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Methamphetamine use and neuropsychiatric factors are associated with antiretroviral nonadherence

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Abstract

The present study assesses the impact of methamphetamine (METH) on antiretroviral (ART) adherence among HIV+ persons, as well as examines the contribution of neurocognitive impairment and other neuropsychiatric factors (i.e., major depressive disorder (MDD), Antisocial Personality Disorder (ASPD), and Attention Deficit Disorder (ADHD)) for ART nonadherence. We examined HIV+ persons with DSM-IV-diagnosed lifetime history of METH abuse/dependence (HIV+/METH+; $n = 67$) as compared to HIV+ participants with no history of METH abuse/dependence (HIV+/METH-; $n = 50$). Ancillary analyses compared these groups with a small group of HIV+/METH+ persons with current METH abuse/dependence (HIV+/CU METH+; $n = 8$). Nonadherence was defined as self-report of any skipped ART dose in the last four days. Neurocognitive functioning was assessed with a comprehensive battery, covering seven neuropsychological domains. Lifetime METH diagnosis was associated with higher rates of detectable levels of plasma and CSF HIV RNA. When combining groups (i.e., METH+ and METH- participants), univariate analyses indicated co-occurring ADHD, ASPD, and MDD predicted ART nonadherence (p 's < 0.10; not lifetime METH status or neurocognitive impairment). A significant multivariable model including these variables indicated that only MDD uniquely predicted ART nonadherence after controlling for the other variables ($p < 0.05$). Ancillary analyses indicated that current METH users (use within 30 days) were significantly less adherent (50% prevalence of nonadherence) than lifetime METH+ users and HIV+/METH- participants, and that neurocognitive impairment was associated with nonadherence (p 's < 0.05). METH use disorders are associated with worse HIV disease outcomes and ART medication nonadherence. Interventions often target substance use behaviors alone to enhance antiretroviral treatment outcomes; however, in addition to targeting substance use behaviors, interventions to improve ART adherence may also need to address coexisting neuropsychiatric factors and cognitive impairment to improve ART medication taking.

Keywords

HIV/AIDS; Cognition; Medication Adherence; Antiretroviral; Methamphetamine

Introduction

Sustained adherence to antiretroviral therapy (ART) regimens remains a challenge among HIV infected (HIV+) persons even in the context of new combination medications and decreased dosing schedules (Bangsberg et al., 2001). Suboptimal ART adherence can lead to virologic rebound, development of drug-resistant strains of HIV, and more rapid progression to AIDS (Gifford et al., 2000; Hinkin et al., 2002; Hirsch et al., 2000). Many factors may present barriers to successful adherence among persons with HIV (e.g., side effects, lack of social support) (Malta, Strathdee, Magnanini, & Bastos, 2008). Also of potential importance are psychiatric diagnoses, including Antisocial Personality Disorder (ASPD), Major Depressive Disorder (MDD), and Attention Deficit Hyperactivity Disorder (ADHD), which are common among HIV+ persons and persons with substance abuse or dependence (Atkinson & Grant, 1994; Brook et al., 2002; Brooner, Bigelow, Strain, & Schmidt, 1990; Brooner, Greenfield, Schmidt, & Bigelow, 1993; Chan, Dennis, & Funk, 2006; Mellins et al., 2009); these psychiatric diagnoses have also been linked to poor medication adherence in non-substance using populations (e.g., Bose, Varanasi, & Mo, 2009; Safren et al., 2007; Tucker et al., 2003).

Of growing concern, is the role that methamphetamine (METH) has on ART nonadherence given the high prevalence of METH use among HIV infected individuals (Chander, Himelhoch, & Moore, 2006; Des Jarlais, 1999; Palepu et al., 2003; Wood et al., 2003; Marquez, Mitchell, Hare, John, & Klausner, 2009). A previous study has shown that HIV+ individuals taking ART medications and actively using METH (toxicology positive) were at a greater risk for higher HIV RNA viral loads and lower CD4 counts compared to both HIV + individuals with a history of METH dependence but not actively using, and those without a history of METH use (Ellis et al., 2003). Moreover, a recent comprehensive review showed that stimulant use directly and negatively impacts HIV disease progression even in light of adequate self-reported adherence to antiretroviral medications (Carrico et al., 2011).

METH use has also been independently associated with deleterious neurocognitive effects including impairments in episodic memory, executive functions, motor skills, language, and information processing speed (Scott et al., 2007). As HIV is also independently associated with neurocognitive deficits (Heaton et al., 2010; Woods et al., 2009a), the potential double impact of substance use among HIV+ persons can cause additional neurocognitive complications. For example, the combined effects of HIV+ infection and METH use (HIV+/METH+) have been shown to have additive deleterious effects compared to the neurocognitive impairment observed in persons infected with HIV+ alone with specific deficits in working memory, learning, recall and motor skills (Rippeth et al., 2004). Of particular relevance is that previous studies of HIV+ persons have established an association between cognitive impairment and decline in real world adaptive function, including medication adherence (Burton, Strauss, Hultsch, & Hunter, 2006; Hinkin et al., 2002; Su, Chen, Wang, Lin, & Wu, 2008; Thames et al., 2010; Vigil et al., 2008). As such, HIV+ persons with co-occurring METH use are likely at an additional risk for declines in everyday functioning as a consequence of such additive neurocognitive deficits.

Despite the poor adherence levels found in these co-occurring conditions and the relevance of neurocognitive functioning for medication adherence (Hinkin et al., 2004; Hinkin et al., 2007; Woods et al., 2009b), we are unaware of any studies that have comprehensively evaluated recency of METH use, neurocognition and the presence of co-occurring major psychiatric comorbidities for antiretroviral adherence. Therefore, the aims of the present study are to 1) compare adherence rates between HIV+ persons with current and past METH use disorders as compared to HIV+ persons without METH histories and relate these to HIV disease indicators and self-reported medication adherence, 2) examine the neurocognitive

predictors of antiretroviral adherence specific to an HIV+ population with METH use disorders, and 3) to examine the possible influence of other psychiatric comorbidities for adherence.

Method

Participants

We identified 67 HIV+ persons with a lifetime history of DSM-IV-diagnosed METH abuse or dependence and met criteria for METH abuse or dependence within 18 months of their study assessment (HIV+/LT METH+); we also classified a small group of participants ($n = 8$) that met criteria for current METH abuse or dependence at the time of assessment (HIV+/CU METH+; METH use within the previous 30 days). Finally, we identified 50 HIV+ individuals without a history of METH abuse or dependence (HIV+/METH-) (see Table 1 for participant demographic information). All participants were toxicology negative for stimulants at the time of evaluation and neurocognitive testing.

Participants were screened for inclusion prior to enrollment in the study. Individuals with histories of neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 minutes, and central nervous system neoplasms or opportunistic infections), schizophrenia or other psychotic disorders were excluded (both assessed via self-reported history of diagnosis and/or based on currently prescribed medications with follow-up queries for reason for medication prescription) whereas persons with affective disorders without psychotic features (e.g., bipolar disorder, major depressive disorder) were included. Additional exclusion criteria for both groups included meeting DSM-IV criteria for the following: alcohol dependence within the last year; other drug dependence within 5 years of the evaluation (with the exception of alcohol or marijuana); abuse within the past 1 year prior to the evaluation of drugs other than METH (e.g., cocaine, opioids; again with the exception of alcohol or marijuana); or positive urine toxicology at the time of evaluation (again with the exception of alcohol or marijuana).

Assessments

Substance abuse or dependence and major depressive disorder diagnoses—

METH use was defined as a lifetime or current (METH use within the previous 30 days) diagnosis of METH abuse or dependence by DSM-IV criteria using the Composite International Diagnostic Interview (CIDI; Wittchen, 1993; World Health Organization, 1990). The CIDI is a lay-administered diagnostic tool, which follows DSM-IV diagnostic criteria. A review of the CIDI reported interrater reliability to be excellent across studies and diagnostic categories (Kappa range: 0.67 to .98; Wittchen, 1994). The administration of the CIDI was supervised by licensed clinical psychologists (DJM, SPW). Diagnoses of alcohol/other substance abuse or dependence and major depressive disorder (MDD) were also determined via the CIDI.

Attention Deficit Hyperactivity Disorder and Antisocial Personality Disorder—

Diagnoses of lifetime ADHD and ASPD were assigned using the ADHD (Module L) and ASPD (Module P) Modules of the Diagnostic Interview Schedule-IV (DIS-IV; Robins et al., 1995). The DIS-IV is a fully structured, lay-administered clinical interview that assesses for the presence of clinical disorders based on DSM-IV diagnostic criteria.

Antiretroviral adherence—Medication adherence was evaluated with the AIDS Clinical Trials Group (ACTG) 4-day adherence self-report questionnaire (Chesney et al., 2000). The ACTG 4-day adherence questionnaire assessed nonadherence to any antiretroviral

medications over the previous four days; nonadherence was defined as report of any skipped dose.

Neurocognition—All participants completed a comprehensive neurocognitive test battery assessing seven different neuropsychological (NP) domains: verbal fluency, executive functions, speed of information processing, learning, recall, working memory, and motor skills (see Heaton et al., 2010 for specific listing of tests).

Raw NP test scores were converted into *T*-scores using demographically adjusted norms to control for the effects of age, education, gender, and where available ethnicity (Cherner et al., 2007; Heaton et al., 2004, Norman et al., 2011). The demographically corrected *T*-scores were then converted into global (GDS) and domain deficit (DDS) scores according to a standardized approach (Carey et al., 2004; Woods, Scott, Fields, Poquette, & Troster, 2008). A GDS score greater than or equal to 0.5 was used to define global NP impairment.

Statistical Analyses—Demographic, disease related variables, and ART adherence differences were examined between the lifetime HIV+/METH+ users (HIV+/LT METH+) and HIV+/METH− groups using between-group ANOVAs and chi-square analyses, or the nonparametric equivalent, where appropriate. A multivariable logistic regression model was conducted to examine the unique contributions of *a priori* hypothesized neuropsychiatric predictors of nonadherence, including METH status (i.e., LT METH+ vs. METH−), global neurocognitive impairment, ADHD, ASPD, or lifetime MDD diagnosis. The univariate relationship between each predictor and ART adherence was assessed using chi-square analyses, and those predictors that reached a predetermined threshold (i.e., $p \leq 0.10$) were included in the final model. Nonparametric correlations were utilized to assess the relationship between METH use characteristics and other HIV disease related variables and adherence. Finally, ancillary analyses were conducted to examine these relationships among the cohort of currently using HIV+/CU METH+ participants ($n = 8$).

Results

HIV+/LT METH+ participants were generally comparable to HIV+/METH− participants across demographic and HIV disease variables (see Tables 1 and 2). The cohort was mostly male and Caucasian, on average had about one year of college education, and were fairly healthy (mean nadir CD4 range 178.3-165.9, current CD4 range 626.1-504.5 across groups). However, HIV+/LT METH+ participants were younger ($p = 0.014$) and met criteria for lifetime substance abuse/dependence diagnoses more often than the HIV+/METH− participants. In terms of lifetime METH use characteristics, the average age of first use for the HIV+/LT METH+ participants was about 28 years old and the average total quantity of lifetime METH use was 2143 grams used across a cumulative 2186 days. On average, the HIV+/LT METH+ participants last reported using METH about 10 months prior to their current study visit.

Self reported adherence between the HIV+/LT METH+ and HIV+/METH− participants did not significantly differ; however, 10% of the HIV+/METH− participants reported nonadherence to ARTs compared to 18% of the HIV+/LT METH+ participants ($\chi^2 = 1.4$, $p = 0.22$, $\Phi = 0.11$; see Table 2). HIV+/LT METH+ participants were more likely to have detectable HIV plasma viral loads (45% detectable; $\chi^2 = 10.4$, $p = 0.001$, $\Phi = 0.31$) and CSF viral loads (21% detectable; $\chi^2 = 4.8$, $p = 0.03$, $\Phi = 0.24$) than the HIV+/METH− participants (16% in plasma and 3% in CSF detectable).

In order to examine the contribution of neuropsychiatric conditions (i.e., ADHD, ASPD and lifetime MDD), neurocognition, and LT METH use to self-reported ART adherence

behaviors, we created a multivariable regression model; only those predictors that reached a cutoff of $p = 0.10$ in univariate analyses were included in the model (see Table 3). Comorbid ADHD, ASPD, and lifetime MDD diagnosis each predicted reported ART nonadherence at the given threshold and were therefore included in the model. The model accounted for a small but significant amount of the variance (13%) in ART nonadherence ($\chi^2 = 11.6$, $p = 0.009$). Only lifetime MDD diagnosis uniquely predicted ART nonadherence after accounting for the other predictors in the model ($\chi^2 = 4.49$, $p = 0.034$); individuals with a lifetime MDD diagnosis were 5.42 times more likely to be nonadherent than those without MDD (OR = 5.42, $p = 0.015$).

Having a current or lifetime diagnosis of any other substance abuse or dependence (i.e., alcohol, cannabis, cocaine, methamphetamine, hallucinogen, inhalant, opioid, PCP, or sedative) was not associated with self-reported ART adherence in either METH group (p 's > 0.05). Additionally, age of METH use onset and first use, cumulative LT quantity of METH used, cumulative duration of METH use in days, or last use of METH were not predictive of ART adherence within the LT METH group (p 's > 0.05). Self-reported ART adherence was not directly associated with any of the HIV-related disease variables (i.e., current CD4, nadir CD4, proportion with detectable viral load in plasma or CSF), or co-occurring hepatitis C infection in either group (p 's > 0.05).

Ancillary Analyses

When the current HIV+/METH+ participants (HIV+/CU METH; $n = 8$) were compared to HIV+/LT METH+ and HIV+/METH- participants, omnibus tests indicated significant group differences on self-reported adherence ($\chi^2 = 6.6$, $p = 0.04$, $\Phi = 0.25$); specifically, HIV+/CU METH+ users were the most nonadherent at 50% compared to either group (vs. 18% HIV+/LT METH+: $\chi^2 = 3.7$, $p = 0.05$; vs. 10% HIV+/METH-: $\chi^2 = 6.5$, $p = 0.01$). Additionally, HIV+/CU METH+ participants had more detectable HIV RNA in both CSF and plasma compared to HIV+/METH- participants (CSF detectable: 42% vs. 3%, $\chi^2 = 7.0$, $p = 0.008$, $\Phi = 0.50$; plasma detectable: 50% vs. 16%, $\chi^2 = 4.0$, $p = 0.046$, $\Phi = 0.29$) but not compared to HIV+/LT METH+ participants (p 's > 0.05).

Among the HIV+/CU METH+ participants, global NP impairment predicted ART nonadherence such that 100% of the globally NP impaired participants ($n = 3$) skipped an ART dose over the previous four days ($\chi^2 = 6.1$, $p = 0.01$, $\Phi = 0.77$). Rates of neurocognitive impairment were not significantly different between the groups (Table 1); however, given the small sample size of the HIV+/CU METH+ group, any analyses that include this group should be considered preliminary. Additionally, comorbid ADHD, ASPD, or lifetime MDD were not associated with ART nonadherence among the HIV+/CU METH+ participants (p 's > 0.05).

Discussion

Our findings show that HIV+ persons with a lifetime history of METH abuse/dependence have worse HIV disease despite comparable rates of ART medication adherence. Neuropsychiatric factors, particularly LT MDD, may be a strong indicator of ART nonadherence in the context of a LT METH use disorder. Our study also shows preliminary evidence that persons with a current METH use disorder display the most significant difficulties with nonadherence in which neurocognitive impairment is the strongest predictor; importantly, however, our sample of currently using METH participants was very small and therefore these results should be interpreted with caution.

We found that both current and historic use of METH negatively impacted disease status (i.e., plasma and CSF HIV RNA viral loads) as compared to those without a history of

METH use. These disease indicator findings are consistent with previous research that has shown worse HIV progression among HIV+ stimulant users even without worse antiretroviral adherence (e.g., Carrico et al., 2011). However, the fact that HIV disease outcomes remain worse even when persons are in recovery from methamphetamine abuse/dependence has important implications for interventions that aim to improve medication adherence in the context of substance use disorders. Different interventions are likely needed for persons in recovery as compared to those who are still continuing to use methamphetamine to improve both medication adherence and HIV disease outcomes.

In the present study, only among those HIV-infected persons with current METH use disorders was neurocognitive impairment significantly associated with self-reported antiretroviral nonadherence. These findings may be explained by the fact that nonadherence among current METH users is the consequence of the combined insult of methamphetamine and HIV on the brain that results in impaired neurocognitive functioning, which then negatively influences the ability to manage and adhere to antiretroviral medications (Rippeth et al., 2004; Marquez et al., 2009). Alternatively, neurocognitive impairment may not be the driving force behind nonadherence; it may be that the disrupted lifestyles resulting from current methamphetamine use leads to nonadherence and that more advanced disease and methamphetamine result in neurocognitive impairment independent of adherence. As has been previously suggested, neurocognitive impairment may be both a risk for nonadherence as well as a consequence of nonadherence (Ettenhofer et al., 2010).

Our study is one of the first to show the neuropsychiatric factors most associated with nonadherence among HIV+ substance users and that these factors likely differ depending on whether the methamphetamine disorder is current or remote. In particular, we found that among our HIV+ lifetime METH users, co-occurring psychiatric factors were predictive of ART nonadherence (i.e., ADHD, ASPD, LT MDD) with LT MDD being the strongest predictor despite comparable levels of current depressive symptoms between the two groups. Current METH use appears to be an independent and strong predictor of nonadherence. Adherence may be so negatively impacted in the context of current METH use, other factors become relatively inconsequential, but among users in recovery, psychiatric comorbidities likely play a more significant role in nonadherence. In contrast to previous studies, co-occurring diagnosis of current MDD was not a significant predictor of self-reported ART adherence among the HIV+/METH groups. This result is likely a reflection of the small number of participants that qualified for current MDD diagnosis in each of the groups (i.e., Current METH: $n = 1$; LT METH: $n = 10$; METH-: $n = 6$).

A limitation of the current study is the importance of other factors previously identified in the literature such as intention to take medications (Reback, Larkins, & Shoptaw, 2003), social support (Bouhnik et al., 2002), and homelessness (Waldrop-Valverde, 2005; Coady, 2007), which may be affected by current METH use that were not assessed in the present study but also may have played an important role. Moreover, METH negatively affects reward circuits in the brain (Leventhal et al., 2008) and may decrease motivation to adherence to medications; this possibility was also not examined. Additionally, our study is limited by the use of self-reported medication adherence evaluation, which may underestimate actual adherence difficulties (Lu et al., 2008); however, any endorsement of nonadherence is likely to be valid (Arnsten et al., 2001; Levine et al., 2006). Finally, our group of HIV+ participants with current METH use disorders was very small, limiting the power and generalizability of our ancillary findings.

Overall, our findings suggest that HIV+ persons with a METH use disorder are particularly susceptible to worse HIV disease outcomes, and, as a result, these persons are at a higher risk of transmitting HIV. It is a common clinical assumption that substance use negatively

affects antiretroviral adherence during periods of active use. Less clinically obvious, but supported by our study findings, is that worse HIV disease may persist after METH remission occurs, and that ART adherence may be driven by the presence of other psychiatric comorbidities.

Future intervention methods likely need a multi-pronged approach to improving adherence and HIV disease outcomes among those with both current as well as remote METH use disorders. The HIV literature has shown that mental health difficulties among HIV+ individuals can negatively influence both adherence behaviors and biologic disease progression (Blashill, Perry & Safren, 2011). Among current METH users, the present study indicates that interventions should focus on both decreasing substance use behaviors and accounting for neurocognitive impairments to improve adherence. To this end, some studies have already shown the effectiveness of technological mobile interventions such as text messaging reminders to improve adherence in HIV infection, particularly among those with memory difficulties (Puccio et al., 2006; Chang et al., 2008; Safren et al., 2003; Andrade et al., 2005).

Among HIV+ persons in remission from a METH disorder, interventions may need to focus on other co-occurring psychiatric comorbidities as these appear to be particularly associated with nonadherence to ART medications. Additionally, it is important for clinicians and researchers alike to recognize that lifetime psychiatric diagnoses may impact current HIV disease indicators even if persons do not currently report significant symptoms (i.e., diagnosis of current MDD was not predictive of non-adherence in this study, but lifetime MDD was). Worse HIV disease may be due to yet undefined direct links between depression on HIV progression (e.g., via immune modulation factors) or possibly via inconsistent adherence behaviors that are not typically captured via self-report measures of adherence (Healthy Living Project Team, 2007). Interventions focused on individuals with longstanding neuropsychiatric difficulties may need to focus more on risk reduction given the indications that HIV disease may continue to be less well controlled even in periods of substance use remission. Furthermore, multimodal interventions may want to address other neuropsychiatric factors linked to worse HIV disease outcomes such as stress reduction techniques (Bottonari et al., 2010) and improving quality of life (Safren et al., *in press*). The convergence of HIV, substance use, and neuropsychiatric difficulties creates a complex problem for treating and improving outcomes for persons suffering from these various conditions. Clearly, additional studies are necessary to develop and design appropriate interventions for these difficult-to-treat individuals.

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Table 1

Demographic and disease variables for HIV+ participants with lifetime versus current DSM-IV-TR methamphetamine abuse or dependence diagnosis.

Variable	HIV+/LT METH (<i>n</i> = 67) (a)	HIV+/CU METH (<i>n</i> = 8) (b)	HIV+/METH- (<i>n</i> = 50) (c)	Omnibus <i>p</i> -values
Age	41.9 (6.6)	40.5 (5.7)	45.5 (9.0)	0.03; c>a
Gender (% M)	90%	100%	86%	0.32
Education (yrs)	13.0 (2.2)	13.3 (2.9)	13.0 (1.9)	0.95
Ethnicity				0.50
Caucasian	64%	75%	64%	
Black	12%	13%	22%	
Asian	3%	0%	0%	
Hispanic	19%	13%	10%	
Other	1%	0%	2%	
HCV	40%	25%	30%	0.42
Proportion NCI	34.3%	37.5%	28%	0.72
LT Substance Dx				
Alcohol	82%	63%	46%	<0.001; a>c
Cannabis	46%	38%	26%	0.08
Cocaine	55%	13%	14%	<0.001; a>b,c
Hallucinogen	16%	13%	4%	0.053
Opioid	3%	13%	6%	0.49
LT Methamphetamine Use		(<i>n</i> = 9)		
Cumulative quantity (grams)	2143 (3572)	1066 (1236)	338 (734)	0.30
Cumulative duration (days)	2186 (2032)	1404 (2161)	399 (806)	0.06
Age first use	27.6 (8.4)	24.4 (7.3)	29.7 (10.8)	0.46
Last use (days)	313.1 (694.2)	15.8 (11.1)	3523.6 (3930.7)	<0.001; b<a<c
ADHD diagnosis	19%	0%	16%	0.21
ASPD diagnosis	16%	13%	9%	0.48
LT MDD diagnosis	15%	13%	12%	0.90

Note: LT=Lifetime; CU = Current; HCV = Hepatitis C co-infection; NCI = Neurocognitively impaired; ADHD=Attention Deficit Hyperactivity Diagnosis; ASPD=Antisocial Personality Disorder; MDD = Major Depressive Disorder.

Table 2

Antiretroviral adherence and HIV disease information.

Variable	HIV+/LT METH+ (<i>n</i> = 67) (a)	HIV+/CU METH+ (<i>n</i> = 8) (b)	HIV+/METH- (<i>n</i> = 50) (c)	Omnibus <i>p</i> -values
ART nonadherence	18%	50%	10%	0.018; b>c
Detectable plasma				
HIV viral load	45%	50%	16%	0.004; a,b>c
Detectable CSF				
HIV viral load	21%	42%	3%	0.019; a,b>c
AIDS	58%	50%	70%	0.324
Nadir CD4	178.3 (157.9)	263.8 (242.0)	165.9 (159.5)	0.304
Current CD4	626.1 (1219.9)	573.0 (296.7)	504.5 (218.0)	0.775

Note: LT = Lifetime; CU = Current; ART = antiretroviral; CSF = cerebrospinal fluid.

Table 3

Multivariable logistic regression showing that Lifetime MDD status significantly predicts current antiretroviral (ART) nonadherence.

Univariate analyses predicting ART adherence		
	χ^2	p-value
METH status (LT METH+ vs. METH-)	1.44	0.23
Global Neurocognitive Impairment	0.05	0.83
ADHD [§]	5.82	0.016
ASPD [§]	3.41	0.065
Lifetime MDD [§]	5.79	0.016
Multivariable model predicting ART adherence:		
$\chi^2 (3, N = 114) = 11.6, p = 0.009, R^2 = 0.13$		
	χ^2	p-value
Lifetime MDD [*]	4.49	0.034
ADHD	1.59	0.21
ASPD	0.80	0.37

Note: LT = Lifetime; ADHD = Attention Deficit Hyperactivity Disorder; ASPD = Antisocial Personality Disorder; MDD = Major Depressive Disorder.

[§] p = 0.10

^{*} p < 0.05