $p=0.53$).

Caregiver–child agreement in perception of pain

Caregivers tended to underreport the participant's pain. Of the 207 children (HIV+ and HIV−) who self-reported pain in the last two months, only 52% of caregivers reported that their child had experienced pain (Figure 2). Of the 102 youth reporting that their pain interfered with everyday activities, only 22% of caregivers recognized such interference. When examined by HIV status, recognition by caregivers of child-reported pain during the last two months was 58% for HIV+ versus 41% for controls.

Association of psychiatric symptoms with self-reported pain

HIV-infected youth self-reporting pain had significantly higher mean symptom severity scores for GAD ($p<0.001$), MDD ($p<0.001$), and DD ($p<0.001$) than those not reporting pain (Figure 3). Similarly, caregivers of HIV+ youth reported greater symptom severity for each domain for the subjects with pain (GAD: 3.78 vs 3.00, $p=0.01$; MDD: 4.46 vs 3.79, $p=0.05$; DD: 3.70 vs 3.08, $p=0.04$). In contrast, there were no significant associations between pain and symptom severity in HIV-uninfected subjects as reported by either youths or their caregivers.

Logistic regression models for HIV+ subject-reported pain in the last two months showed an increased odds ratio of pain for each one-unit increase in the psychiatric severity score for generalized anxiety (OR: 1.14, $p=0.03$), major depression (OR: 1.15, $p=0.03$), and dysthymia (OR: 1.18, $p=0.01$) (Table 3). These associations persisted after adjustment for age and gender in the HIV-infected subjects, but were not observed in the uninfected controls. Additional factors explored were race, type of primary caregiver, education level of caregiver, and household income; these factors were consistently not significant.

Our study included 457 families, 91 of which had more than one child enrolled and 44 with both HIV+ and HIV− siblings participating. Accounting for clustering within families using GEE models had essentially no impact on estimated associations between psychiatric symptom severity and pain; estimated odds ratios in Table 3 were unchanged. However, caregivers reporting pain in one child were much more likely to report pain in a sibling (within-family correlation of approximately 0.20 overall), while subject-reported pain showed a lower within-family correlation (about 0.10).

Discussion

This is the first study to identify pain prevalence and its' association with psychiatric symptomatology in a large cohort of HIV-infected children compared to uninfected controls recruited from HIV-affected households. Our most important finding is a high prevalence of pain across all age groups, HIV-infected or not, with 37% of all subjects and 41% of HIV-infected children reporting pain during the two months prior to enrollment.

These rates are similar to the 44% reported in a recent Thai study (Lolekha et al., 2004) but higher than the 20% of 985 HIV-infected children spontaneously reporting pain in an earlier report from Pediatric AIDS Clinical Trials Group 219C observational data (Gaughan et al., 2002) based on symptom distress reported on the General Health Assessment for Children (GHAC). Comparison with our results to that report is problematic given differences in study design, measurement tools, subject age range, and the available treatment options. The increased prevalence of pain reported by Hirschfeld (59%) in the pre-HAART era (Hirschfeld, Moss, Dragisic, Smith, & Pizzo, 1996) may have been due to more advanced disease (<25% with >500 CD4 cells) and treatment with potentially toxic dual nucleoside antiretroviral agents.

Similar to other studies, we observed a higher rate of pain among all females than males (41% in the past two months vs 33%), and especially high rates of pain among HIV-infected females (47% vs 33% in uninfected females). Studies on both adults and youth have shown that females report higher levels of pain than males (Edwards, Haythornthwaite, Sullivan, & Fillingim, 2004; Fillingim, 2000; Martin, McGrath, Brown, & Katz, 2007). Behaviors to manage pain also differ, with males more likely to cope with pain through behavioral distraction, whereas females tend toward seeking social support and psychological relief through two ultimately negative mechanisms, internalization, and catastrophic thinking (Keogh & Eccleston, 2006; Lynch, Kashikar-Zuck, Goldschneider, & Jones, 2007).

Like Hirschfeld et al. (1996), we also found a higher rate of pain among younger HIV-infected children than among older ones. In fact, the overall difference in pain between HIV-infected and uninfected subjects was primarily attributable to that observed in younger children (46% vs 28%). We speculate that a heightened experience of pain with medical procedures in younger patients might contribute to this difference, perhaps underscored by less mature pain processing pathways and a more limited repertoire of coping mechanisms. Unexplored in this study, but perhaps relevant might be age-related differences in systemic inflammatory response to HIV-1 infection, with more inflammatory pain present in younger subjects.

We found that among HIV-infected children, females, those of White race, and those with an AIDS diagnosis had increased odds of reporting pain. The association of increased pain for those with CDC Class C is consistent with that previously reported by Gaughan et al. (2002). CD4% and viral load were not predictive of pain after adjustment for CDC class, perhaps because our study population was relatively healthy. Importantly, there was no association between any of the four antiretroviral agents examined and an increased prevalence of pain.

Stress is a known amplifier of pain in children (Ostberg, Alfvén, & Hjern, 2006). In our study, caregivers of HIV-uninfected subjects were less likely to have completed high school and tended to have lower household incomes, suggesting less access to resources. These data suggest that exposure to greater socioeconomic stresses may have contributed to the increased background rate of pain in the uninfected population, whereas perhaps other social stressors were more contributory in HIV-infected subjects.

Our data are consistent with past studies of pain in children documenting poor agreement between children's self-report of pain and those by their parents or primary caregivers (Chambers, Reid, Craig, McGrath, & Finley, 1998; Kelly, Powell, & Williams, 2002; Singer, Gulla, & Thode, 2002). Of all subjects reporting pain in the two months prior to enrollment, just slightly over half of the caregivers recognized pain in their child, and less than one quarter of the caregivers were aware that pain was severe enough to affect their child's daily activities. Agreement between child and caregiver reports of pain was higher

for HIV-infected subjects than controls (58% vs 41%), possibly reflecting increased sensitization to health issues or fewer socioeconomic stressors being present to distract the caregiver in the households of HIV-infected children.

Our data showed that HIV-infected children who reported pain had higher symptom severity scores for anxiety and depression. Even after adjustment for age, gender, and HIV status, we found that as the severity of generalized anxiety, major depression, or dysthymia symptoms increased, the odds of reported pain in our study subjects also increased, particularly among children with HIV infection. This finding warrants further exploration in pediatric studies evaluating associations between psychiatric symptoms, pain, and circulating proinflammatory cytokines, as have been identified in adults (Miller & O'Callaghan, 2005; Strouse, 2007; Wieseler-Frank, Maier, & Watkins, 2005).

Our study has several limitations. We did not obtain a detailed past pain history, and therefore did not examine the possibility of a confounding effect from early childhood painful conditions or ongoing chronic illness in HIV-uninfected controls. Pain diaries were not used; the possibility of recall bias exists. We did not obtain a pain history for primary caregivers. Child reports of current pain have been shown to be associated with parents' self-reported pain (Schanberg et al., 2001). A comparison group of children unaffected by HIV was not included, leaving unexamined the question of how our controls compare to other uninfected children.

In conclusion, we have identified a high prevalence of self-reported pain in HIV-infected children and adolescents compared to HIV-uninfected controls living in an HIV-affected household, more so in females and younger subjects. An AIDS diagnosis was associated with increased OR of reported pain, yet contrary to expectations, disease severity reflected by a CDC Class C disease, a low CD4% and high viral load were not predictive of pain. Economic and family stressors appear to be less a factor in reported pain in HIV+ than HIV-uninfected children. The high proportion of reported pain amongst uninfected children underscores the importance of querying for these stressors in the primary care setting when providing services for children living in an HIV-affected household. Lastly, increasing severity of generalized anxiety, major depression, and dysthymia symptoms in HIV-infected children were associated with significantly increased odds of pain. Queries concerning pain and psychiatric symptomatology should be incorporated into the primary and specialty care of HIV+ children and adolescents; children HIV-uninfected despite prior exposure and those living in a household with an HIV+ individual.

Acknowledgments

This work was supported by the National Institute of Allergy and Infectious Diseases Pediatric AIDS Clinical Trials Group, the National Institute of Child Health Pediatric and Perinatal HIV Clinical Trials Network, the National Institute of Mental Health, and National Institute of Allergy and Infectious Diseases cooperative agreement (AI-41110) for the Statistical and Data Management Center of IMPAACT. We would like to thank Kimberly Hudgens for her operational support of this study as well as Janice Hodge for data management.

The following institutions and individuals participated in IMPAACT P1055: San Juan City Hospital, Puerto Rico: M. Acevedo-Flores, L. Angeli, M. Gonzalez, D. Guzman; Yale University School of Medicine: W. Andiman, L. Hurst, A. Murphy, SUNY-Stony Brook: D. Ferraro, M. Kelly, L. Rubino; University of South Florida – Tampa: P. Emmanuel, J. Lujan Zilberman, C. Rodriguez, C. Graisbery; Harbor UCLA Medical Center: M. Keller, S. Wettgen, S. Sullivan, J. Hayes; Duke University Medical Center: K. Whitfield, S. Patil, J. Wilson, M.J. Hassett; UCSD Maternal, Child, and Adolescent HIV: S. Spector, L. Stangl, M. Caffery, R. Viani; Tulane/LSU Maternal/Child M. Silio, T. Alchediak, C. Borne, S. Bradford; University of Florida Jacksonville: M. Rathore, A. Mirza, K. Thoma, C. Griggs; New York University: S. Deygo, W. Borkowsky, S. Chandwani, M. Rigaud; Mount Sinai School of Medicine, NY: R. Posada, M. Dolan; UCLA-Los Angeles/Brazil AIDS Consortium (LABAC): K. Nielsen, N. Falgout, J. Geffen, J. Deville; University of Colorado-Denver: R. McEvoy, E. Barr, S. Paul, P. Michalek; Harvard Medical School-Children's Hospital Boston: S. Burchett; Long Beach Memorial Medical Center, Miller Children's Hospital: A. Deveikis; Harbor-UCLA Medical Center, Harbor: M. Keller; University of Maryland Medical Center:

V. Tepper; Children's Memorial Hospital-Chicago: R. Yogev; University of Miami: G. Scott; UCSF Pediatric AIDS: D. Wara; Jacobi Medical Center-Bronx: A. Wiznia; University of Washington Children's Hospital Seattle: L. Frenkel; SUNY Upstate Medical University: L. Weiner; Wayne State University Detroit: E. Moore; Howard University-Washington DC: S. Rana; University of Southern California-Los Angeles: S. Kapetanovic; South Florida Children's Diagnostic and Treatment Center-Ft Lauderdale: A. Puga; St. Jude Research Hospital-Memphis, TN: P. Garvie;

The Children's Hospital of Philadelphia: R. Rutstein; St. Christopher's Hospital for Children-Philadelphia: R. LaGuerre; Bronx-Lebanon Hospital: M. Purswani; St. Luke's-Roosevelt Hospital Center-NY: S. Arpadi; University of Massachusetts Medical School: K. Luzuriaga; Metropolitan Hospital Center-NY: M. Bamji.

The first and corresponding authors attest to having full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1.

A multiple logistics regression model was used to determine the percentage of HIV-infected versus uninfected control participant's self-reporting pain in the past two months within each age group and gender. Difference in reported pain between HIV-infected and controls varied significantly by age group ($p=0.03$).

Figure 2.

The percentage of primary caregivers acknowledging pain in their child compared to all children's self-report of pain. In general, pain was under-recognized by caregivers, as was pain's impact upon activities of daily living among the pediatric study participants.

Figure 3.

The association of pain with mean psychiatric symptom severity score in HIV-infected children. The mean symptom severity score is represented on the Y-axis. Across all domains, primary caregivers perceived their child to have less pain and a lower level of psychiatric symptomatology than the child self-reported.

Table 1

Demographic characteristics of study participants.

	Total	HIV+	HIV−	<i>p</i> -Value ^a
Gender	<i>N</i> =576	<i>N</i> =320	<i>N</i> =256	0.45 ^b
Male	285 (49%)	163 (51%)	122 (48%)	
Female	291 (51%)	157 (49%)	134 (52%)	
Race/ethnicity (self-report)				
White, non-Hispanic	84 (15%)	45 (14%)	39 (15%)	
Black, non-Hispanic	285 (49%)	174 (54%)	111 (44%)	
Hispanic	207 (36%)	101 (32%)	106 (41%)	
Age group at enrollment				<0.001 ^c
Median age at enrollment	12.4 years	13.1 years	11.3 years	
6–11 years old at enrollment	265 (46%)	118 (37%)	147 (57%)	
12+ years old at enrollment	311 (54%)	202 (63%)	109 (43%)	
<i>Gender and age</i>				
Male	285	163	122	
6–11 years	132	60 (37%)	72 (59%)	
12+ years	153	103 (63%)	50 (41%)	
Female	291	157	134	
6–11 years	129	55 (35%)	74 (55%)	
12+ years	162	102 (65%)	60 (45%)	
Primary caregiver (PCG)				<0.001 ^d
Biological parent(s)	339 (59%)	139 (43%)	200 (78%)	
Other relative, foster, adoptive	237 (41%)	181 (57%)	56 (22%)	
Primary caregiver education				0.01 ^d
≤ Eighth grade	60 (10%)	21 (7%)	39 (15%)	
Some high school	128 (22%)	70 (22%)	58 (23%)	
High school graduate and above	373 (65%)	220 (69%)	153 (60%)	
Missing data	15 (3%)	9 (3%)	6 (2%)	
PCG household income/year				0.001 ^b
<\$20,000/year	289 (50%)	134 (42%)	155 (61%)	
>\$20,000/year	225 (39%)	144 (45%)	81 (31%)	
Missing data	62 (11%)	42 (13%)	20 (8%)	

^aMissing data excluded.^bFisher's exact test.^cKruskal–Wallis test.^dPearson's chi-squared test.

Table 2

Subject reported pain by HIV infection status.

	Total (N=576)	HIV+ (N=320)	HIV- (N=256)	p-Value^a
Pain in the <i>last two months</i>	212 (37%)	130 (41%)	82 (32%)	0.04 ^b
Males	94	34%	31%	0.70 ^b
Females	118	47%	33%	0.01^b
Pain in the <i>last two weeks</i>	141 (24%)	91 (28%)	50 (19%)	0.02^b
Males	58	25%	14%	0.03^b
Females	83	32%	25%	0.19 ^b
Duration <i>>one week</i>	92 (16%)	64 (20%)	28 (11%)	0.03^c
Males	36	14%	10%	0.85 ^c
Females	56	26%	11%	0.01^c

^a Unknowns excluded: missing pain assessments: six in last two months, four in last two weeks, seven in pain duration >one week.

^b Fisher's exact test.

^c Pearson's chi-square test.

Note: Bold values are statistically significant at less than 0.05.

Table 3

Symptom severity on the presence of subject and caregiver reported pain in the last two months adjusted for age, sex, and age by sex interaction and in all subjects, for HIV status and age by HIV interaction.

Subgroup	Psychiatric symptom	Reporter	N	OR (adjusted)	95% Confidence interval	p-Value (adjusted)
All subjects	Generalized anxiety	Subject	558	1.07	(1.03, 1.12)	0.002
		Caregiver	556	1.08	(1.01, 1.15)	0.02
	Major depression	Subject	558	1.06	(1.02, 1.10)	0.004
		Caregiver	556	1.06	(1.00, 1.13)	0.07
HIV-infected	Dysthymia	Subject	558	1.07	(1.03, 1.11)	0.001
		Caregiver	556	1.09	(1.01, 1.16)	0.02
	Generalized anxiety	Subject	311	1.14	(1.01, 1.28)	0.03
		Caregiver	309	1.13	(0.97, 1.32)	0.11
	Major depression	Subject	311	1.15	(1.02, 1.30)	0.03
		Caregiver	309	1.14	(0.97, 1.33)	0.13
HIV-uninfected	Dysthymia	Subject	311	1.18	(1.04, 1.33)	0.01
		Caregiver	309	1.18	(0.97, 1.44)	0.10
	Generalized anxiety	Subject	247	1.08	(0.96, 1.22)	0.18
		Caregiver	247	1.22	(0.96, 1.56)	0.11
	Major depression	Subject	247	1.08	(0.97, 1.21)	0.16
		Caregiver	247	1.25	(0.95, 1.64)	0.11
	Dysthymia	Subject	247	1.08	(0.96, 1.20)	0.20
		Caregiver	247	1.31	(0.96, 1.81)	0.09

Note: Odds ratios refer to the odds ratio of pain given a one-unit increase in the psychiatric severity score. These models show that as the severity of the reported symptom increased, the odds of reported pain also increased. Bold values are statistically significant at less than 0.05.