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Substance Use and its Association with Psychiatric Symptoms in Perinatally HIV-infected and HIV-Affected Adolescents

Paige L. Williams

Center for Biostatistics in AIDS Research, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115, USA

Department of Biostatistics, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA, USA

Erin Leister and Miriam Chernoff

Center for Biostatistics in AIDS Research, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115, USA

Sharon Nachman

Department of Pediatrics, Stony Brook University, Stony Brook, NY, USA

Edward Morse

Tulane University Health Sciences Center, New Orleans, LA, USA

Vinnie Di Poalo

Robert Wood Johnson University Hospital, Hazlet, NJ, USA

Kenneth D. Gadow

Department of Psychiatry and Behavioral Science, Stony Brook University, Stony Brook, NY, USA

Abstract

Drug use in combination with psychiatric illness may lead to unsafe sexual risk behavior and increased risk for secondary HIV transmission among adolescents with HIV infection. We compared the prevalence of substance use for perinatally HIV-infected youth to uninfected adolescents living in families affected by HIV infection, and evaluated the association of psychiatric symptoms with risk of substance use. Among 299 adolescents (196 HIV+, 103 HIV–) aged 12–18 years enrolled in IMPAACT P1055, a multisite US cohort study, 14% reported substance use at enrollment (HIV+: 13%, HIV–: 16%). In adjusted logistic regression models, adolescents had significantly higher odds of substance use if they met symptom criteria for ADHD [adjusted odds ratio (aOR) = 2.7, Wald $\chi^2 = 5.18$, $P = 0.02$], major depression or dysthymia (aOR = 4.0, Wald $\chi^2 = 7.36$, $P = 0.01$), oppositional defiant disorder (aOR = 4.8, Wald $\chi^2 = 12.7$, $P = 0.001$), or conduct disorder (aOR = 15.4, Wald $\chi^2 = 28.12$, $P = 0.001$). Among HIV-infected youth, those with lower CD4 lymphocyte percentage (CD4% < 25%) had significantly increased risk of substance use (aOR = 2.7, Wald $\chi^2 = 4.79$, $P = 0.03$). However, there was no overall association of substance use with HIV infection status, and the association between psychiatric symptoms and substance use did not differ by HIV status. Programs to prevent substance use should target both HIV-infected and uninfected adolescents living in families affected by HIV infection, particularly those with psychiatric symptoms.

Keywords

Psychiatric symptoms; Substance use; Adolescents; HIV; Perinatal HIV exposure; ADHD; Conduct disorder; Major depressive disorder; Generalized anxiety; Oppositional defiant disorder

Introduction

The HIV-1 virus enters the developing central nervous system of perinatally-infected children and may result in chronic neuroinflammation, which in turn may adversely impact brain development and diminish neuropsychiatric functionality [1, 2]. Adolescents perinatally-infected with HIV have been reported to have a high rate of psychiatric symptoms, particularly attention deficits and depression [3-14]. However, rates have also been noted to be very high among perinatally HIV-exposed but uninfected youth from similar family backgrounds [10-12, 15, 16]. Factors which may contribute to development of such psychiatric symptoms include low socioeconomic status and parental or caregiver mental health issues [15, 16]. Children from poor and minority families are generally less likely to receive appropriate intervention for mental health concerns than those of more affluent families, yet low-income children with perinatally-acquired HIV may be better connected to health care delivery systems than those without such chronic health concerns [14, 15]. Thus, somewhat paradoxically, HIV-infected youth with psychiatric conditions may be more likely to be identified and receive psychiatric treatment [11, 12]. These issues are of increasing public health importance, given that over 100,000 women were living with HIV in the US in 2006, and almost 9,000 children were born to HIV-infected women [17].

Previous studies in youth with psychiatric issues such as attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) have reported increased rates of substance use [18-22]. In particular, disruptive behaviors including ADHD, ODD, and CD may predispose youth to later substance use, or may conversely reflect early behavioral manifestations of risk for psychopathology such as substance use disorders [23]. Adolescents experiencing chronic and often painful conditions such as HIV infection [24] may be more likely to self-medicate with illicit substances if not receiving appropriate medical treatment. In addition, adolescents with HIV infection often face additional home environment factors such as poverty, maternal depression, caregiver substance use, and stressful life events, which may contribute to higher risk of substance use. Many of these environmental factors are also shared by uninfected children born to HIV-infected mothers [15, 16].

A recent study by Mellins et al. [10] evaluated psychiatric conditions including substance use disorders in a cohort of 340 youth aged 9–16 years, including 206 children with HIV infection and 134 perinatally exposed HIV-uninfected youth. Using the Diagnostic and Statistical Manual (DSM) of Mental Disorders system to define disorders, they found that 12 children (3.5%) met the criteria for a substance use disorder. The rate appeared slightly lower among HIV-infected than among the HIV-uninfected group (1.9% vs. 6.0%), but the small number with substance use in this relatively young cohort (mean age 12.2 years) prevented further evaluation of differences adjusting for important demographic and caregiver characteristics.

P1055 was a multicenter, prospective observational study conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network to better understand the impact of HIV on development of psychiatric symptoms in a cohort of perinatally HIV-infected children and adolescents aged 6–17 years at study entry. Enrolled participants aged 12 and older self-reported on use of tobacco, alcohol, marijuana, and illicit

substances; substance use in these adolescents was also collected from their primary caregivers. The objectives of this study were to estimate the prevalence of adolescent substance use, compare rates of substance use between perinatally HIV-infected and control participants from a similar background, and to evaluate the association of substance use with psychiatric symptoms. We hypothesized that adolescents with HIV infection would have greater risk of substance use due to the challenges of living with a chronic and often painful disease in combination with both the relatively common occurrence of mental health problems noted previously in this population and need to manage stressful home environments during the already challenging teenage years. At the same time, we hypothesized that the excess risk of substance use in HIV-infected adolescents would be mediated by a greater likelihood of receiving treatment for psychiatric conditions, reducing the need to self-medicate with illicit substances.

Methods

Study Design and Participants

The IMPAACT P1055 study was designed to evaluate the prevalence and severity of psychiatric symptoms in HIV-infected children aged 6–17 years at entry 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. The “HIV-affected” control group was selected to provide a group which was socioeconomically comparable and similar with respect to family and household stresses. Enrollment was stratified by age at entry (<12 years vs. ≥12) and sex within each group, with a target accrual of 100 subjects within each age-sex stratum in an attempt to balance the two groups. The study design included an entry visit along with two follow-up visits at approximately 1 year and 2 years after enrollment, although this analysis considers only data from the entry visit. HIV-infected and control subjects were recruited into P1055 from 29 IMPAACT sites in the United States and Puerto Rico after review and approval of the research protocol by the Institutional Review Boards of participating institutions. Written informed consent was obtained from the participants' legal guardians prior to enrollment, and written assent was obtained from the participating adolescent.

All participants were required to have been living with the same parent or primary caregiver for at least 12 months prior to evaluation, and not known to be cognitively incapable of responding to the study questionnaires (IQ < 70). At study entry, demographic and household characteristics were collected on all subjects. Some subjects were enrolled at age 17 but turned 18 prior to their study entry visit. For HIV-infected subjects, health characteristics (CD4%, HIV-1 plasma viral load, CDC Clinical Classification) and a lifetime history of antiretroviral treatment were obtained. History of major medical and psychiatric diagnoses and use of psychotropic medications were collected. The study opened in June 2005, closed to new enrollees September 2006, and completed the 2 years of follow-up in December 2008. Additional details of the study conduct have been described previously [11, 12].

Psychiatric and Substance Use Measures

Psychiatric assessments were based on youth and care-giver-completed Symptom Inventory instruments (YI-4 and CASI-4R, respectively) [25-27] which were used to evaluate the symptoms of ADHD, Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), Dysthymic Disorder (DD), ODD, and CD. The 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; thus the analysis relies on both a continuous

severity score measure and a binary (yes/no) symptom cutoff indicator. The symptom cutoff indicator was considered met if indicated by either the caregiver or the adolescent, consistent with the approach of Mellins et al. [10]. A combined symptom cutoff and severity score was calculated for MDD or dysthymia. Severity scores for ADHD Hyperactive type (ADHD-H) and Inattentive type (ADHD-I) were considered separately, but a single symptom cutoff was calculated for any type of ADHD.

In addition to assessments of psychiatric symptoms, adolescents aged 12 and older completed assessments of substance use and their caregivers completed instruments which collected both their assessment of their child's substance use along with their own self-reported substance use. Adolescents were classified as "substance users" if either they self-identified as a substance user (i.e., reported use of marijuana, alcohol, or other illegal drugs), or their caregiver identified that the adolescent was a user of these substances. Tobacco use was collected but not considered an indicator of substance use in our analysis. We also evaluated whether the youth or caregiver reported any "trouble functioning" caused by use of illegal drugs use or alcohol. We predicted that behavioral problems including disruptive and antisocial behavior would put both HIV-infected and HIV-affected youth at higher risk for substance use.

Statistical Analyses

We conducted a cross-sectional analysis of prior or current substance use reported at study entry by participants or their caregivers for adolescents aged 12 and older. Prevalence of substance use was compared between HIV-infected and control subjects using Fisher's exact tests. Comparisons of demographic characteristics between groups (both HIV-infected versus uninfected, and substance users versus non-users) were performed using Fisher's exact test for characteristics other than age, for which a Wilcoxon rank sum test was used. Multiple logistic regression models were fit to evaluate the effect of HIV status along with psychiatric symptoms and severity on reported substance use adjusting for age, gender, and other potential confounders. Unadjusted odds ratios (ORs) and adjusted ORs (aORs) are presented along with their corresponding 95% confidence intervals (CIs), Wald χ^2 test statistics, and *P*-values. Sensitivity analyses were conducted using generalized estimating equation (GEE) models to account for clustering of siblings within the same family. In summarizing results, two-sided *P*-values < 0.05 were considered statistically significant. All analyses were conducted using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Demographics

A total of 319 HIV-infected and 256 uninfected control subjects were enrolled into P1055 between June 2005 and September 2006, including 309 adolescents aged 12 or greater at the entry visit. Ten of these subjects were excluded due to missing substance use or psychiatric symptom information from either the youth or caregiver reports. Characteristics of the 299 adolescents (196 HIV-infected and 103 controls) included in the analysis are summarized in Table 1, by both HIV status and by reported substance use. The median age was 14.7 years; half were female, 46% Black, and 38% Hispanic. The HIV-infected group was slightly older (8–9 months, on average), and were more likely to be black non-Hispanic than the uninfected control group (53% vs. 34%, Fisher's exact test *P* = 0.002). HIV-infected subjects were also significantly less likely to have a biological parent as primary caregiver, and less likely to have an annual household income less than \$20,000. Past or current use of psychiatric medications was reported by 22%, primarily stimulants (15%) or antidepressants (10%). Among the 196 HIV-infected subjects, 22% had a past or current AIDS diagnosis (CDC Clinical Class C). The median CD4 percentage was 30%, with over half the group

(54%) having less than 400 copies/ml HIV-1 RNA. Use of HAART with or without a protease inhibitor at the time of study entry was reported by 80% of the HIV-infected adolescents.

Prevalence of Substance Use

Overall, 41 of the 299 participants (14%) were identified as substance users by either the participant or their caregiver; reported substance use consisted mostly of alcohol ($n = 32$) or marijuana use ($n = 24$), with only one adolescent using other illegal drugs. Among the 41 subjects classified as substance users, 21 (51%) were reported to have some trouble functioning due to this substance use. Smoking of tobacco was reported for 24 youth (8%), and 26% of caregivers reported smoking tobacco themselves; however, smoking tobacco was not included in measures of substance use. Adolescents with any reported substance use were significantly older than non-users (median 15.8 years vs. 14.6 years, Wilcoxon rank sum statistic = 4.07, $P < 0.001$); 29 of 129 adolescents aged 15 or older (22%) reported use as compared to 12 of 170 (7%) aged 14 or under. There was no difference in the proportion of substance users and non-users who were currently taking or had previously received psychiatric medications.

A relatively large percentage of caregivers self-reported using substances themselves (39%), with 37% reporting alcohol use (34% drank “sometimes”, 3% drank “often” or “very often”), 5% reporting marijuana use (3% used sometimes, 2% used “often” or “very often”), and 1 (<1%) reporting use of other illegal drugs. Care-givers were also questioned about their own use of prescription drugs, and 6 (2%) reported overuse of prescription drugs. The caregivers of adolescent substance users were more likely to be users themselves (54% vs. 37%, Fisher's exact test $P = 0.06$). In addition, caregivers of adolescent users were more likely to be high school graduates than those of non-users (83% vs. 67%, Fisher's exact test $P = 0.05$).

Assessment of Substance Use by HIV Status

There was no overall difference in the percentage of substance users between HIV-infected versus control subjects; 25 of 196 HIV-infected adolescents reported substance use (13%) versus 16 of 103 control participants (16%, unadjusted Wald $\chi^2 = 0.44$, $P = 0.51$). However, given the imbalance in demographic and caregiver characteristics between HIV-infected and control groups, adjusted analyses were also conducted. After adjustment for age group, sex, race, and caregiver characteristics, there remained no association between HIV status and reported substance use (aOR = 0.67, 95% CI: 0.31, 1.49, Wald $\chi^2 = 0.94$, $P = 0.33$, Table 2).

The final multiple logistic regression model indicated that subjects 15 years and older had almost four times the risk of substance use as compared to younger adolescents (aOR = 3.78, 95% CI: 1.75, 8.13, Wald $\chi^2 = 11.53$, $P = 0.001$) and those with a caregiver other than a biological parent had significantly lower risk (aOR = 0.43, 95% CI: 0.19, 0.94, Wald $\chi^2 = 4.47$, $P = 0.03$) (see Table 2). The odds of substance use among participating adolescents was doubled among those whose caregivers also reported substance use, although after adjustment this association was only marginally significant (aOR = 2.01, 95% CI: 0.98, 4.12, Wald $\chi^2 = 3.62$, $P = 0.06$). Similarly, low caregiver education was associated with reduced odds of adolescent substance use in crude models, but became non-significant after adjustment for other factors.

Association of Substance Use with HIV Disease Severity in HIV-Infected Youth

In addition to evaluating differences in substance use by HIV infection status, we also considered whether there was any association of measures of HIV disease severity with risk of substance use within the subgroup of HIV-infected subjects. Substance users had a lower

median CD4 cell count and lower median CD4% than non-users (440 vs. 638 cells/mm³ and 23% vs. 31%, respectively), and a higher percentage of substance users had HIV viral load > 400 copies/ml (63% vs. 43%, Fisher's exact test $P = 0.08$). The percent with prior CDC class C diagnosis was also slightly higher in users as compared to non-users, although not significantly so (28% vs. 22%, Fisher's exact test $P = 0.45$). The percent receiving HAART treatment was similar for substance users and non-users (79% vs. 84%). After adjustment for age and caregiver relationship (biological parent or not), there was no association between HIV viral load or CDC class on risk of substance use among the 196 HIV-infected subjects. However, there remained a significant elevation in risk of substance use for those with CD4% < 25% (aOR = 2.70, Wald $\chi^2 = 4.79$, $P = 0.03$), and a marginally significant elevation in risk for those with CD4 count < 350 cells/mm³ (aOR = 2.43, Wald $\chi^2 = 2.83$, $P = 0.09$).

Association of Substance Use with Psychiatric Symptoms

The rates of psychiatric conditions (based on exceeding symptom cutoffs) were relatively high in this adolescent cohort, with 20% meeting symptom cutoffs based on either youth or caregiver reports for ADHD, 12% for CD, 15% with ODD, and 11% with either major depression or dysthymia (see Table 3). Generalized anxiety was reported at slightly lower rates (7%). Overall, 32% met symptoms cutoffs for at least one of the targeted conditions. However, there were no significant differences in rates of these conditions between HIV-infected and HIV-uninfected controls in this adolescent cohort, consistent with the evaluation of the entire cohort reported previously [12].

Youth with psychiatric conditions based on exceeding symptom cutoff scores from either youth or caregiver reports were more likely to be substance users: 25% of the adolescents meeting criteria for at least one condition were classified as substance users, as compared to 8% of those meeting none of the psychiatric conditions (Fisher's exact test $P < 0.001$). In logistic regression models, those meeting specific symptom cutoffs for ADHD, CD, major depression/dysthymia, and ODD had significantly elevated risk of substance use (Table 4). More specifically, 23% of those with ADHD reported substance use as compared to 11% of those without ADHD (aOR = 2.70, 95% CI: 1.15, 6.35, Wald $\chi^2 = 5.18$, $P = 0.02$), and 27% of those with major depression or dysthymia reported substance use as compared to 12% of those without depression or dysthymia (aOR = 3.96, 95% CI: 1.46, 10.68, Wald $\chi^2 = 7.36$, $P = 0.01$). The association was particularly striking for CD, for which 49% reported substance use as compared to 9% of those without CD (aOR = 15.4, 95% CI: 5.6, 42.3, Wald $\chi^2 = 28.12$, $P = 0.001$). Those meeting generalized anxiety cutoffs also tended to have higher risk of substance use, but not significantly so (aOR = 2.63, Wald $\chi^2 = 2.64$, $P = 0.10$).

Logistic regression models adjusting for demographic and caregiver characteristics also showed that as the severity of the reported symptoms increased, the odds of substance use also increased. The symptom severity scores as based on the youth self-reports showed a consistent significant association of severity of ADHD-H, CD, generalized anxiety, major depression/dysthymia, and ODD with risk of substance use, with a 7–55% increase in odds of substance use for each additional point on the severity scale. Caregiver-assessed severity scores tended to be much lower on average, and only CD and ODD severity scores showed a significant association with risk of substance use. Further analyses were conducted to evaluate the “dose-response” relationship between youth-reported severity scores and odds of substance use, by breaking the severity score into quartiles and estimating the incremental effect of each quartile versus the lowest quartile of severity scores. These analyses demonstrated across all domains that the association between severity scores and substance use was primarily attributable to an increased risk of substance use for those with severity scores in the highest quartile (see Fig. 1).

HIV infection status was not a significant predictor of substance use in any of the models evaluating the association between symptom cutoffs or severity with risk of substance use, as summarized in Table 4. However, in these adjusted models, the estimated ORs for HIV status tended to be consistently less than one, suggesting lower risk of substance use for HIV-infected versus uninfected controls after adjusting for other factors. We also investigated possible effect modification of the relationship between psychiatric symptoms and substance use by HIV infection status, but found no significant differences in these relationships for HIV-infected and uninfected controls. In addition, within the subset of HIV-infected subjects, there was no qualitative change in the estimated effects of psychiatric symptoms on risk of substance use after adjustment for measures of HIV disease severity, including CD4% < 25%.

Finally, we conducted sensitivity analyses of the findings described above to evaluate the impact of family composition on our results. The P1055 study encouraged enrollment of siblings, and overall 20% of families participating in the study enrolled more than one participant. The subgroup of 299 adolescents in our analysis included 257 families, with 223 enrolling only a single child and 34 (13%) enrolling multiple children. Due to the common effects of both genetics and household environment, it is more likely that children within a household will have similar traits, both in terms of psychiatric symptoms and substance use. We repeated the above logistic regression analyses using GEE models, accounting for within-family correlation with an exchangeable correlation structure. Although we observed moderate within-family correlation in reported substance use, there was minimal effect of accounting for such correlation on the association between symptom conditions and severity on odds of substance use.

Discussion

In this study, we identified a relatively high prevalence of substance use in 12–18 year old HIV-infected and uninfected control children, with 14% of participating adolescents and 22% of those aged 15 or older having self-reported or caregiver-reported use of alcohol, marijuana, or other illegal drugs. These rates are substantially higher than reported in a similar cohort of perinatally HIV-exposed children studied by Mellins et al., where 2% of HIV-infected and 6% of uninfected were classified with substance use disorder using DSM-IV criteria [10]. The slightly higher observed substance use rates in our study may be partly attributable to the lower age range in the cohort studied by Mellins et al. (mean age = 12.2 years vs. 14.7 in our study).

Consistent with other studies in the general adolescent population, we found a strong association of psychiatric symptoms with substance use, particularly for CD, ODD, and depressive disorders (major depression and dysthymia), and to lesser extent for ADHD and generalized anxiety. The increased risk we observed for CD and oppositional disorder is consistent with the “cascade” model proposed by Martel et al. [17], who proposed that inattention/hyperactivity would increase risk for conduct problems, and conduct problems would in turn increase risk for substance abuse. The pathway between CD and substance use has been similarly demonstrated by others [28].

We observed no increase in risk of substance use for HIV-infected subjects, either with or without adjustment for psychiatric symptoms or severity. In addition, the relationship between psychiatric symptoms and risk of substance use did not appear to differ between those who were infected versus uninfected. Since HIV-infected youth receiving appropriate health care may be more likely to be treated with medications for psychiatric conditions, as demonstrated by other work on this cohort [11], we hypothesized that such psychiatric medication use may be associated with lower risk of substance use while those not receiving

such treatment may be more likely to self-medicate with illicit substances. However, we did not find any association of psychiatric medication use on the risk of substance use in our cohort. The suggestion of slightly lower risk of substance use among HIV-infected subjects, although not statistically significant, may reflect the additional family and emotional support provided either directly or indirectly through HIV clinics to the HIV-infected adolescents.

While there was no overall association of HIV infection status with risk of substance use, we observed increased risk of substance use among HIV-infected youth with more severe HIV disease. In particular, youth with lower CD4% had more than twice the odds of substance use, even after adjustment for age and other risk factors. For other measures of disease severity, such as prior CDC class C diagnosis and HIV RNA viral load, associations with increased risk of substance use were observed in crude analyses but not after adjustment for age. The attenuation of risk estimates after adjustment for age was to be expected given the generally greater HIV disease severity among the older youth (15–18 years) in our study, many of whom were born prior to the availability and/or widespread use of effective ART combinations used in current HAART regimens. In addition, the older youth were slightly less likely to be on HAART (77% vs. 82%) and more likely to be on no ART (16% vs. 6%). Thus, the effects of increased risk of substance use for older HIV-infected youth may reflect both increased risk-taking behavior of the older children, which was also observed among our control group, along with concurrent effects of less effective treatment and more severe HIV disease. These results differed from those found in a study conducted among 350 HIV-infected youth by Rotheram-Borus et al. [29], in which HIV-infected youth with AIDS tended to use fewer hard drugs, and were less likely to have prior use than those without AIDS of both marijuana (59% vs. 79%) and alcohol (84% vs. 94%). However, their study was conducted in an older population (mean age 21 years), and lower levels of substance use were observed among youth with AIDS despite higher levels of emotional distress and mental health counseling visits compared to asymptomatic youth with HIV.

In our original design for this study, we had hypothesized that HIV-infected children would have higher rates of psychiatric problems than control children affected by HIV. This hypothesis was based on limited anecdotal evidence of psychiatric problems in HIV-infected children and adolescents which had been published when our study was designed in 2004. However, it was also based on a scientifically-based rationale regarding the ability of HIV to penetrate the central nervous system, high rates of pain noted in HIV-infected children in prior studies, and a vulnerability model of the psychological effect of chronic childhood diseases, including HIV infection, on the maturing brain. Secondly, we had hypothesized that the higher rate of psychiatric problems which we expected to see among the HIV-infected adolescents would in turn lead to a higher rate of substance use. Since 2004, our study and several similar studies have found that there are high rates of psychiatric problems among all children living in households affected by HIV, whether the children themselves are HIV-infected or not. These rates are higher than observed in the US population for several specific conditions. However, the rates of psychiatric problems do not seem to be increased by HIV infection itself, suggesting that household environment and parental interaction may be stronger forces in shaping psychological health of their children.

Our study has several limitations. First, our cross-sectional analysis of data collected at study entry can only reveal associations rather than causal effects. Future analyses of this recently closed study will evaluate the association of psychiatric conditions reported at the study entry visit with development of incident substance use. Because the cohort has aged in the two-year follow-up period, we would expect the substance use to increase as the pre-adolescents age into adolescence. Another limitation is that our control group of HIV-uninfected youth was a mixture of two different groups: seroreverters (perinatally HIV-exposed but uninfected), and youth living in a household with an HIV-infected member. In

fact, most perinatally HIV-exposed youth also reported living in a household with an HIV-infected family member, and the control group appears very similar demographically to the seroreverter group studied by Mellins et al. [10]. Similar to the Mellins study, we found that the HIV-infected youth were less likely to live with a biological parent (instead living with a grandparent, older relative, or foster parent), and perhaps as a consequence had higher household income and caregiver education level. Racial and ethnic backgrounds were also similar to the Mellins study. However, the lack of balance between the two groups with respect to caregiver and household characteristics points to the difficulties in identifying the ideal control group for comparing to HIV-infected adolescents.

However, our study also has several strengths. First, the assessment of psychiatric conditions is based on DSM-IV criteria, but in a confidential questionnaire format that encourages accurate responses. Use of symptom severity scores allows a continuous scoring approach which provides additional power for detecting associations. Our data and modeling strategy allowed confirmation of results after adjustment for participants from the same households (25% of participants). In addition, while prior studies were often limited to a single geographic area, we had wide geographic representation from our 29 US study sites, increasing the generalizability of our findings.

In conclusion, we have evaluated the prevalence and predictive factors for substance reported by adolescents participating in IMPAACT P1055 and their association with psychiatric symptoms. Contrary to expectations, HIV-infected children were not significantly more likely to report substance use. However, increasing severity of anxiety and depression symptoms in both HIV-infected and HIV-affected adolescents were associated with significantly increased odds of substance use. These patterns are important to identify as early as possible, since drug use in combination with psychiatric illness may lead to unsafe sexual risk behavior and increased risk for secondary HIV transmission [30-36]. It appears clear that HIV-affected adolescents also have high rates of both psychiatric conditions and substance use, and the number of such youth in the US is growing [17]. These adolescents are particularly vulnerable, since they are at risk for multiple types of poor outcomes [37, 38], yet may not be identified in typical health care settings. Thus, targeting of both HIV-infected youth and those living in households affected by HIV who have psychiatric conditions is extremely important for public health programs; intervention programs should address both populations for maximum benefits.

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Appendix

Institutions and site staff who enrolled participants to the study IMPAACT P1055, conducted by the International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) group:

Children's Hospital Boston, Div. of Infectious Diseases: S Burchett; UCLA-Los Angeles/Brazil AIDS Consortium: K Nielsen, N Falgout, J Geffen, JG Deville; Long Beach Memorial Medical Center, Miller Children's Hospital: A Deveikis; Harbor—UCLA Medical Center—Dept. of Peds, Div. of Infectious Diseases: M Keller; Univ. of Maryland Med. Ctr., Div. of Ped. Immunology & Rheumatology: V Tepper; Chicago Children's: R Yogev; UCSF Pediatric AIDS CRS: D Wara; UCSD Maternal, Child, and Adolescent HIV: SA Spector, L Stangl, M Caffery, R Viani; DUMC Ped; K Whitfield, S Patil, J Wilson, MJ Hassett; New York University: S Deygoo, W Borkowsky, S Chandwani, M Rigaud; Jacobi Medical Center Bronx: A Wiznia; Univ. of Washington Children's Hosp. Seattle: L Frenkel; USF—Tampa: P Emmanuel, J Zilberman, C Rodriguez, C Graisbery; Mount Sinai School of Medicine, NY: R Posada, MS Dolan; San Juan City Hospital: M Acevedo-Flores, L Angeli, M Gonzalez, D Guzman; Yale Univ. School of Medicine—Dept. of Peds., Div. of Infectious Disease: WA Andiman, L Hurst, A Murphy; SUNY Upstate Med. Univ., Dept. of Peds: L Weiner; SUNY Stony Brook: D Ferraro, M Kelly, L Rubino; Howard Univ. Washington DC: S Rana; University of Southern California: S Kapetanovic; Univ. of Florida Jacksonville: MH Rathore, A Mirza, K Thoma, C Griggs; Univ. of Colorado Denver: R McEvoy, E Barr, S Paul, P Michalek; South Florida CDC Ft Lauderdale: A Puga; St. Jude/UTHSC: P Garvie; The Children's Hosp. of Philadelphia: R Rutstein; St. Christopher's Hosp. for Children: R LaGuerre; Bronx-Lebanon Hospital: M Purswani; Metropolitan Hospital Center: M Bamji; WNE Maternal Pediatric Adolescent AIDS: K Luzuriaga.

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Fig. 1. Estimated probability of substance use by quartiles of symptom severity and age group (12–14 years vs. 15–18 years) for youth-assessed conduct disorder **(a)** and depression or dysthymia **(b)**. Models adjusted for HIV status, age, gender, race, psychiatric medication use, and caregiver relationship, education, and substance use

Demographic and caregiver characteristics of 299 adolescents participating in IMPAACT P1055, by HIV status and reported substance use

Table 1

	Total (N = 299)	HIV status		Substance use ^a		Users versus non-users P-value*
		HIV-infected (N = 196)	HIV-uninfected (N = 103)	Not a user (N = 258)	User (N = 41)	
HIV status						
HIV-infected	196 (66%)	196 (100%)	–	171 (66%)	25 (61%)	0.60
HIV-uninfected	103 (34%)	–	103 (100%)	87 (34%)	16 (39%)	
Female	149 (50%)	95 (48%)	54 (52%)	129 (50%)	20 (49%)	1.00
Race/ethnicity						
White non-hispanic	47 (16%)	32 (16%)	15 (15%)	43 (17%)	4 (10%)	0.57
Black non-hispanic	138 (46%)	103 (53%)	35 (34%)	118 (46%)	20 (49%)	
Hispanic	114 (38%)	61 (31%)	53 (51%)	97 (38%)	17 (41%)	
Age at entry visit (years)						
Median	14.8	14.9	14.4	14.6	15.8	<0.001
Age 12–14	170 (57%)	100 (51%)	70 (68%)	158 (61%)	12 (29%)	
Age 15–18	129 (43%)	96 (49%)	33 (32%)	100 (39%)	29 (71%)	
Participant psychiatric medication use						
Current	38 (13%)	28 (14%)	10 (10%)	33 (13%)	5 (12%)	1.00
Current or previous	67 (22%)	54 (28%)	13 (13%)	56 (22%)	11 (27%)	0.55
Caregiver substance use ^b	115 (39%)	72 (37%)	43 (42%)	93 (37%)	22 (54%)	0.06
Caregiver is biological parent ^b	141 (48%)	73 (38%)	68 (67%)	117 (45%)	24 (59%)	0.18
Household income<\$20,000 ^b	140 (53%)	78 (46%)	62 (63%)	118 (52%)	22 (59%)	0.38
Caregiver not HS graduate ^b	93 (31%)	59 (31%)	34 (35%)	86 (33%)	7 (18%)	0.05

* P-value calculated using Fisher's exact test for all comparisons of characteristics between substance users versus non-users except for age, for which a Wilcoxon rank sum test was used (Wilcoxon rank sum statistic = 4.07, $P < 0.001$)

^a Substance use (alcohol, marijuana, or other illegal drugs) reported by participant or their caregiver

^b 4 participants missing information on caregiver substance use, 4 missing caregiver relationship to participant, 33 missing household income level, 1 missing caregiver education level

Unadjusted and adjusted effects of HIV infection and other factors on risk of substance use in adolescents aged 12–18 years in IMPAACT P1055

Table 2

Covariate	Crude OR for substance use (95% CI)	Wald χ^2	P-value	Adjusted OR for substance use ^a (95% CI)	Wald χ^2	P-value
General demographic and caregiver characteristics in overall cohort (N = 299)						
HIV-infected versus uninfected	0.79 (0.40, 1.57)	0.44	0.51	0.67 (0.31, 1.49)	0.94	0.33
Age 15–18 versus 12–14	3.82 (1.86, 7.83)	13.38	<0.001	3.78 (1.75, 8.13)	11.53	0.001
Female versus male	0.95 (0.49, 1.84)	0.02	0.88	1.09 (0.53, 2.23)	0.05	0.82
Race						
Black versus white/other	1.82 (0.59, 5.63)	1.09	0.30	2.49 (0.75, 8.25)	2.22	0.14
Hispanic versus white/other	1.88 (0.60, 5.93)	1.17	0.28	2.67 (0.79, 9.07)	2.48	0.12
Received psychiatric medications	1.32 (0.62, 2.80)	0.53	0.47	1.94 (0.81, 4.65)	2.21	0.14
Caregiver not biological parent	0.60 (0.31, 1.18)	2.17	0.14	0.43 (0.19, 0.94)	4.47	0.03
Caregiver not HS graduate	0.42 (0.18, 1.00)	3.86	0.05	0.44 (0.18, 1.10)	3.09	0.08
Caregiver substance use	2.00 (1.03, 3.90)	4.20	0.04	2.01 (0.98, 4.12)	3.62	0.06
HIV disease severity risk factors among HIV-infected (N = 196) ^b						
Prior CDC class C diagnosis	1.41 (0.55, 3.63)	0.50	0.48	1.41 (0.52, 3.82)	0.47	0.50
HIV viral load > 400 copies/ml	2.19 (0.91, 5.27)	3.03	0.08	1.97 (0.79, 4.92)	2.11	0.15
CD4 count <350 cells/mm ³	2.49 (0.94, 6.61)	3.33	0.07	2.43 (0.86, 6.84)	2.83	0.09
CD4% < 25%	2.97 (1.26, 6.98)	6.22	0.01	2.70 (1.11, 6.56)	4.79	0.03

IMPAACT international maternal pediatric and adolescent AIDS clinical trials, OR odds ratio, CI confidence interval, CDC centers for disease control and prevention, HS high school

^a Adjusted for all other demographic and caregiver characteristics shown in top panel

^b Each HIV disease covariate separately adjusted for age and caregiver relationship (1 participant missing CD4 count and CD4%, 1 subject missing HIV viral load)

Table 3
Prevalence and severity of psychiatric symptoms as assessed by youth and their caregivers, overall and by substance use status

Psychiatric condition/domain	Total (N = 299)	Substance use reported by youth or their caregiver		Wilcoxon rank sum statistic	P-value ^d
		Not user (N = 258)	User (N = 41)		
Attention deficit hyperactivity disorder (ADHD)					
Meets symptom cutoff ^b , N (%)	60 (20%)	46 (18%)	14 (34%)	–	0.02
ADHD-hyperactive					
Youth severity score, mean (S.D.)	7.36 (4.84)	7.12 (4.49)	8.93 (6.50)	1.25	0.21
Caregiver severity score, mean (S.D.)	4.09 (4.55)	3.97 (4.47)	4.80 (5.03)	1.01	0.31
ADHD-inattentive					
Youth severity score, mean (S.D.)	8.81 (4.60)	8.68 (4.41)	9.61 (5.63)	0.75	0.46
Caregiver severity score, mean (S.D.)	7.92 (5.87)	7.95 (6.01)	7.71 (4.94)	0.10	0.92
Conduct disorder					
Meets symptom cutoff ^b , N (%)	35 (12%)	18 (7%)	17 (41%)	–	<0.001
Youth severity score, mean (S.D.)	1.83 (2.90)	1.40 (1.72)	4.51 (5.93)	5.05	<0.001
Caregiver severity score, mean (S.D.)	1.43 (2.40)	1.13 (1.87)	3.34 (4.01)	4.12	<0.001
Oppositional defiant disorder (ODD)					
Meets symptom cutoff ^b , N (%)	46 (15%)	31 (12%)	15 (37%)	–	<0.001
Youth severity score, mean (S.D.)	6.64 (4.22)	6.27 (3.91)	8.98 (5.33)	3.37	<0.001
Caregiver severity score, mean (S.D.)	4.30 (3.80)	3.99 (3.60)	6.24 (4.49)	3.38	<0.001
Generalized anxiety					
Meets symptom cutoff ^b , N (%)	20 (7%)	15 (6%)	5 (12%)	–	0.17
Youth severity score, mean (S.D.)	5.98 (4.13)	5.66 (3.86)	7.98 (5.18)	2.86	0.004
Caregiver severity score, mean (S.D.)	3.19 (3.02)	3.11 (3.04)	3.68 (2.87)	1.49	0.14
Major depression or dysthymia					
Meets symptom cutoff ^b , N (%)	33 (11%)	24 (9%)	9 (22%)	–	0.03
Youth severity score, mean (S.D.)	14.52 (8.57)	13.83 (7.91)	18.85 (11.10)	3.18	0.001
Caregiver severity score, mean (S.D.)	7.88 (5.89)	7.64 (5.63)	9.45 (7.21)	1.56	0.12

^a P-values calculated using Fisher's exact test for comparisons of percent meeting symptom cutoff, and using a Wilcoxon rank sum test for comparison of severity scores, with test statistics indicated

^b As assessed by either the adolescent or their caregiver

Table 4

Association of psychiatric symptoms and HIV infection status with risk of substance use

Domain/condition	Effect of psychiatric symptom or symptom severity on risk of substance use		Effect of HIV status (HIV+ vs. HIV-) on risk or substance use	
	Adjusted OR ^a (95% CI)	Wald χ^2 P-value	Adjusted OR ^b (95% CI)	Wald χ^2 P-value
Based on exceeding symptom cutoff				
Any ADHD	2.70 (1.15, 6.35)	5.18 0.02	0.77 (0.34, 1.72)	0.41 0.52
Conduct disorder	15.39 (5.60, 42.3)	28.12 0.001	0.91 (0.38, 2.19)	0.04 0.84
Oppositional defiant disorder	4.79 (2.03, 11.32)	12.74 0.001	0.79 (0.35, 1.75)	0.35 0.56
Generalized anxiety	2.63 (0.82, 8.45)	2.64 0.10	0.71 (0.32, 1.56)	0.74 0.39
Major depression or dysthymia	3.96 (1.46, 10.68)	7.36 0.01	0.80 (0.35, 1.79)	0.30 0.58
Based on youth-assessed symptom severity score				
ADHD-hyperactive	1.12 (1.04, 1.21)	8.62 0.003	0.70 (0.31, 1.57)	0.76 0.38
ADHD-inattentive	1.04 (0.96, 1.13)	0.76 0.38	0.69 (0.31, 1.54)	0.81 0.37
Conduct disorder	1.55 (1.30, 1.85)	23.02 0.001	1.09 (0.44, 2.72)	0.04 0.85
Oppositional defiant disorder	1.17 (1.08, 1.27)	14.04 0.001	0.85 (0.37, 1.95)	0.14 0.70
Generalized anxiety	1.14 (1.05, 1.24)	9.78 0.002	0.80 (0.35, 1.83)	0.27 0.60
Major depression or dysthymia	1.07 (1.03, 1.11)	10.51 0.001	0.69 (0.30, 1.57)	0.78 0.38
Based on caregiver-assessed symptom severity score				
ADHD-hyperactive	1.07 (0.99, 1.16)	3.22 0.07	0.67 (0.30, 1.48)	0.97 0.33
ADHD-inattentive	0.98 (0.92, 1.05)	0.29 0.59	0.68 (0.30, 1.50)	0.92 0.34
Conduct disorder	1.28 (1.12, 1.46)	13.67 0.001	0.75 (0.33, 1.70)	0.48 0.49
Oppositional defiant disorder	1.14 (1.04, 1.25)	8.43 0.004	0.72 (0.32, 1.61)	0.63 0.43
Generalized anxiety	1.03 (0.92, 1.16)	0.33 0.57	0.68 (0.31, 1.51)	0.88 0.35
Major depression or dysthymia	1.02 (0.97, 1.08)	0.57 0.45	0.70 (0.31, 1.55)	0.77 0.38

OR odds ratio, CI confidence interval, ADHD attention deficit hyperactivity disorder

^a Adjusted for HIV infection status, age, sex, race/ethnicity, psychiatric medication status, and caregiver relationship, education, and substance use status^b Adjusted for psychiatric symptom (cutoff or severity), age, sex, race/ethnicity, psychiatric medication status, and caregiver relationship, education, and substance use status