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Substance Use is a Risk Factor for Neurocognitive Deficits and Neuropsychiatric Distress in Acute and Early HIV Infection

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Abstract

The acute and early stages of HIV infection (AEH) are characterized by substantial viral replication, immune activation, and alterations in brain metabolism. However, little is known about the prevalence and predictors of neurocognitive deficits and neuropsychiatric disturbances during this period. The present study examined the impact of demographic, HIV disease, and substance use factors on HIV-associated neurocognitive impairment and self-reported neuropsychiatric distress among 46 antiretroviral-naïve adults with median duration of infection of 75 days, relative to sample of 21 HIV seronegative (HIV-) adults with comparable demographics and risk factors. Participants were administered a brief neurocognitive battery that was adjusted for demographics and assessed executive functions, memory, psychomotor speed, and verbal fluency, as well as the Profile of Mood States (POMS), a self-report measure of neuropsychiatric distress. Odds ratios revealed that AEH participants were nearly four times more likely than their seronegative counterparts to experience neurocognitive impairment, particularly in the areas of learning and information processing speed. Similarly, AEH was associated with a nearly five-fold increase in the odds of neuropsychiatric distress, most notably in anxiety and depression. Within the AEH sample, HIV-associated neurocognitive impairment was associated with problematic methamphetamine use and higher plasma HIV RNA levels, whereas neuropsychiatric distress was solely associated with high-risk alcohol use. Extending prior neuroimaging findings, results from this study indicate that HIV-associated neurocognitive impairment and neuropsychiatric distress are highly prevalent during AEH and are associated with high-risk substance use.

Keywords

HIV; substance abuse; viral load; neuropsychiatry; AIDS dementia complex

Introduction

Despite advances in the management and treatment of HIV infection, HIV-associated neurocognitive disorders (HAND) remain highly prevalent. Recent estimates suggest that approximately 40–50% of HIV-infected individuals receiving modern combination antiretroviral therapy (cART) experience HAND (Heaton et al., 2010), which has been associated with a host of adverse functional consequences (e.g., unemployment, medication nonadherence; for a review, see Gorman et al., 2009). However, reasons for the persistence of HAND in the cART era remain elusive. One hypothesis is that the development of HAND in chronic infection may be influenced by adverse immune and virologic events that occur during the critical acute and early (AEH) stages of the disease (e.g., Schacker, Hughes, Shea, Coombs, & Corey, 1998). During the AEH period, approximately 40–90% of infected individuals experience symptoms of an acute retroviral syndrome (Kerndt et al., 2009; Schacker et al., 1996; Zetola & Pilcher, 2007), which can include a wide range of virologic, immunologic, and neurological complications (e.g., meningitis; Schacker et al., 1996), the severity of which has been associated with adverse complications during chronic infection, such as high levels of HIV disease progression (e.g., Lyles et al., 2000). The AEH period of infection is also characterized by high levels of HIV replication and compartmentalization (e.g., Pilcher et al., 2004), including to the central nervous system (CNS; Tambussi et al., 2000), as well as increased risk of transmission (e.g., Pao et al., 2005). Thus, detection and treatment of HAND during the AEH phase may be critical in the prevention of adverse CNS and functional consequences that are commonly observed during chronic infection (e.g., HAND; Ellis et al., 2011).

The neurobiological substrates of the CNS complications observed in AEH are not well understood, but preliminary evidence has identified several potential candidate mechanisms, including neuroinflammatory and immunopathogenic processes, emergence of dual tropic virus, viral-host interactions, and inadequate immune responses. For example, evidence for rapid depletion of gut-associated lymphocyte tissue (GALT) has been observed in individuals with primary HIV infection, which can lead to an increased inflammatory response and greater migration of infected immune cells into the CNS (e.g., Brenchley et al., 2004). In addition, Marcotte et al. (2003) found that HIV-infected individuals with high plasma viral loads and low CD4 counts during the year after seroconversion were six times more likely to later develop HAND. Clinical investigations into the nature and extent of CNS effects during AEH are also scant, but four recent neuroimaging studies have provided evidence of altered brain structure and function in AEH. For example, reduced cerebral blood flow (Ances et al., 2009) as well as elevated myo-inositol concentrations (Lentz et al., 2011) have been found in the basal ganglia of individuals with AEH. Similarly, alterations in brain metabolism have also been found in the frontal cortex (e.g., reduced levels of N-acetyl aspartate, choline concentrations, and glutamate-glutamine concentrations) during AEH (Lentz et al., 2009). Most recently, Wang et al. (2011) also found preliminary fMRI evidence for alterations of functional connectivity in the lateral occipital resting state network, which was correlated with poorer performance on measures of visuo-motor coordination.

Only two studies to date have examined the neurocognitive impact of AEH. Moore et al. (2011) reported that the overall neurocognitive performance of 39 individuals with AEH (median duration of infection 16 weeks, interquartile range 10–41) fell intermediate to their seronegative adult and chronic HIV-infected groups. Although overall cognitive performance of both the AEH and HIV- groups was significantly better than the chronically infected individuals (i.e., median duration of infection greater than four years), no statistically significant differences emerged between the AEH and HIV- groups. Wang et al. (2011) also examined cognitive performance in individuals with AEH (i.e., average duration

of infection less than one year) relative to HIV-individuals and found evidence for deficits in information processing speed and working memory (Wang et al., 2011). While there is preliminary evidence to suggest early neuroimaging and neurocognitive changes in HIV infection, these findings await replication and extension to determine predictors of HAND in AEH, including the possible role of neuropsychiatric factors, such as depression and substance use disorders.

Indeed, individuals with AEH may also be at greater risk for neuropsychiatric disorders. In a recent study, up to 85% of individuals with AEH met criteria from the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV*; American Psychiatric Association, 1994) for a history of substance use disorders and over half met criteria for a lifetime diagnosis of a mood disorder (Atkinson et al., 2009). Specifically, individuals with AEH show an increased prevalence of both recent (41% vs. 10%) and lifetime (79% vs. 37%) alcohol use disorders compared to the general population (Atkinson et al., 2009), as well as increased methamphetamine (MA) use (40% of recent seroconverters vs. 21% HIV- individuals report ever using MA; Plankey et al., 2007). Importantly, among chronically infected individuals, alcohol use disorders are associated with lower health related quality of life and increased psychiatric comorbidities (Rosenbloom et al., 2007), while MA use increases the risk of viral replication (Gavrilin, Mathes & Podell, 2002), HAND (Rippeth et al., 2004), and cART nonadherence (Moore et al., 2012). Of particular note, both alcohol and MA use disorders are associated with increased HIV transmission risk (Weinhart & Carey, 2000; Plankey et al., 2007). With regard to mood disorders, Moore and colleagues' (2011) observed an elevated prevalence of Major Depressive Disorder in their AEH cohort relative to seronegative adults but not as compared to chronically infected persons. Additionally, in chronic HIV infection, neuropsychiatric symptoms of depression, anxiety, and apathy are each associated with poorer outcomes in everyday functioning (e.g., Kamat et al., 2012), including cART nonadherence (e.g., Barclay et al., 2007), high risk sexual practices (e.g., Kennedy et al., 1993), unemployment (e.g., Heaton et al., 2004a), poorer health-related quality of life (Tucker et al., 2003), and mortality (Sevigny et al., 2007). Accordingly, it is critical to better characterize and understand the role of such neuropsychiatric factors in people with AEH as they may play a significant role in treatment planning (e.g., ability to maintain ART adherence) and, particularly, HIV transmission risk.

Collectively, these studies suggest that HIV causes CNS dysfunction early in the course of infection, which warrants further investigation given evidence to suggest that early neurological and immunological events may be predict HIV disease progression (e.g., Schacker et al., 1998). Despite elevated risk for CNS dysfunction and HIV transmission, little is known with regard to the neurocognitive and neuropsychiatric abnormalities observed in AEH, or to their clinical correlates. Thus, the current study aims to extend the existing AEH literature by determining the severity, profile, and predictors of neurocognitive and neuropsychiatric difficulties in AEH individuals relative to demographically similar seronegative adults in hopes of providing insight into the early detection and treatment and/or prevention of such debilitating impairments.

Methods

Participants

This study included 46 antiretroviral-naïve individuals with AEH who were enrolled in a supplement to a NIDA-funded Program Project on the CNS effects of HIV and MA, which was housed at the UCSD HIV Neurobehavioral Research Program (HNRP). Acute or early HIV-1 infection was defined as: a) positive HIV-1 RNA (Amplicor, Roche) with negative HIV EIA or rapid test; *or* b) HIV RNA positive and Western Blot indeterminate with no more than 3 positive bands; *or* c) HIV RNA positive, EIA or rapid test positive and less-

sensitive (detuned) EIA consistent with very recent infection ($OD < 0.3$ by Vironostika, or equivalent by Vitros ECI or OraQuick detuned). Individuals were excluded if they had a history of neurologic disorders unrelated to HIV infection (e.g., stroke, uncontrolled seizure disorder, head injury with loss of consciousness greater than 30 minutes), psychotic disorder unrelated to use of MA (e.g., schizophrenia), or any other condition that would invalidate neurocognitive testing (e.g., severe visual or hearing impairment). Duration of HIV infection was estimated an algorithm that evaluated the following data collected at study entry: 1) HIV-1 serologic tests, 2) detuned EIA testing, and 3) HIV RNA levels. HIV disease characteristics for the AEH sample are summarized in Table 1.

Twenty-one HIV- individuals enrolled in the UCSD Translational Methamphetamine AIDS Research Center (TMARC) within the HNRP were also included in this study as a comparison group. Exclusion criteria for this seronegative group were identical to the AEH cohort. MA and alcohol use diagnoses were established using *DSM-IV* (American Psychiatric Association, 1994) criteria as determined by the Composite International Diagnostic Interview (CIDI; Version 2.1; World Health Organization, 1998). Individuals with AEH were broadly comparable to the seronegative group in terms of demographic characteristics, including age, education, sex, and ethnicity ($p > 0.05$; See Table 1).

Procedures

The procedures involved in this study were approved by the human subjects institutional review board at the University of California, San Diego. Each participant provided written, informed consent, and was administered a comprehensive medical, psychiatric, and neuropsychological evaluation.

Alcohol Use—High-risk alcohol use in the AEH cohort was assessed via the Alcohol Use Disorders Identification Test (AUDIT), which is a 10-item interview developed by a six-country World Health Organization collaborative project as a screening measure for harmful alcohol consumption (Saunders, Aasland, Babor, De La Fuente & Grant, 1993). The AUDIT covers several domains of alcohol use (i.e., alcohol consumption, drinking behaviors, and alcohol-related problems) and demonstrates good reliability, construct validity, and criterion validity (Reinert & Allen, 2007). A cut-point score greater than seven indicating that participants would likely meet diagnostic criteria for alcohol use diagnoses was used in all analyses as it shows strong sensitivity and specificity in previous studies (Reinert & Allen, 2007) and was therefore utilized in all analyses in the current study. Using this cutpoint, 31.8% ($n=14$; See Table 1) of the AEH group was identified as at risk for alcohol use disorders, which was comparable to the rate 33.3% ($n=7$) of lifetime alcohol use disorders in the HIV- comparison sample as determined by the CIDI ($p = 0.903$; See Table 1).

Methamphetamine Use—A modified version of the Drug Abuse Screening Test (DAST; i.e., DAST-MA modified for MA as the target drug) was used to assess MA use in the AEH group. The DAST is a 28-item, self-report measure of problematic substance use (Skinner, 1982) with moderate to high levels of test-retest, inter-item, and item-total reliabilities as well as moderate to high levels of validity, sensitivity, and specificity across both clinical and research settings (Yudko, Lozhkina & Fouts, 2007). Responses to the DAST-MA are binary (i.e., yes/no) items each with a value of one point, yielding a possible total score range from 0 to 28. Scores greater than five provide the optimum cutoff threshold signifying that participants would likely meet DSM criteria for MA abuse or dependence diagnoses (Gavin, Ross, & Skinner, 1989). By this classification system, approximately 11.1% ($n=5$) of the AEH sample was considered at risk for MA use disorders, which was similar to the 14.3% ($n=3$) of the HIV- comparison group who met criteria for lifetime MA use diagnoses as determined by the CIDI ($p = 0.716$; See Table 1). Due to the small number of AEH

participants that met the clinical cutoff for MA abuse or dependence, the DAST-MA was utilized as a continuous variable in analyses.

Neuropsychiatric Disturbance Assessment—Current neuropsychiatric disturbance was assessed using the Profile of Mood States (POMS; McNair, Lorr & Droppleman, 1981), which is a 65-item, self-report measure of current (i.e. the week prior to evaluation) affective distress. Participants were asked to rate themselves with regard to various adjectives (e.g., “unhappy”) on a five-point Likert-type scale ranging from 0 (i.e., “not at all”) to 4 (i.e., “extremely”). Scores for individual adjectives are grouped into six subscales (i.e., Tension/Anxiety, Depression/Dejection, Anger/Hostility, Fatigue/Inertia, and Confusion/Bewilderment), which are used to derive a total mood score (i.e., POMS Total Mood Disturbance). Raw scores from the POMS were converted to z-scores based on a published healthy adult sample (Nyenhuys, Yamamoto, Luchetta, Terrien, & Parmentier, 1999). A cutoff of >1.5 standard deviations above the normative sample was used to indicate clinically elevated neuropsychiatric disturbance on the POMS.

Neuropsychological Assessment—The neuropsychological evaluation included an estimate of pre-morbid verbal IQ (i.e., the reading subtest of the Wide Range Achievement Test, Revision 3 (WRAT-3; Wilkinson, 1993) alongside a brief neuropsychological test battery assessing five cognitive domains including: executive functions (i.e., Trail Making Test Part B; TMT B; Army Individual Test Battery, 1944; Heaton et al., 2004b), episodic learning and memory (i.e., Hopkins Verbal Learning Test-Revised; HVLTR Total Trials 1–3 and Delayed Free Recall Trial; Benedict, Schretlen, Groninger, & Brandt, 1998; Norman et al., 2011); information processing speed (i.e., Trail Making Test Part A; TMT A; Army Individual Test Battery, 1944; Heaton et al., 2004b), fine motor skills (i.e., Grooved Pegboard Dominant and Non-dominant hand; Heaton et al., 2004b; Kløve, 1963), and verbal fluency (i.e., animals and actions; Benton, Hamsher, & Sivan, 1994; Woods et al., 2005a).

Raw scores for each of the neuropsychological tests were converted to T-scores using demographically-adjusted normative standards (Heaton et al., 2004b; Norman et al., 2011; Woods et al., 2005a). T-scores were then converted to deficit scores (Carey et al., 2004a), which range from 0 (T-score > 39; no impairment) to 5 (T-score < 20; severe impairment). The individual test deficit scores were then averaged to derive a Global Deficit Score (GDS) to provide an index of overall cognitive functioning. A standard cut-off score of 0.5 was used to classify individuals with global neurocognitive impairment (Carey et al., 2004a).

Data analyses

For each dichotomous outcome variable of clinical impairment (i.e., neurocognitive impairment and clinically significant neuropsychiatric disturbance), parallel analyses were performed in the following manner. First, logistic regressions were conducted to determine the overall significance of AEH group status to the primary neurocognitive and neuropsychiatric dependent variables separately, followed by subsequent logistic regressions to examine AEH group differences on individual domains of neurocognition or neuropsychiatric functioning. Next, Wilcoxon Rank-Sum or chi-square tests were performed within the AEH sample to explore the demographic, psychiatric, and HIV disease differences by clinical impairment status. Finally, all statistically significant variables were then entered into logistic regressions predicting clinical impairment. A critical alpha of 0.05 was used for each analysis.

Results

Neurocognitive

Sixty-one percent of AEH participants evidenced global neurocognitive impairment (NCI), which was a significantly higher rate as compared to the HIV- sample (28.6%; $p = 0.014$; see Figure 1). AEH participants were 3.89 times more likely to be neurocognitively impaired than their seronegative counterparts (95% confidence interval: 1.32, 12.67). Overall impairment was primarily driven by differences in information processing speed (Trail-Making Test A; 51.1% vs. 14.3%; OR: 3.55 [95% confidence interval: 1.21, 11.54]; $p = 0.004$) and verbal learning (HVLRT Total Trials 1–3; 58.7% vs. 28.6%; OR: 6.27 [95% confidence interval: 1.81, 29.50]; $p = 0.02$). Proportions of impairment on all individual neurocognitive tests in the AEH and HIV- samples are displayed in Figure 1.

Within the AEH sample, Wilcoxon Rank-Sum tests revealed a significant relationship between global NCI and DAST-MA scores (Hedge's $g = 0.71$; $p = 0.005$), whereby greater risk of MA use disorders was associated with worse neurocognitive functioning. Additionally, neurocognitively impaired AEH participants had more severe viremia, such that higher levels HIV RNA in plasma were observed among persons with global NCI (Hedge's $g = 0.55$; $p = 0.046$). No other demographic (e.g., education), psychiatric (e.g., AUDIT or POMS), or HIV (e.g., duration of infection) characteristics displayed in Table 1 were related to neurocognitive impairment ($ps > 0.10$).

DAST-MA and plasma viral load were then entered into a logistic regression predicting global NCI, which yielded a significant overall model [$\chi^2(2, N=44) = 9.77, p = 0.008$]. The DAST-MA was the sole independent predictor of global NCI ($\chi^2 = 6.36, p = 0.012$), such that for each unit increase in DAST-MA score, an individual was 1.38 (95% CI: 1.07, 2.08) times more likely to be neurocognitively impaired. In this multivariable analysis, the association with plasma viral load fell to trend-level ($\chi^2=3.18, p = 0.075$).

Neuropsychiatric

As shown in Figure 2, approximately 52% of AEH participants reported elevated POMS total mood scores, which was significantly higher than was observed in the HIV- sample (19.1%; $p = 0.01$); AEH participants were 4.64 times more likely to have elevated POMS scores (95% CI: 1.45, 18.05). Significant differences between the study groups were observed for proportions of individuals who were clinically elevated on the POMS Tension/Anxiety [51.1% vs. 14.3%; OR: 5.57 (95% confidence interval: 1.38, 37.69); $p = 0.01$] and Confusion/Bewilderment [51.1% vs. 14.3%; OR: 5.33 (95% confidence interval: 1.25, 34.35); $p = 0.02$] POMS subscales. A trend-level difference on proportion of clinically elevated Depression/Dejection subscale scores was observed ($p = 0.06$), though a post-hoc analysis indicated a significant difference when using the continuous raw scores of that scale ($p < 0.001$; Hedge's $g = 0.99$). Proportions of clinically elevated scores on the Anger/Hostility, Vigor/Activation, and Fatigue/Inertia subscales were not statistically different between the study groups (all $ps > 0.10$).

Within the AEH sample, individuals with elevated POMS Total Mood Disturbance scores were 3.75 times more likely to be high-risk alcohol users (95% CI: 1.004, 16.34), as measured by the AUDIT ($p = 0.049$). No other demographic, psychiatric (e.g., DAST-MA), neurocognitive, or HIV disease variables were related to neuropsychiatric distress (all $ps > 0.10$).

Discussion

The present study sought to examine the profile and predictors of neurocognitive impairment and neuropsychiatric disturbances in individuals with AEH. Extending the scant previous neurocognitive research on this topic (e.g., Moore et al., 2011), our results revealed elevated rates of both neurocognitive impairment and neuropsychiatric distress in the AEH sample that were significantly higher than their matched seronegative counterparts. These data support prior neuroimaging findings suggesting alterations in brain metabolism, blood flow, and functional connectivity in the early phase of HIV infection (e.g., fronto-striatal pathways; Ances et al., 2009). Of clinical relevance, given the high rates of HIV transmission that have been observed during the AEH period (e.g., Brenner et al., 2007), these neurocognitive and neuropsychiatric factors may play a significant role in risk-related behaviors during this critical stage of HIV disease. Furthermore, this study provides valuable insight with regard to the clinical factors associated with these neurocognitive and neuropsychiatric disturbances, particularly MA and alcohol use, which are often independently implicated in risky sexual behaviors and HIV transmission, and could also be targeted for intervention.

In the present AEH sample, 61% of individuals were classified as neurocognitively impaired (i.e., a GDS of ≥ 0.5) on an abbreviated battery of tests designed to be sensitive to HAND. This proportion is slightly higher than is typically seen in chronic HIV infection (e.g., 40–50%; Heaton et al., 2011) and is nearly double that which was observed in Moore and colleagues' AEH sample (2011). Several factors may be contributing to the high rate of HIV-associated neurocognitive impairment in this study. First, the present sample of individuals with AEH was examined much closer to their estimated date of infection than in the Moore et al. study (i.e., 11 vs. 16 weeks, respectively). Thus, it is possible that we captured the CNS functioning of our cohort during the height of their adverse inflammatory processes and altered brain metabolism, which may have made our AEH sample more vulnerable to neurocognitive impairment. To this end, we observed a significant relationship between neurocognitive impairment and plasma viral load, suggesting that increased viremia at this time point might be directly related to worse neuropsychological outcomes, as consistent with the findings of Marcotte et al (2003). The elevated rate of NCI may also simply be due to sampling differences. Another possible explanation is that the neurocognitive battery administered included tests that are particularly sensitive to incident brain injury, particularly HAND (Carey et al., 2004b). However, battery selection is unlikely to fully explain this finding because, despite a relatively elevated rate of impairment in our seronegative comparison group that was matched on numerous neurocognitive risk factors that are similarly sensitive to such tests (e.g., substance use), we still observed a statistically significant difference between groups and nearly a fourfold increase in impairment in AEH.

The overall pattern of neurocognitive deficits observed in this AEH sample varies from what one would expect in the cART era. In more recently studied chronically infected HIV samples, the most frequently observed neurocognitive deficits are in the domains of learning and executive functions (Heaton et al., 2011). Indeed, our sample exhibited the highest rates of impairment on a test of verbal list learning (i.e., HVLT-R) relative to seronegative counterparts, as consistent with the post-cART era experience of the HIV epidemic. However, the AEH sample also showed greater deficits on a test of information processing speed (i.e., Trail-Making Test Part A) relative to the comparison group, a finding that is more consistent with pre-cART era neurocognitive deficits (Heaton et al., 2011). Nevertheless, this finding is also consistent with the results Wang et al. (2011) report in their AEH cART era cohort. This may be reflective of a more global, diffuse neural process that is consistent with the cascade of neuroinflammatory events in the early days of HIV infection. This pattern of deficits may be critical in explaining the high rates of HIV

transmission during the AEH period. For instance, individuals with decreased information processing speed may be unable to adequately process rapidly evolving social situations that may lead to risk behaviors. Similarly, persons with deficits in verbal learning may have difficulty effectively acquiring pro-health messages related to HIV prevention (e.g., public health campaigns to encourage clean needle use) and treatment. Future studies may wish to include other aspects of memory (e.g., prospective memory; Carey et al., 2006) and executive functions (e.g., planning; Cattie et al., 2012) that may be especially important to the clinical implications of HAND in AEH (e.g., carrying a condom or remembering to bring a clean needle to an event).

Overall, HIV-associated neurocognitive impairment in the AEH sample was most strongly associated with high-risk MA use. Independently, MA dependence is associated with damage to dopaminergic frontostriatal circuitry and often results in mild-to-moderate neurocognitive deficits in verbal learning and information processing speed (e.g., Scott et al., 2007; Woods et al., 2005b). In the context of AEH, additive neuroinflammatory processes effects of MA and HIV combined may exacerbate this damage and thereby produce the profile observed. Such additive damage at the neural level has been observed in the context of chronic HIV infection and is hypothesized to be a result of a combination of increased dopaminergic and glutaminergic transmission (MA) as well as cytokines, inflammatory responses, and other neurotoxins that stimulate glutaminergic cells (HIV), which may result in apoptosis, vascular pathology, and damage to both grey and white matter (Chana, et al., 2006). Based on the cross-sectional and present-focused nature of our data, it is unknown whether the assessed MA use existed prior to HIV infection (and was the method by which the individual became HIV-infected) or whether MA use at this assessment was reactionary to knowledge of HIV status, and therefore more acute (cf. chronic MA use). However, our groups were matched on MA use, which helps to suggest that the NP impairment in the AEH sample was not solely due to MA, but instead a combination of risk factors for some participants. Unfortunately, we are not able to rule out the possibly confounding effects of polysubstance (e.g., cocaine, opioids) use or examine specific MA use parameters, as the DAST did not include information regarding onset, duration, and frequency of use. Nevertheless, the specificity of the observed finding to MA is at least partially supported by the absence of significant associations between HAND and alcohol use in this AEH cohort.

In addition to providing insight regarding the neurocognitive profile of AEH, the neuropsychiatric features of this cohort may yield important, and potentially clinically useful, insights into this stage of HIV disease. Notably, findings from two previous AEH cohorts reported levels of depressive symptomatology that were mildly elevated relative to the general population (i.e., Atkinson et al., 2009) or seronegative adults (i.e., Moore et al., 2011). In contrast, the present study compared an AEH cohort to seronegative comparison participants on a global, multifactorial measure of neuropsychiatric distress (i.e., POMS). Analyses of the POMS Total Mood Disturbance summary score revealed significantly higher rates of distress among AEH individuals compared to the HIV- group and was roughly comparable to levels that have been observed in chronically infected HIV+ individuals (e.g., Cattie et al., in press). Moreover, using the normative cut point, over 50% of AEH individuals were experiencing clinically elevated affective distress compared to less than 20% of the seronegative comparison participants. In the same way that lifetime mood disorder onset typically precedes HIV seropositivity notification (Atkinson et al., 2009), elevated neuropsychiatric symptoms may also have preceded these individuals' awareness of their HIV status. Nevertheless, such an elevation may be of great importance during the AEH period because they may impact the individual's response to learning of his or her HIV seropositive status, such as a possible exacerbation of affective symptoms or an increase in maladaptive behaviors (e.g., substance use). Although there is some evidence to suggest

that, on average, AEH individuals typically utilize adaptive coping behavior (Atkinson et al., 2009), it is not clear whether these findings generalize to all individuals with AEH, or whether these adaptive coping strategies would facilitate these individuals following current best-practice recommendations (e.g., initiating cART despite potential side effects). Furthermore, given the evidence of elevated rates of mood disorders and mood symptoms in chronic HIV infection, it may be the case that these adaptive coping strategies are not sufficient to prevent a long duration of symptoms or possible recurrence of symptoms, suggesting that formal psychotherapeutic intervention in the AEH period may be beneficial for both short-term and long-term psychiatric outcomes.

One advantage of the POMS is that it includes a multifactorial assessment of different aspects of neuropsychiatric distress. In our study, the AEH group reported significantly greater elevations than the comparison subjects on the Confusion/Bewilderment and Tension/Anxiety subscales. A trend-level elevation in the Depression/Dejection subscale of the POMS was observed in AEH, which was confirmed by a follow-up analysis of continuous normative z-scores. This evidence of depressive mood converges with prior data on MDD in AEH from Moore et al. (2011), who showed higher lifetime rates of MDD in AEH. However, we did not observe group differences in clinical elevations of the Anger/Hostility, Fatigue/Inertia, Anger/Hostility. This pattern of findings may suggest that self-reported distress in this cohort may be specific to certain clusters of affective symptoms, rather than global affective complaints.

With regard to anxiety, mild levels of anxiety have been observed in AEH groups previously (Atkinson et al., 2009), even when measured weeks to months after notification of HIV-seropositive status. In the current cohort, the rate of clinically elevated anxiety symptoms exceeded that of depression symptoms, suggesting that anxiety was the strongest contributor to the overall elevation in total mood disturbance. Unlike mood disorders, for which evidence suggests that onset of these psychiatric conditions preceded these individuals' awareness of their HIV seropositive status (i.e., notification of positive test results; Atkinson et al., 2009), it is possible that increases in anxiety symptoms may be a consequence of AEH status. Findings from a cross-sectional investigation such as the present study cannot definitively address this question, but due to the persistence of new HIV transmission this is a potentially important issue to address. Specifically, newly infected individuals may benefit from interventions targeting anxiety symptoms in the AEH period. Anxiety disorders are also common in chronically-infected individuals (Atkinson & Grant, 1994), and it is possible that a similar pattern may be observed with anxiety symptoms as with depression symptoms, whereby individuals with clinically significant symptoms in the early stages of infection may be more likely to exhibit symptoms in clinical range up to one year later (Perry et al., 1993).

Further examination of the total mood disturbance score predictors revealed only high-risk alcohol use to be associated with elevated rates of overall affective distress in the present AEH cohort. A high prevalence of lifetime alcohol use disorders has previously been reported among AEH individuals, with onset largely preceding the notification of HIV serostatus similar to mood disorders (Atkinson et al., 2009). Therefore, it is possible that this association is simply due to pre-existing problems with alcohol use that continue into the AEH period. Alternatively, the demonstrated anxiolytic properties of alcohol use (e.g., Steele, Southwick, & Pagano, 1986) suggest that risky levels of drinking may be more directly related to the elevated anxiety symptoms observed among AEH individuals, regardless of whether those increased anxiety symptoms preceded HIV serostatus notification or were a consequence of AEH status. These findings also might also suggest that the AEH individuals in the present cohort may not have been using primarily adaptive coping strategies (cf. Atkinson et al., 2009) and instead initiated or continued high-risk

drinking in response to seropositive status awareness. This relationship is ecologically relevant given that risky alcohol use during the AEH period increase risk of HIV transmission (e.g., Raj et al., 2009).

Interestingly, although the rates of both neurocognitive impairment and affective distress are high in AEH, there is likely discordance between the individuals who experience these respective effects, as well as in the relationships between the predictors and their respective outcomes. Indeed, we observed elevations in both the POMS Confusion/Bewilderment scores and objective neurocognitive impairment; however, performance and complaints did not relate to one another, which has been a consistent finding across the chronic HIV infection literature (e.g., Rourke et al., 1999). Due to the cross-sectional nature of the present study, we cannot address the timing and intersection of these problems with our data, but several considerations emerge. For example, one possibility is that risky alcohol use and illicit MA use may be antecedents to elevated affective distress and neurocognitive impairment, respectively, irrespective of AEH status. Alternatively, AEH may precipitate both affective distress and neurocognitive impairment via neurobiological mechanisms (e.g., dopaminergic disruption), which may subsequently result in AEH individuals abusing alcohol and/or MA. Another possibility is that both risky alcohol use and/or MA use were pre-existing conditions in these AEH individuals before they were notified of their HIV seropositive status, and their use of these substances persisted into their AEH period. Although our data do not directly support this notion, it is also possible that MA use in the AEH context likely negatively impacts neurocognitive performance, whereas elevated anxiety in the AEH period may lead to and increase in risky alcohol use. Future prospective investigations may address these possibilities with longitudinal data.

Regardless of the timing of onset and the directional nature of these relationships, it is clear that individuals in the AEH period may benefit from early detection and remediation of affective distress, alcohol and substance use, and neurocognitive impairment. It is possible that presence of these factors, alone or in combination, may represent risk factors for later consequences, such as continued psychiatric and substance use problems, as well as further neurocognitive decline. Individuals with such constellations of risk factors may also be at increased risk for declines in everyday functioning (Weber et al., 2012). As such, early intervention may reduce these risks, thereby improving long-term health outcomes. Furthermore, intervening on these factors with remediation and psychoeducation at this time point may also significantly curb risk behaviors that allow for HIV transmission and continue the epidemic.

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Figure 1.

Proportions of AEH individuals reporting elevated scores relative to the HIV- group on the Profile of Mood States (POMS) Total Mood Disturbance and individual subscales. * represents significant differences between proportions of clinically elevated scores (p-values < 0.05); † represents trend-level differences between proportions of clinically elevated scores.

Figure 2. Rates of global and domain-specific neurocognitive impairment in AEH relative to HIV- individuals. * represents significant differences between proportions (p-values < 0.05).

Table 1

Demographic, Psychiatric and HIV-Disease Characteristics of the Study Groups.

Variable	HIV- (n =21)	AEH (n = 46)	p-value
Demographic Characteristics			
Age (years)	34.4 (10.8)	32.2 (10.6)	0.435
Education (years)	13.8 (2.3)	14.5 (2.2)	0.257
Sex (% male)	90.5%	100.0%	0.095
Ethnicity (% Caucasian)	66.7%	52.2%	0.263
Estimated Premorbid Verbal IQ ^a	102.1 (11.9)	103.5 (11.5)	0.673
Psychiatric Characteristics			
Alcohol Use Diagnoses ^b	33.3%	31.8%	0.903
MA Use Diagnoses ^b	14.3%	11.1%	0.716
HIV Disease Characteristics			
Duration of Infection (days)	-----	75.0 (25.0, 87.0)	-----
Current CD4 (cells/ μ L) ^c	-----	609.0 (431.0, 717.5)	-----
Plasma RNA (log ₁₀ copies/mL) ^c	-----	4.9 (3.9, 5.5)	-----

Note. Means (standard deviation) unless otherwise specified.

^aBased on the reading subtest of the Wide Range Achievement Test (WRAT-3).

^bProportions of alcohol and methamphetamine users within the AEH group are based on "at risk" Alcohol Use Disorders Identification Test (AUDIT) and Drug Abuse Screening Test (DAST) classifications, respectively, and based on alcohol and methamphetamine dependence diagnoses as indicated by the CIDI for individuals within the HIV- group.

^cMedian (interquartile range).

HIV=Human Immunodeficiency Virus. AEH = Acute and early HIV infection. NP = Neuropsychological. MA = Methamphetamine. CD4 = Cluster of differentiation 4. RNA = Ribonucleic acid.