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ORIGINAL PAPER

Problematic Alcohol Use Among Individuals with HIV: Relations with Everyday Memory Functioning and HIV Symptom Severity

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Abstract Problematic alcohol use has been shown to negatively impact cognitive functions germane to achieving optimal HIV health outcomes. The present study, a secondary data analysis, examined the impact of problematic alcohol use on aspects of everyday memory functioning in a sample of 172 HIV-infected individuals (22 % female; $M_{age} = 48.37$ years, SD = 8.64; 39 % Black/non-Hispanic). Additionally, we tested whether self-reported memory functioning explained the relation between problematic alcohol use and HIV symptom severity. Results indicated that problematic patterns of alcohol use were associated with lower total memory functioning, retrieval (e.g., recall-difficulty) and memory for activity (e.g., what you did yesterday) and greater HIV symptom severity. Memory functioning mediated the relation between problematic alcohol use and HIV symptom severity. However, the direction of this relation was unclear as HIV symptom severity also mediated the relation between problematic alcohol use and memory functioning. Findings highlight the importance of integrated care for HIV and alcohol use disorders and suggest that routine alcohol and cognitive screenings may bolster health outcomes among this vulnerable population.

Keywords Alcohol · Drinking · Cognitive · Memory · HIV · Symptoms

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Introduction

Heavy and problematic alcohol use is highly prevalent among HIV-infected individuals [1], with estimates of use documented as high as 63 % among HIV clinic patients [2–8]. Indeed, the rate of alcohol use disorders among HIV-infected individuals is markedly higher than that observed in the general population [9, 10]. Importantly, both HIV and problematic alcohol use have significant implications for memory functioning, which is vital to successful adherence to complicated medication regimens and effectiveness of cognitive and behavioral interventions for HIV. Although previous research has shown that heavy alcohol use is associated with a host of negative HIV health outcomes, including poor medication adherence [2, 7, 8, 11–16], increased immune suppression [15, 17, 18], reduced effectiveness of therapeutic regimens [5], faster HIV disease progression [19], lower survival rates [20], and worse health-related quality of life [21], less is known about its

impact on self-reported memory functioning and HIV symptom severity.

Further, greater HIV symptom burden is associated with reduced health-related quality of life, an outcome that has gained increased significance as treatments for HIV infection have improved [22, 23]. Thus, in order to provide a richer clinical conceptualization to inform intervention and treatment efforts, it is important to determine how problematic alcohol use impacts these domains in this already vulnerable population.

HIV disease progression poses significant risk for compromised cognitive efficiency (e.g., executive dysfunction) and memory functioning (as indexed by neuropsychological testing) [24–28], and although antiretroviral therapy (ART) can reduce neurocognitive impairment [29], mild forms still persist in a large proportion of individuals with HIV [30, 31]. Of note, cognitive impairment, and memory dysfunction more specifically, is associated with worse treatment outcomes among HIV-infected individuals [27, 32–34] and is known to reduce the effectiveness of interventions aimed at optimizing adherence and reducing risk behavior [35]. Memory dysfunction has also been observed among individuals with heavy drinking and alcohol use disorders [36, 37] and these changes can persist even following an extended period of abstinence [38, 39]. The effects of alcohol on memory varies substantially across social drinkers and chronic alcoholics [37, 40], and mild neurocognitive deficits are more notable at heavier drinking levels (i.e., 21+ drinks per week [37], 6–7 plus drinks daily [41]).

These independent bodies of research suggest that the combination of problematic alcohol use and HIV may exert a negative additive or synergistic effect on neuropsychological indices of memory functioning. However, the literature speaking to these associations is mixed [42]. Compared to healthy controls and participants with a single diagnosis, individuals with co-occurring HIV and alcohol dependence or abuse have been shown to perform worse on measures of immediate and delayed memory [WMS-R; 43], and on selective memory processes (immediate episodic memory WMS-R [44]). In contrast, Rothlind et al. [16] did not observe differences on measures of verbal and visual learning and memory in a comparison of light/non-drinking and heavy drinking (100+ drinks/month past 3 years) HIV-infected individuals. Similarly, no differences in verbal or non-verbal memory emerged in a comparison of HIV-infected and HIV-uninfected African-Americans with no drinking and light, moderate and heavy drinking [45]. Finally, no differences in learning and memory were observed in a comparison of HIV positive and HIV negative males with and without a history of alcohol abuse [46].

Mixed evidence for the combined impact of alcohol use and HIV infection on memory functioning may be attributable to different stratifications of alcohol use (i.e., dependence versus non-dependence; number of drinks consumed), presence of co-occurring substance use and mental health conditions, as well as assessment method. For example, standardized laboratory-based neuropsychological testing tends to assess performance at a single time point and in a highly specific contextual setting [47]. Indeed, the ecological validity of using neuropsychological tests to assess cognitive function having been questioned [48] due to the nature of laboratory settings for neuropsychological testing, the potential for interactive effects of increased demands on cognition in everyday settings and cognitive deficits, and compensatory strategies that may be effective for a laboratory-based task (e.g., Modified Wisconsin Card Sorting Task) but are not reflected in self-reported memory skills [49]. Although neuropsychological tests provide objective data for specific cognitive deficits, it has been argued that subjective cognitive measures are more sensitive indices for everyday memory functioning [see 50, 51], such as patients' experience of everyday memory failures or milder, more variable cognitive struggles that fluctuate over time [e.g., 52–54]. Use of self-report measures (i.e., meta-memory) may therefore provide a complimentary lens through which to examine the effects of problematic alcohol use on memory functioning among individuals with HIV. For instance, self-reported memory functioning has been shown to explain variance in self-reported medication management over and beyond that accounted for by neuropsychological test measures [55].

At present there is a general dearth of empirical investigation of the impact of varying levels of alcohol use on self-reported and everyday memory functioning among those with HIV. This is unfortunate given the well-established associations between memory dysfunction and poor HIV-related outcomes [24, 55] and lower perceived quality of life among individuals with HIV [21, 56]. Further, because even moderate alcohol use may be harmful in this vulnerable population [1, 57], such questions are relevant for the effective implementation of interventions that heavily tax memory, learning and attention. It is also important to examine these relations in the context of co-occurring substance use and mood disorders, which are common in this population [9]. Accordingly, the primary objective of the current study is to examine the extent to which problematic patterns of alcohol use impact different facets of self-reported everyday memory functioning among a sample of HIV-infected individuals. We hypothesize that problematic alcohol use will be associated with greater perceived memory dysfunction among individuals with HIV, even after controlling for medication adherence, depression, and co-occurring substance use. Given that

problematic alcohol use and memory functioning are known to independently influence HIV outcomes [e.g., 5, 11, 32, 35], our secondary aim is to assess the extent to which poor perceived memory functioning may serve as an indirect pathway between problematic alcohol use and HIV symptom severity. Specifically, we hypothesize that self-reported memory functioning will mediate (i.e., explain) the association between problematic alcohol use and HIV symptom severity.

Method

Participants

Participants were 172 HIV-infected individuals drawn from a larger study of cannabis use and HIV [58]. Participants were recruited via flyers placed throughout VA medical centers and community outpatient HIV clinics in the San Francisco Bay area. For inclusion in the study, participants had to be (1) HIV positive; (2) currently prescribed at least one antiretroviral medication; (3) undergoing treatment at an outpatient HIV treatment clinic. In addition, participants had to meet criteria for either (a) current cannabis dependence, (b) current (past 30 day) non-dependent cannabis use, or (c) no recent history (past 6 months) of cannabis use (see *Cannabis Use and Dependence* in the measures section for further detail).

Measures

Demographic Information

Demographic characteristics including age, gender, ethnicity/race, marital status, and years of education were collected during the screening and interview process. Clinical characteristics, including time since receiving HIV diagnosis and absolute CD4 lymphocyte count (cells/uL), were collected from patients' medical record at his/her HIV clinic.

Memory Functioning

The 27-item Everyday Memory Questionnaire (EMQ [59, 60]) is an established self-report measure that describes a number of daily activities that might involve forgetting. Participants use a 9-point Likert scale to rate the frequency with which they experience each event (1 = "Not at all in the last 6 months," 5 = "More than once a month, but less than once a week," 9 = "More than once a day"). The EMQ is comprised of 5 subscales: Retrieval (6 items; e.g., "Forgotten you were told something and had to be reminded."), Task monitoring (8 items; e.g., "Done some

routine thing twice by mistake."), Conversational monitoring (5 items; e.g., "Repeated to someone what you had just told them."), Spatial memory (3 items; e.g., "Forgotten where things are normally kept."), and Memory for activities (4 items; e.g., "Had to go back and check whether you had done something."). Items can also be summed to generate a total memory functioning score and higher scores reflect a higher frequency of memory problems. The psychometric properties and construct validity of the EMQ have been extensively studied in healthy [59] and clinical populations [61–63]. Additionally the EMQ has been employed in studies with cannabis users [64], ecstasy and poly-drug/alcohol users [65] and the measure has demonstrated sensitivity to differential use of alcohol [66].

Problematic Alcohol Use and Alcohol Abuse and Dependence

The Alcohol Use Disorder Identification Test (AUDIT [67]) is a 10-item self-report measure developed by the World Health Organization to identify individuals with alcohol problems. The AUDIT assesses three domains: alcohol dependence, harmful drinking (drinking that causes direct negative consequences on mental or physical health, or social or occupational functioning), and hazardous drinking (drinking that increases risk for serious future problems). Most items are rated on a 5-point Likert scale ranging from (0) *never* to (4) *daily or almost daily*. In the present study, items were summed to generate an index of total alcohol problems. A wealth of literature attests to the strong psychometric properties of the AUDIT [see 67], in addition to its use for the detection of problematic drinking in HIV-infected samples [2]. Alcohol abuse and dependence were determined by the Structured Clinical Interview-Non-Patient Version for DSM-IV (SCID-I–N/P [68]).

HIV Symptoms and ART Side Effects

The Health Status Questionnaire (HSQ) is a 43-item measure developed by the AIDS Clinical Trials Group to assess health status and outcomes for HIV and AIDS patients [69]. The HSQ assesses general health and energy, as well as social, physical, and cognitive functioning. The HSQ also assesses 20 common HIV symptoms/ART side effects (e.g., fatigue, physical symptoms, mood disturbance) experienced in the past 4 weeks on a five point Likert-type scale (0 = "I do not have this symptom" to 4 = "I have this symptom and it bothers me a lot"). Within the present study, similar to prior work [70], we do not differentiate between HIV symptoms and ART side effects due to their significant overlap. A total score was used to index the frequency/severity of the 20 self-reported HIV symptoms/ART side effects, with lower scores suggesting

a relative absence of symptoms/side effects. The HSQ has shown good psychometric properties [69] and internal consistency in the current sample was excellent ($\alpha = 0.93$).

Self-Report Measure of Antiretroviral Medication Adherence

The Adherence questionnaire (AQ) is a 28-item measure that assesses prescribed ART medication doses, the frequency of taking medications at the correct times and in the correct manner, rated on a 7 point Likert-type scale (0 = "never" to 6 = "all the time"), and the reasons for missed doses [69]. The AQ is derived from the AIDS Clinical Trials Group's self-report medication adherence measure and has shown good psychometric properties [69]. The total number of missed doses in the past 2 weeks and the total number of possible doses during the past 2 weeks were used to yield a 2-week percent self-reported adherence score. This score was then dichotomized to reflect either 100 % adherence or less than 100 % adherence. A 2 week recall period was used because some studies suggest that shorter recall periods allow for more accurate self-reports but with enough variance (e.g., inclusion of weekends) to yield valuable data [71]. The AQ was included in the current study to control for the effects of medication non-adherence on memory functioning and HIV symptom severity.

Cannabis Use and Dependence

Cannabis dependence status was determined by the SCID-I–N/P for DSM-IV [68]. Criteria for cannabis dependence were consistent with DSM-IV criteria [72] with the addition of withdrawal as proposed for DSM-5 [73]. Participants were classified as non-dependent cannabis users if they reported any cannabis use in the past 30 days, but did not meet criteria for cannabis dependence. Participants with no cannabis use in the past 6 months were classified as nonusers. The Marijuana Smoking History Questionnaire (MSHQ [74]) is a 21-item measure that assesses the frequency, patterns, and history of cannabis use. Participants who reported any cannabis use in the past 6 months ($n = 98$) were asked to provide additional information indicating the number of times they had used cannabis during the month prior to assessment. In the present study, cannabis use status was included as a covariate in all analyses (to account for the recruitment criterion in the parent study) and the MSHQ was used to describe frequency of cannabis use.

Tobacco Use and Dependence

The 7-item Fagerström Test for Nicotine Dependence (FTND [75]) was only completed by participants who endorsed tobacco smoking ($n = 87$) and it assesses the extent to which individuals are dependent on nicotine (e.g., "How soon after you wake up do you smoke your first cigarette?"). A single item from the FTND was employed to index the rate of tobacco use (i.e., average number of cigarettes smoked per day). Participants who did not report smoking were assigned a value of zero. Tobacco use was examined as a potential covariate because previous research demonstrates that HIV-related symptom burden is higher among current smokers compared to nonsmokers [76].

Other Illicit Drug Use

Current cocaine/amphetamine and opioid abuse and dependence were assessed using the SCID-I–N/P [68]. Co-occurring substance use disorders are highly prevelant among individuals with HIV [77] and thus these diagnoses were examined as potential covariates and information on recent use was included for descriptive purposes.

Depression

Current Major Depressive Disorder and Dysthymia were assessed using the SCID-I–N/P [68]. Given that depression is associated with both self-reported memory functioning [78] and HIV health outcomes and symptoms [79, 80], a current diagnosis of depression was included as a covariate in all analyses.

Procedure

Participants were recruited via informational flyers posted throughout a VA Medical Center and in numerous San Francisco Bay Area outpatient HIV clinics. Upon contacting the research team, individuals were provided with a detailed description of the study. Interested individuals were screened on the phone for eligibility and, if eligible, scheduled for a study appointment where they provided written consent to participate in the research study. The SCID-I–N/P was administered by trained research assistants and all interviews were audio-recorded and diagnoses were confirmed by the last author following a review of recorded interviews. Participants then completed the above-described measures. All study procedures were approved by a university Institutional Review Board (IRB).

Data Analyses

Descriptive statistics and alpha reliability coefficients were calculated for all measures. Number of cigarettes smoked per day, problematic alcohol use (AUDIT total score) and memory functioning (EMQ total score and subscale scores) were log-transformed to correct for positive skew. A value

of 1 was added to variables including zero prior to their transformation. Bivariate Pearson correlations were conducted to examine relations between the EMQ total score and subscale scores, problematic alcohol use, and HIV symptom severity.

Bivariate spearman and pearson correlations were then performed to assess associations between memory functioning, HIV symptom severity and potential covariates (i.e., age, level of education, cigarette smoking rate, cannabis dependence, stimulant abuse and dependence, opioid abuse and dependence, self-reported medication adherence, current depression diagnosis). Based on these analyses, level of education, cannabis dependence and current depression diagnosis were included as covariates in all regression models. Self-reported adherence, although unrelated to memory functioning or HIV symptom severity, was included in the model to ensure that we accounted for variance in outcomes that could be explained by poor medication adherence. Six hierarchical linear regressions were performed to determine the impact of problematic alcohol use on total memory functioning as well as each individual facet of memory functioning. For the five individual memory facets we used a Bonferroni correction with alpha set at 0.01 for an overall rejection level of 0.05. Self-reported medication adherence was entered as a covariate on step 1. Level of education was entered as a covariate in Step 2. In step 3, two dummy coded variables were entered for cannabis use status (cannabis dependent group served as the reference group). In step 4, current depression diagnosis was entered. Finally in step 5, problematic alcohol use was entered to determine how much additional variance in memory functioning was explained by problematic alcohol use after controlling for all covariates.

Mediation Analyses

Previous research has implicated memory functioning as a potential pathway through which problematic alcohol use may be related to HIV symptom severity [e.g., 11]. Given that both alcohol problems and self-reported memory functioning correlated with HIV symptom severity in the present sample, a series of regression models were performed to determine whether memory functioning mediated the relation between problematic alcohol use and HIV symptom severity [81]. Self-reported medication adherence, highest level of education, cannabis dependence and current depression diagnosis were entered as covariates at steps 1, 2, 3 and 4 respectively, in all models to ensure any relations observed were not accounted for by these variables. First, to test for mediation, problematic alcohol use was regressed on HIV symptom severity (pathway C). Second, to reduce redundancy, results from the primary analyses were used to determine pathway A, the relation

between problematic alcohol use and self-reported total memory functioning (the hypothesized mediator). Third, total self-reported memory functioning was regressed on the outcome variable (i.e., HIV symptom severity), after controlling for problematic alcohol use (Pathway B and C'). Last, both bootstrapping and Sobel tests [see 82, 83] were used to confirm findings from the Baron and Kenny [81] mediational tests.

Finally, as the mediational analyses were conducted among cross-sectional data, an additional model was tested to comprehensively assess directionality of the observed effect whereby the proposed mediator (self-reported memory) and criterion variable (HIV symptom severity) were reversed [82, 84, 85]. To account for potential overlap of cognitive symptoms on the HIV symptom severity measure and the EMQ, mediation analyses were also conducted using a HIV symptom severity score that excluded cognitive symptoms. No differences emerged between models using the different scoring systems and thus the results presented represent all HIV symptoms.

Results

Descriptive Analyses

Of the 172 participants, 37 were female and mean age was 48.37 (SD = 8.64). In terms of ethnicity, 39 % of participants identified as Black/Non-Hispanic, 29.7 % as Caucasian, 14 % as Black/Hispanic, 11 % as Hispanic, 1.1 % as Asian, and 5.2 % as "Other." The majority of participants were never married (46 %), 22 % were married or living with someone and the remainder of the sample was widowed (6 %), separated (10 %) or divorced (16 %). In terms of education, 15 % of participants did not finish high school, 20 % graduated high school, 38 % had some college and the remainder of the sample reported completion of a 2-year degree or higher.

Participants had been diagnosed with HIV for an average of 14.43 years (SD = 7.96; range 1–33) and average absolute CD4 lymphocyte count (cells/uL) count was 543.68 (SD = 288.65; range 8–1547). Average total HIV symptom severity on the Health Status Questionnaire was 31.28 (SD = 18.27; range 0–80). Average percent medication adherence in the past 2 weeks on the AQ was 94.8 % (SD = 14 %; range 0–100) and 69 % of the sample was 100 % adherent. Nineteen percent (n = 34) of the sample met DSM-IV criteria for current Major Depressive Disorder or Dysthymia. Table 1 displays descriptive statistics for prevalence of alcohol, cannabis, stimulant and opioid use disorder and patterns of alcohol, cannabis, cigarette, stimulant and opioid use in the current sample.

Rate of cigarette use was not associated with EMQ subscales or total score or HIV symptom severity. Cannabis dependence was not related to total EMQ score or subscale scores but was positively related with HIV symptom severity ($\rho = 0.18$, $p < 0.05$). Self-reported medication adherence in the past 2 weeks was not related to the EMQ or HIV symptom severity. Higher level of education correlated with lower frequency of Task Monitoring difficulties on the EMQ ($r = -0.21$, $p < 0.01$) and lower HIV symptom severity ($r = -0.17$, $p < 0.05$).

Table 1 Descriptive statistics for substance use disorders, alcohol consumption patterns, cannabis use, tobacco smoking, cocaine/stimulant use and opioid use

	N	%
Drinking frequency		
Never	65	38
Monthly or less	39	23
2–4 times a month	30	17
2–3 times a week	20	12
4 or more times a week	18	10
Number of drinks on typical drinking day		
0	63	37
1–2	65	38
3–4	29	17
5–6	6	3
7 or more	9	5
Binge drinking frequency (4+ female/6+ male)		
Never	106	62
Less than monthly	37	21
Monthly	12	7
Weekly	9	5
Daily or almost daily	8	5
Current alcohol dependence or abuse	23	13
Cannabis dependence and use		
Cannabis dependent	55	32
Cannabis use but not dependent	58	34
No cannabis use	59	34
Current cocaine amphetamine dependence or abuse	11	6
Used in any form past 3 months	34	20
Current opioid dependence or abuse	3	2
Used in any form past 3 months	9	5
	Mean(SD)	Range
Times used cannabis in past month ($n = 99*$)	36.40(43.28)	0–240
Tobacco use and dependence		
Number of cigarettes smoked per day ($n = 85$)	12.14(11.22)	0–80
Fagerstrom test of nicotine dependence ($n = 87$)	2.78(1.69)	0–9

* Data do not include participants with no cannabis use in the past 6 months

Current diagnosis of stimulant abuse or dependence or opioid abuse or dependence was not associated with any of the EMQ subscales or HIV symptom severity. Problematic alcohol use (AUDIT) positively correlated with total memory problems as well as specific difficulties with retrieval, conversational monitoring and memory for activities. Self-reported memory problems across all domains of the EMQ positively correlated with HIV symptom severity. See Table 2 for descriptive statistics for the EMQ and AUDIT and for a complete correlation matrix.

Primary Analyses

Results from the six hierarchical linear regressions revealed that above and beyond the effects of medication adherence, level of education, cannabis dependence, and current depression diagnosis, problematic alcohol use explained a significant amount of variance in total self-reported memory functioning, retrieval (e.g., forgetting events, prospective memory) and memory for activities (e.g., what you did yesterday). Problematic alcohol use, although significant at $p < 0.05$, did not explain a significant proportion of variance in conversational monitoring (e.g., tracking of content) following the Bonferroni adjustment ($p < 0.01$). Finally, problematic alcohol use did not explain variance in spatial memory (e.g., getting lost) or task monitoring (e.g., problems in performing various tasks). See Table 3 for a summary of these analyses.

Mediation Analyses

The relation between problematic alcohol use and HIV symptom severity (C pathway) was examined first. After controlling for variance accounted for by medication adherence, education, cannabis dependence, and current depression diagnosis, problematic alcohol use was significantly and positively related to HIV symptom severity ($\beta = 0.18$, $t = 2.47$, $p < 0.02$). Pathway A was examined in the primary analyses and results showed that problematic alcohol use was significantly and positively related to self-reported memory functioning after controlling for potential covariates. A final regression analysis was conducted to simultaneously examine: (1) the relation between self-reported memory functioning and HIV symptom severity while accounting for variance related to problematic alcohol use (B pathway) and (2) the relation between problematic alcohol use and HIV symptom severity (C' pathway) while accounting for variance related to self-reported memory functioning. Results indicated that self-reported memory functioning (hypothesized mediator) was associated with higher HIV symptom severity ($\beta = 0.32$, $t = 4.02$, $p < 0.001$). However, the significant

Table 2 Descriptive statistics and correlations among problematic alcohol use, perceived memory functioning and HIV symptom severity

	EMQ total	Retrieval	Task monitoring	Conversational monitoring	Spatial memory	Memory for activities	AUDIT
Mean	77.99	20.05	18.77	13.33	8.86	14.44	8.46
SD	45.43	12.33	12.91	8.50	6.99	8.14	8.77
N	168	169	168	169	169	170	172
Range	28–216	6–54	8–66	5–45	4–39	4–36	0–45
Alpha α	0.96	0.92	0.89	0.84	0.76	0.82	0.89
AUDIT	0.19* N = 168	0.21** N = 169	0.13 N = 168	0.19* N = 169	0.09 N = 169	0.22** N = 170	–
HIV symptom severity	46** N = 168	0.42** N = 169	0.43** N = 168	0.43** N = 169	0.34** N = 169	0.38** N = 170	0.22** N = 172

* $p < 0.05$; ** $p < 0.01$. *AUDIT* alcohol use disorders identification test, *EMQ* everyday memory questionnaire. Correlations are performed with log transformed EMQ and AUDIT variables

relation between problematic alcohol use and HIV symptom severity became non-significant after accounting for variance associated with self-reported memory functioning and other covariates ($\beta = 0.13$, $t = 1.75$, $p = 0.08$). This suggests that self-reported memory functioning fully mediated the relation between problematic alcohol use and HIV symptom severity (see Fig. 1).

A Sobel test [83] suggested that the inclusion of self-reported memory functioning significantly decreased the strength of the association between problematic alcohol use and HIV symptom severity ($z = 2.09$; $p < 0.04$); the associated standardized beta weight decreased from 0.18 to 0.13. The bootstrapped 95 % confidence interval with 5,000 iterations was 0.31–5.32 [82]. Of note, in the final model, participants with a current depression diagnosis had higher HIV symptom severity ($\beta = 0.22$, $t = 2.77$, $p < 0.01$).

Follow-up analyses in which the mediator (self-reported memory functioning) and criterion variable (HIV symptom severity) were reversed revealed that HIV symptom severity fully mediated the relation between problematic alcohol use and self-reported memory functioning (Sobel Test $z = 2.10$, $p < 0.04$; bootstrapped 95 % CI 0.01–0.16). These results suggest that HIV symptom severity (even after removing cognitive symptoms) and self-reported memory functioning were interrelated, and that self-reported memory functioning did not provide a single, distinct mediational relation between problematic alcohol use and HIV symptom severity.

Discussion

The present study sought to determine the influence of problematic alcohol use on self-reported memory functioning, and to assess relations with HIV symptom severity among a sample of HIV-infected individuals. Consistent with hypotheses and previous research [e.g., 36, 37], problematic alcohol use was associated with lower ratings of overall everyday memory functioning as well as increased difficulty with retrieval and memory for activities. Importantly, this pattern of results suggests that problematic alcohol use tended to specifically impact retrieval-based over processing-based aspects of memory functioning. Also of note, problematic alcohol use exhibited a direct and potent effect on these aspects of perceived memory functioning even after accounting for co-occurring substance use and depression (current diagnosis of Dysthymia or Major Depressive Disorder). Finally, perceived memory functioning mediated (i.e., explained) the relation between problematic alcohol use and HIV symptom severity, though the direction of this relation was unclear and possibly reciprocal.

Findings from the present study lend support to clinical researchers' call for initiatives to tailor substance abuse treatment and HIV risk-reduction programs to better address impediments posed by cognitive impairment [see 86]. For instance, techniques to improve multi-modal encoding (e.g., verbal, visual) of clinical information (e.g., coping skills, risk-reduction practices, medication instructions) may be particularly beneficial in helping to reduce retrieval-failures observed in the current study. External cueing systems (e.g., alarms, appointment reminders, checklists) and environmental supports (e.g., computerized clinician reminders) in treatment clinics can also be employed. In addition, although the cross-sectional nature of these data does not permit us to draw conclusions about causality, interventions to remediate cognitive functioning may also improve outcomes in this particularly vulnerable population. For instance, computerized neuroscience-based cognitive remediation programs that target attention, memory and executive functioning (e.g., PssCogRehab, Psychological Services Inc; BrainHQ, Posit Science) could help augment existing treatments by enhancing patients'

Table 3 Perceived memory functioning by medication adherence (Step 1), education (Step 2), cannabis dependence (Step 3), current depression diagnosis (Step 4) and problematic alcohol use (Step 5)

		EMQ Total	Dependent variables: EMQ total and individual memory Facets				
			Retrieval	Task monitoring	Conversational monitoring	Spatial memory	Memory for activities
Step	Independent variables	Betas (sr^2)	Betas (sr^2)	Betas	Betas (sr^2)	Betas (sr^2)	Betas (sr^2)
1	Medication adherence	−0.14	−0.13	−0.08	−0.15	−0.13	−0.14
	Multiple R^2	0.02	0.02	0.01	0.02	0.02	0.02
2	Medication adherence	−0.13	−0.13	−0.07	−0.14	−0.12	−0.14
	Education	−0.15	−0.09	−0.21**(0.05)	−0.14	−0.13	−0.02
	Multiple R^2	0.04	0.03	0.05	0.04	0.03	0.02
	ΔR^2	0.02	0.01	0.05**	0.02	0.02	0.00
3	Medication adherence	−0.12	−0.12	−0.06	−0.12	−0.14	−0.12
	Education	−0.14	−0.08	−0.20*(0.04)	−0.12	−0.14	0.01
	Cannabis not dependent	−0.12	−0.13	−0.07	−0.14	−0.02	−0.15
	Cannabis no use	−0.08	−0.07	−0.06	−0.12	0.09	−0.07
	Multiple R^2	0.05	0.04	0.06	0.06	0.04	0.04
	ΔR^2	0.01	0.01	0.01	0.02	0.01	0.02
4	Medication adherence	−0.13	−0.13	−0.07	−0.13	−0.14	−0.13
	Education	−0.07	−0.01	−0.15	−0.05	−0.09	−0.06
	Cannabis not dependent	−0.05	−0.06	−0.02	−0.07	−0.02	−0.08
	Cannabis no use	−0.01	0.00	−0.01	−0.05	0.13	−0.01
	Current depression diagnosis	0.45**(0.20)	0.44**(0.19)	0.38**(0.14)	0.43**(0.19)	0.31**(0.10)	0.42**(0.18)
	Multiple R^2	0.24	0.22	0.19	0.23	0.13**	0.21
	ΔR^2	0.19**	0.19**	0.13**	0.18**	0.09	0.17**
5	Medication adherence	−0.11	−0.11	−0.06	−0.11	−0.13	−0.11
	Education	−0.08	−0.03	−0.16*(0.03)	−0.07	−0.10	0.04
	Cannabis not dependent	−0.02	−0.02	0.002	−0.04	0.04	−0.05
	Cannabis no use	0.04	0.06	0.03	−0.01	0.16	0.05
	Current depression diagnosis	0.44**(0.20)	0.43**(0.19)	0.37**(0.14)	0.43**(0.19)	0.31**(0.09)	0.42**(0.18)
	AUDIT	0.18*(0.04)	0.19**(0.04)	0.12	0.16*(0.03)	0.11	0.21**(0.05)
	Multiple R^2	0.27	0.26	0.20	0.26	0.15	0.24
	ΔR^2	0.03*	0.03**	0.01	0.02*	0.01	0.04**

** $p \leq 0.01$(critical p value of Bonferroni correction for tests involving five memory facets); * $p < 0.05$

Fig. 1 Perceived everyday memory functioning as a mediator of the association between problematic alcohol use and HIV symptom severity
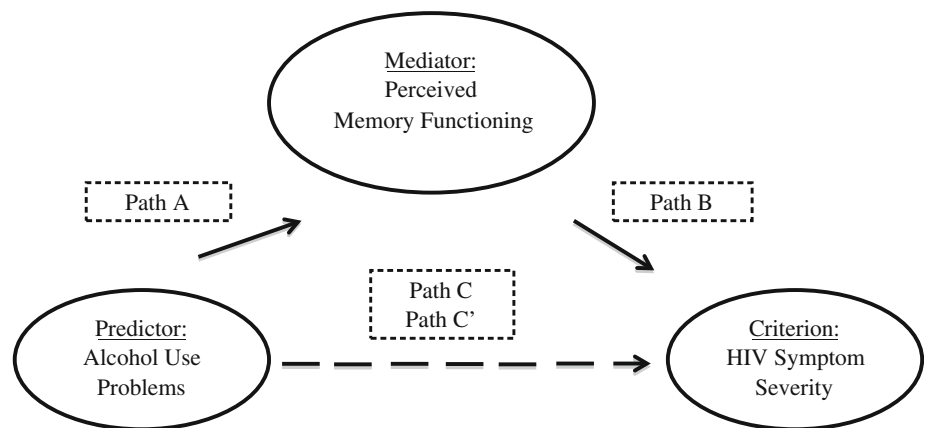
cognitive reserve and mental flexibility to adhere to complex treatment regimens and encode, retrieve and employ HIV transmission-prevention skills [e.g., 87, 88].

As hypothesized, perceived memory functioning provided an indirect pathway for the relation between problematic alcohol use and HIV symptom severity. Thus, one possibility is that the deleterious effects of problematic alcohol use on memory functioning explain the relation between problematic alcohol use and HIV symptom severity. For instance, problematic alcohol use may negatively impact memory for events (e.g., taking medications) and retrieval (e.g., coping skills retrieval) that may increase HIV-risk behaviors and reduce adherence and general self-care and ultimately, increase HIV symptom severity. Importantly though, reversal of the mediational model indicated that HIV symptom severity explained the relation between problematic alcohol use and self-reported memory functioning. As such, HIV symptom severity and memory functioning were interrelated and the extent to which memory functioning offers a distinct mediational pathway between problematic alcohol use and HIV symptom severity is unclear.

The blurred directionality observed in our mediation models is believed to highlight the complexity associated with comorbid health conditions that commonly characterize this population, and their impact on HIV health outcomes. More likely, and as articulated in previous work [35], the relations between memory functioning, HIV outcomes and alcohol use are reciprocal. Among HIV-infected individuals, problematic alcohol use is associated with worse HIV health outcomes [e.g., 2, 5, 7, 8, 11–19] which ostensibly result in increased HIV symptom severity and lower overall quality of life. Adding to the clinical profile, HIV disease progression (i.e., heightened symptom burden) is commonly associated with neurocognitive impairment [24–28]. Given the high prevalence of alcohol problems among HIV-infected individuals coupled with its observed negative impact on memory functioning, routine screening for problematic alcohol use in HIV care settings is thus imperative [14, 89]. In the current sample, problematic alcohol use and all domains of self-reported memory functioning were associated with higher HIV symptom severity. Accordingly, this research combines with previous work to suggest that HIV symptom severity is intricately related to both alcohol consumption and memory functioning and that they should be considered collectively in clinical settings.

Results from the current study are consistent with the literature in several respects. Previous research indicates that alcohol and drug use exert greater effects on neurocognitive function in HIV-infected versus non-infected individuals [e.g., 90] and, thus, HIV is posited to potentiate and exacerbate the impact of alcohol and drug use on neurocognitive functioning [46, 91]. Although no comparison group was available, our findings appear to support this notion and indicate that both problematic alcohol use and HIV symptom severity are associated with lower everyday memory functioning among individuals with HIV. In addition, HIV-infected individuals with a current depression diagnosis were at increased risk for reduced memory functioning and heightened HIV symptom severity, which is also consistent with previous research [78–80]. Findings here also broadly align with research employing animal models of HIV infection which have shown that HIV can cause neuroplastic changes that impair cellular learning process implicated in memory [92]. Such models also demonstrate that HIV infection can alter the metabolism of alcohol, which has direct consequences for alcohol-induced expression of genes that affect neurotransmission (i.e., synaptic signaling and neuronal functioning [93]). Combined, these data, collected at multiple levels of analysis, suggest that HIV infection has a direct impact on learning and memory and that it may also increase vulnerability to the effects of alcohol consumption on memory functioning. Consideration of the impact of problematic alcohol use on memory functioning may therefore further enrich our understanding of health outcomes among individuals with HIV.

The current study is characterized by several strengths including examination of varying levels of alcohol use, comprehensive interview-based assessment of medication adherence, psychiatric illness, and co-occurring substance use, as well as evaluation of patient-perceived everyday memory functioning. However the current study is not without limitations. First, although the presented mediational results represent an important first step, without a prospective design our findings have limited interpretability [94]. Future studies should longitudinally examine the influence of perceived memory functioning and problematic alcohol use on HIV symptom severity to confirm directionality of observed effects. Second, HIV symptom severity is a subjective self-report measure and represents only one index of HIV health. Future research should use a multi-method approach to determine how problematic alcohol use and self-reported memory functioning impact objective measures of adherence (e.g., MEMS cap), engagement with care (e.g., clinic attendance) and biological markers of HIV disease severity (e.g., viral load).

Third, we did not simultaneously employ laboratory-based measures of neuropsychological performance traditionally used to establish cognitive impairment in clinical populations. Indeed discordance between self-reported cognitive functioning and objective indices of neuropsychological performance has been documented among HIV-infected individuals [95]. However, other research has found increased cognitive complaints to predict poorer

neuropsychological test performance and thus supports a relation between self-reported cognitive complaints and neuropsychological skills among HIV-infected individuals [52]. Further, the majority of observed cognitive impairment among HIV-infected individuals in the post-ART era is mild, variable, and may go undetected (asymptomatic neurocognitive impairment, mild neurocognitive disorder [see 27]). As such, it is possible that neuropsychological assessment measures, which possess somewhat less obvious face validity for real world impairment [53], are less sensitive to mild and fluctuating difficulties in everyday memory functioning [e.g., 96, 97]. Hence, our reliance on patient's self-report of memory dysfunction (i.e., meta-memory) offers a unique understanding of how HIV symptom severity and problematic alcohol use can affect subjective experience. Nevertheless, future studies should employ a multimodal assessment of cognitive functioning that includes both self-report and neuropsychological assessment tools. In addition, although the EMQ has been used with cognitively compromised clinical samples [61–63] and is sensitive to differential use of alcohol [66], it has not been employed in previous studies with HIV-infected samples. Of note though, other studies have included similar measures of meta-memory (e.g., Prospective and Retrospective Memory Questionnaire) to assess perceived memory difficulties in HIV-infected samples [98].

Fourth, counter to expectations, our analyses did not reveal an association between self-reported medication adherence and HIV symptom severity. It is possible that memory problems may have impacted accuracy of self-reported adherence (over-inflation, 94 % average adherence). Another potential reason for the lack of association could have been the differing time frames in which HIV symptom severity (past 4 weeks) and medication adherence (past 2 weeks) were assessed. It is possible that recent non-adherence may not yet have rendered increases in symptom severity. Accordingly, the shorter 2-week window in which medication adherence was assessed is a limitation of this study. Future studies should aim to match assessment time periods for medication adherence and HIV symptom severity. In addition, given that some of the named symptoms included affective disturbance, medication adherence alone may not have been sufficient to reduce such symptoms. HIV infection is associated with a wide range of symptoms, and future research should examine the extent which problematic alcohol use and perceived memory functioning impact specific facets of HIV symptoms (e.g., physical, affective, cognitive). Fifth, although our hypotheses were supported above and beyond the effects of sample stratification by cannabis use status, researchers should also examine associations between problematic alcohol use, memory functioning and HIV symptom severity in an a priori study. Last, the current

study did not employ an objective measure of adherence and observed self-reported estimates may have been over-inflated. Other studies with HIV-infected substance users have reported significantly lower adherence ratings with objective measures (e.g., 70–75 % adherence [99]).

In summary, problematic alcohol use, more so than medication non-adherence, current depression, or cannabis or tobacco use, was associated with greater perceived memory dysfunction in this HIV-infected sample. Additionally, perceived memory dysfunction emerged as a factor that may explain why individuals with problematic alcohol use experience increased HIV symptom severity. Accordingly, memory functioning may represent a high-yield trans-disease target for interventions among individuals with co-occurring HIV and substance use disorders (SUD). Further, the current findings, in conjunction with previous work [e.g., 35, 100], suggest that assessment of cognitive functioning should precede symptom-focused empirically-supported interventions in order to bolster outcomes for HIV-infected individuals with problematic alcohol and substance use. Identification of cognitive deficits prior to treatment would afford clinicians the opportunity to modify intervention delivery and preemptively recruit organizational and community resources. Finally, our results highlight the importance of integrated care for this high-risk population [e.g., 14, 101] that includes cross-training initiatives across health disciplines (e.g., memory and alcohol screening), co-location of services [102], enhanced provider communication, monitoring of drug interactions and side effects, and a united, multidisciplinary team approach to combating the serious social and economic consequences that typify HIV infection and substance use.

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