Title

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Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 63(1)

ISSN

1525-4135

Authors

Meyer, Vanessa J
Rubin, Leah H
Martin, Eileen
et al.

Publication Date

2013-05-01

DOI

10.1097/qai.0b013e318289565c

Peer reviewed

Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 May 1; 63(1): 67–76. doi:10.1097/QAI.0b013e318289565c.

HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women

Vanessa J. Meyer, PhD, **Leah H. Rubin, PhD**, **Eileen Martin, PhD**, **Kathleen M. Weber, RN, BSN**, **Mardge H. Cohen, MD**, **Elizabeth T. Golub, PhD**, **Victor Valcour, MD**, **Mary A. Young, MD**, **Howard Crystal, MD**, **Kathryn Anastos, MD**, **Bradley E. Aouizerat, PhD, MAS**, **Joel Milam, PhD**, and **Pauline M. Maki, PhD**

University of Illinois at Chicago, Chicago IL (VG, LHR, EM, PMM); CORE Center/Cook County Health and Hospital System, Chicago IL (KW, MC); Rush University, Chicago IL (MC); Johns Hopkins Bloomberg School of Public Health, Baltimore MD (ETG); University of California San Francisco, CA (VV, BEA); Georgetown University, Washington D.C. (MAY); SUNY Downstate Medical Center, Brooklyn NY (HC); Montefiore Medical Center and Albert Einstein College of Medicine, Bronx NY (KA); University of Southern California, Los Angeles CA (JM)

Abstract

Objective—HIV infection and illicit drug use are each associated with diminished cognitive performance. This study examined the separate and interactive effects of HIV and recent illicit drug use on verbal memory, processing speed and executive function in the multicenter Women's Interagency HIV Study (WIHS).

Methods—Participants included 952 HIV-infected and 443 HIV-uninfected women (mean age=42.8, 64% African-American). Outcome measures included the Hopkins Verbal Learning Test - Revised (HVLT-R) and the Stroop test. Three drug use groups were compared: recent illicit drug users (cocaine or heroin use in past 6 months, n=140), former users (lifetime cocaine or heroin use but not in past 6 months, n=651), and non-users (no lifetime use of cocaine or heroin, n=604).

Results—The typical pattern of recent drug use was daily or weekly smoking of crack cocaine. HIV infection and recent illicit drug use were each associated with worse verbal learning and memory (p's<.05). Importantly, there was an interaction between HIV serostatus and recent illicit drug use such that recent illicit drug use (compared to non-use) negatively impacted verbal learning and memory only in HIV-infected women (p's <0.01). There was no interaction between HIV serostatus and illicit drug use on processing speed or executive function on the Stroop test.

Conclusion—The interaction between HIV serostatus and recent illicit drug use on verbal learning and memory suggests a potential synergistic neurotoxicity that may affect the neural circuitry underlying performance on these tasks.

INTRODUCTION

Despite improved cognitive outcomes following the introduction of combination anti-retroviral therapy (cART), HIV-infected individuals continue to show cognitive impairment,

Address correspondence and reprint requests to: Pauline Maki, PhD, University of Illinois at Chicago, Department of Psychiatry (MC 913), 912 S Wood St, Chicago, Illinois 60612, (312)996-6941, pmaki@psych.uic.edu..

particularly in verbal episodic memory and executive function[1]. Episodic memory is impaired in up to 50% of HIV-infected individuals[2], and these cognitive deficits predict daily functioning[3–5]. HIV-associated deficits in verbal memory are characterized by deficits in executive control of encoding and retrieval mechanisms[6–8], a pattern consistent with a frontal-subcortical involvement. Dependence on illicit drugs is also consistently associated with deficits in cognitive function, including verbal memory[9–14] and executive function[15–18]. Given that the use of illicit substances is common in HIV-infected populations, it is important to understand how HIV-infection and illicit drug use might interact to impact cognitive function.

A number of recent *in vitro* and *in vivo* studies suggest that cocaine directly affects the neuropathogenesis of HIV[19–31]. Cocaine amplifies HIV replication[21,22,25,28,30], including in human astrocytes[29], which can function as cellular reservoirs for HIV in the brain[32]. Cocaine may also increase HIV-infected monocyte migration across the blood-brain barrier[23,24]. Cocaine enhances the neurotoxic effects of the HIV viral protein Tat[19,20,26,27,31]. Similarly, opiates increase neurotoxicity of HIV proteins Tat[33–35] and gp120[35]. Importantly, cocaine and opiates, in combination with HIV proteins, negatively impact hippocampal neurogenesis[36]. Given that the hippocampus is critical for episodic memory, translation of these preclinical findings into clinical studies may lend important new insights into memory function in HIV-infected cocaine users.

Although many studies have investigated the impact of illicit drug use on HIV disease progression, the effects of cocaine and heroin use on cognition in HIV-infected women have not been elucidated[37]. Such studies are critical in light of the myriad sex differences in illicit substance use disorders. Women have higher current and lifetime use of cocaine and are more likely than men to become cocaine-dependent[38–40]. Women who use cocaine are three times more likely to become infected with HIV than women who do not use cocaine[41]. Cocaine use is also associated with accelerated disease progression in women with HIV, even when statistically controlling for anti-retroviral therapy use[42,43] and medication adherence[44]. For example, in the Women's Interagency HIV Study (WIHS), HIV-infected women who used crack cocaine were three times more likely to die of AIDS-related causes than women who did not use crack cocaine, even when controlling for adherence to highly active anti-retroviral therapy (HAART)[44]. Studies of illicit drug use in women generally have not found an effect of opiates on HIV disease progression[43,45].

Our aim was to investigate the impact of HIV infection and illicit drug use on cognition in women. We compared three categories of drug use: recent use, former use, and non-use. Primary outcomes were measures of verbal learning and memory, processing speed, and executive function based on neuropsychological tests with demonstrated sensitivity to HIV-related neurocognitive dysfunction[46–50]. We hypothesized that HIV and illicit drug use, especially cocaine use, would have an interactive effect on verbal learning and memory and executive function.

METHOD

Subjects

All participants were enrolled in the WIHS, the largest prospective, longitudinal, multi-center study of HIV progression in women[51,52]. Study methodology, standardized data collection, and training of interviewers have been previously reported[51,52]. We analyzed cross-sectional data from 947 HIV-infected and 443 HIV-uninfected control participants (mean age=42.8, 64% African-American). The data were collected as part of a study of menopause, cognition, and mood that was incorporated into the WIHS core visits in April 2007 to April 2008 (WIHS visit 25)[53]. Extensive information on demographic and

behavioral variables was obtained, including self-report of recent and past use of alcohol, marijuana, crack cocaine, powder cocaine, and heroin.

Altogether 1901 participants were assessed during that WIHS core visit, and 1552 of those women completed the Hopkins Verbal Learning Test-Revised (HVLT-R). We excluded 157 of those participants because they reported: a) primary language other than English (n=14); b) history of stroke/cerebrovascular accidents (n=18); and/or c) use of antipsychotic medication in the past 6 months (n=130). A comparison of women who were included in this analysis (n=1395; 73% of the overall sample) versus those who were excluded (n=506) showed similar rates of cocaine and heroin use, but women who were included completed more years of education (12.4 vs. 10.6 years, $p<0.001$), performed better on the Wide Range Achievement Test – Revised (WRAT-R) (92.2 vs. 87.3, $p<0.001$), were more likely to be African-American (64% vs. 41%, $p<0.001$) and less likely to be Hispanic (19% vs. 48%, $p<0.001$), were less likely to have depressive symptoms on the Center for Epidemiological Studies-Depression scale (CES-D; 32% vs. 46%, $p<0.001$) or report using antidepressant medication (12% vs. 19%, $p<0.001$), and were more likely to smoke (72% vs. 66%--recent or former, $p=0.01$) and use marijuana (75% vs. 60%--recent+former, $p<0.001$).

Illicit Drug Use

The WIHS collects information on drug use at 6 months intervals consistent with the twice yearly WIHS visit schedule. Women are asked if they have used drugs since their last WIHS visit. If they have used drugs since their last WIHS visit, they are queried about the route of administration (smoking, sniffing, injecting) of each substance as well as their frequency of use. For the current study, recent illicit drug use was defined as self-reported use of crack cocaine, powder cocaine, or heroin since the last WIHS study visit (past 6 months). Former use was defined as any lifetime use of cocaine and/or heroin, but no use since the last WIHS study visit (past 6 months). Non-use was defined as no lifetime use of cocaine and/or heroin. In follow-up analyses focusing on particular drugs, crack cocaine and powder cocaine were combined into one cocaine use variable, as there was insufficient statistical power to separate the two forms of the drug. Frequency data were categorized as: once a month or less; at least once a week but less than once per day; or once a day or more.

Clinical Neuropsychological Measures

Participants completed the HVLT-R and Comalli Stroop test. The HVLT-R is a 12-item list-learning test used to measure verbal episodic memory[54]. Outcomes include total words recalled on Trial 1 (single trial learning) and across each of three learning trials (total learning), number of words recalled after a 25-minute delay (delayed recall), number of words correctly identified on a yes/no recognition test (recognition), percent retention (delayed recall/maximum score on Trial 2 or 3), and learning slope. Recognition scores were calculated by subtracting the number of false positives (incorrectly responding `yes' to a word not presented) from the number of hits (correctly responding `yes' to a word that was presented). The Comalli Stroop Test includes three trials[55] Trials 1 and 2 measure attention and processing speed. Trial 3 measures response inhibition/executive function. On Trial 1, participants name the colors of a series of squares. On Trial 2 they read a series of color names printed in black ink. On Trial 3, participants name the color of the ink but ignore the word (e.g., when shown the word “red” printed in blue ink, say “blue” rather than “red”)[55]. Completion times for all three trials were recorded. The WRAT-R measured reading achievement[56] and served as an index of educational quality[57].

Covariates

Socio-demographic covariates and risk factors for cognitive impairment were selected based on previous literature and included study site, age, years of education, race/ethnicity,

WRAT-R, CES-D (cutoff score of 16)[58], recent self-reported use of antidepressant medication and Hepatitis C virus seropositivity (HCV) [48,59–66]. Other covariates focused on risk behaviors and included smoking status (recent, former, never), recent hazardous alcohol use (> 7 drinks/week or more than 4 drinks in one sitting)[67], and marijuana/hash use (recent, former, never). Additional clinical variables of interest were cART use (i.e., no cART therapy, cART therapy and <95% compliant, cART therapy and ≥95% compliant), recent CD4 count <200 cells/mm3, recent HIV viral load >10,000, CD4 nadir <200 cells/mm3, and duration of ART use.

Statistical Analysis

Five percent of participants were missing WRAT-R scores. Missing values were imputed using a regression based technique with race/ethnicity, age, education, site, and employment as predictors. Time-related outcomes on the Stroop were log-transformed to correct for skewness. All outcome measures were transformed to z-scores to allow for comparison of beta weights across outcome measures in models controlling for the same covariates.

Differences in demographic, behavioral, and clinical characteristics as a function of serostatus, illicit drug use, and their interaction were examined using ANOVAs for continuous variables and Chi-square (X^2) tests for categorical variables. In the overall sample we conducted two series of multivariable regression analyses. The first series focused on the independent effects of serostatus and illicit drug use, adjusting for age, years of education, WRAT-R, race/ethnicity, site, depressive symptoms, self-reported use of antidepressant medication and dementia/encephalopathy (n=59), marijuana use, smoking, hazardous alcohol use, and HCV. We also adjusted for number of prior exposures to the Stroop (range 1–3). (The HVLT had not been previously administered.) The primary set of analyses focused on the interactive effect of serostatus and illicit drug use. When the interaction was significant, we further examined the effect of drug use and frequency within each serostatus group, controlling for the same set of covariates included in the first analyses. Other follow-up analyses focused on HIV-infected women and included recent CD4 count and HIV viral load, CD4 nadir, and use of antiretroviral therapy (ART). All p values are two-sided. The statistical significance level was set at $p<0.05$. Analyses were performed using SAS PROC GENMOD (version 9.2, SAS Institute Inc, Cary, NC).

RESULTS

Population Characteristics

Participants included 952 HIV-infected and 443 HIV-uninfected women. They ranged in age from 22 to 78 years (M=42.8, SD=9.5), with high minority representation (64% African-American, 19% Hispanic). Ten percent (n=140) reported use of cocaine and/or heroin since the previous study visit 6 months earlier; 47% (n=651) reported former use of cocaine and/or heroin, and 43% (n=604) reported never using cocaine and/or heroin in their lifetime. Among recent drug users, 70% had recently used only cocaine, 24% had recently used both cocaine and heroin, and 6% had recently used only heroin. Recent cocaine users mainly smoked crack (74%) or snorted cocaine (26%). Primary modes of recent heroin intake were snorting (17%) and injecting (14%). Critically, as shown in Supplemental Table 1, the typical pattern of recent use was at least daily (32%) or weekly (38%) smoking of crack cocaine (e.g., 73%).

Compared to HIV-uninfected women, HIV-infected women were older, had a higher minority representation, were more likely to be HCV-seropositive and to use antidepressant medication and cigarettes, and were less likely to engage in hazardous drinking, marijuana, and powder cocaine use (p's<0.05, Table 1). Compared to non-users, recent and former

illicit drug users were older, less educated, were more likely to be HCV-seropositive, reported more depressive symptoms and antidepressant medication use, and were more likely to smoke, use marijuana, crack cocaine, powder cocaine, heroin, and engage in hazardous drinking (p's<0.05). Among recent users, HIV-infected women were less likely to sniff/snort cocaine and less frequently injected heroin than HIV-uninfected women (p's<0.05, Supplemental Table 1). Among HIV-infected women, recent users were less likely to be on cART and to adhere to their medication, were on ART for a shorter duration of time, and were diagnosed with HIV more recently than former and non-users (p's<0.05).

Hopkins Verbal Learning Test-Revised (HVLT-R)

Table 2 shows the raw neuropsychological test scores as a function of serostatus and illicit drug use. HIV-infected women performed worse than HIV-uninfected women on total learning, learning slope, delayed recall, and recognition (p's<0.05; see Table 3). In adjusted analyses, recent illicit drug users performed worse than non-users on learning slope (p=0.04), delayed recall (p=0.007), and recognition (p=0.02). Recent drug users also performed worse than former drug users on recognition (p=0.03). Former drug users did not perform differently than non-users on any HVLT measure. The primary finding was that illicit drug use (recent versus nonuse) interacted with serostatus to affect Trial 1, total learning, learning slope, and delayed recall (p's<0.05; see Figure 1), but not recognition (p=0.73). Among HIV-infected women, recent illicit drug users performed worse than non-users on total learning (B=−0.36, SE=0.12, p=0.002), learning slope (B=−0.42, SE=0.12, p<0.001), and delayed recall (B=−0.45, SE=0.12, p<0.001). In contrast, among the HIV-uninfected women, recent users performed similarly to non-users on total learning (B=0.22, SE=0.15, p=0.14), learning slope (B=0.18, SE=0.15, p=0.23), and delayed recall (B=−0.05, SE=0.15, p=0.73), Whereas the interaction between serostatus and drug use for each of the four measures was driven by differences between recent users and non-users at the level of serostatus, for Trial 1 only, the interaction was driven by differences between HIV-infected and uninfected women at the level of drug use. Specifically for Trial 1, the interaction was driven by serostatus effects at the level of drug use; among recent users, HIV-infected women performed worse than HIV-uninfected women (B=−0.47, SE=0.16, p=0.004) whereas among non-users, HIV+ women perform similar to HIV-uninfected women (B=−0.02, SE=0.08, p=0.84).

Follow-up analyses probed the interaction between serostatus and recent drug use further to assess which particular drug (i.e., cocaine with or without heroin; heroin with or without cocaine) contributed to the interaction. Serostatus interacted with cocaine use (recent versus non-use; p's<.05) and heroin use (recent versus non-use; p's<.01) to impact total learning and learning slope. Serostatus interacted with cocaine use (non-use versus recent) but not heroin use to impact delayed recall (p=0.04). Additional analyses focused on dose response by examining the frequency of smoking crack on total learning, learning slope and delayed recall (see Supplemental Table 2). Serostatus interacted with frequency of crack use (≥ 1 week versus non-use) to affect total learning (p= 0.03) and delayed recall (p=0.005). Again the patterns were that drug use impacted performance among HIV-infected women only.

In analyses of HIV-infected women only, the effects of illicit drug use (recent versus non-use) on total learning, learning slope, and delayed recall remained significant after controlling for disease characteristics (i.e., CD4 count, viral load, medication use, duration on ART) (see Table 4). Recent users also performed worse than former users on learning slope and delayed recall, and former users performed worse than non-users on delayed recall. Comparing recent users to non-users on total learning and learning slope, recent heroin use predicted poorer performance (B=−0.42, SE=0.19, p=0.03 and B=−0.58, SE=0.24, p=0.01, respectively). Cocaine use predicted poorer performance on delayed recall (B=−0.32, SE=0.15, p=0.03). There was also a trend for heroin use to predict poorer

performance on delayed recall (B=−0.34, SE=0.20, p=0.08). In HIV-infected women, the effects of smoking crack/cocaine at least once a week versus non-use remained significant on both total learning (B=−0.39, SE=0.19, p=0.04) and delayed recall (B=− 0.40, SE=0.19, p=0.04) after controlling for disease characteristics (i.e., CD4 count, viral load, medication use, duration on ART).

Stroop Test

Neither HIV-infection nor drug use significantly impacted performance on the Stroop test (Trials 1&2 or Trial 3, p's>0.05). In addition, there were no significant interactions between illicit drug use and serostatus on the Stroop Test (p's>0.05).

DISCUSSION

The aim of this study was to investigate the separate and interactive effects of illicit drug use and HIV infection on verbal learning and memory, processing speed, and executive function. To our knowledge this is the first study to examine this issue, and we provide new evidence that in women recent illicit drug use may interact with HIV serostatus to negatively impact verbal learning and memory but not processing speed or response inhibition. The typical pattern of recent drug use was at least daily or weekly smoking of crack cocaine. The pattern of effects across different measures suggests that recent drug use (compared to non-use) affects learning and memory more among HIV-infected than HIV-uninfected women. Cocaine use interacted with HIV serostatus to affect learning and delayed recall, but not recognition. Heroin interacted with HIV serostatus to affect only learning. Serostatus also interacted with frequency of crack cocaine use to negatively affect learning and delayed recall (but not recognition) more in HIV-infected women. HIV infection, regardless of substance use history, was associated with deficits in learning (i.e., impaired total learning, learning slope) and delayed memory (impaired delayed recall, recognition), with no impairment in retention or attention (trial 1). Deficits in verbal learning and memory encoding might have important implications for clinical management of HIV, as neurocognitive deficits have been shown to relate to poor medication treatment adherence among HIV-infected individuals[68]. Our results underscore the importance of effective substance abuse treatment in HIV-infected individuals.

Few studies have sufficient statistical power to test for an interactive effect of HIV and drugs of abuse on cognition[69]. The HIV Neurobehavioral Research Center (HNRC) has investigated additive and potential interactive effects of methamphetamine and HIV. They found additive effects of methamphetamine use and HIV infection on neuropsychological function[70], neural and glial injury[71], and cerebral blood flow (CBF)[72]. The only previous study to investigate the interactive effects of HIV and cocaine use on verbal memory (n= 237 gay and bisexual seropositive and seronegative African-American men) found no significant main effects for serostatus or cocaine use and no interaction of HIV and cocaine use on verbal memory, differences that were attributed to confounding effects of alcohol[73].

Several studies have provided important insights into how HIV serostatus influences cognition among individuals using illicit substances[48,74–77]. Compared to HIV-uninfected drug users, HIV-infected drug users perform worse on tests of procedural learning[74], prospective memory[75], decision-making[78], and working memory[76,77], deficits consistent with the affinity of HIV for the striatum and prefrontal cortex. However, study samples were typically male, of small size (n < 100) and did not include a non-drug using comparison group[48,74–77]. A study of 43 women with a history of illicit drug use did not identify a relationship with cocaine or heroin use within the past 12 months and noted no interaction between HIV status and recent drug use on verbal memory or any cognitive domain;

however, cell sizes were small (e.g. n=9)[79]. We similarly did not find a difference between recent and former users on total learning or delayed recall.

In our full sample of HIV-infected and HIV-uninfected women there were no differences between former drug users and non-users on any neurocognitive outcome, suggesting recovery of cognitive function. In contrast, in our HIV-infected sample, former users performed worse than non-users on delayed recall. This pattern provides further evidence that drug use has a stronger negative impact on cognitive function in HIV-infected women. Recent use may have a larger negative impact than past use due to the synergistic neurotoxicity of HIV viral proteins with cocaine and heroin, with potential for recovery of cognitive function with sustained abstinence[80–82].

Other studies have looked within HIV-infected cohorts for effects of drug use on cognition, but without an HIV-uninfected control group. Our findings are consistent with other findings showing an effect of active cocaine dependence on delayed recall and visuospatial construction in HIV-infected individuals (n=64, 72% male), with recall having the largest effect size (d=.93)[83]. As in the present study, CHARTER (75% male) found no impact of lifetime history of substance use on tests of processing speed and executive function[84]. CHARTER also found that lifetime heroin dosage related to delayed memory. In comparison, we found that delayed memory related to recent use of cocaine, particularly use of crack cocaine more than once per week. Recent heroin use was associated with worse total learning in HIV-infected women. Recent stimulant use was associated with impairments in sustained attention in a sample of 40 HIV-infected individuals; but verbal memory was not examined and cocaine and methamphetamine use were combined[85].

Contrary to our hypothesis, serostatus and illicit drug use did not interact to affect inhibitory control. The scientific literature is mixed with respect to whether drug use impacts Stroop performance. A study of 159 men with at least one substance use disorder found a negative effect of HIV infection on performance during the incongruent condition of a computerized Reaction Time Stroop[48]. Other studies have failed to find a negative effect of cocaine use on Stroop performance in HIV-uninfected individuals[10,15,86] but have found effects on other executive measures such as the go/no test[15,16,87].

The use of the HVLT precludes a clear understanding of whether the interactive effects of HIV and recent drug use represent a deficit in acquisition/encoding, retention, and/or retrieval. However, the pattern of interactions provides tentative support of potential effects on acquisition and retrieval, with spared retention. Specifically, HIV serostatus interacted with recent drug use to affect acquisition (total learning and learning slope) and retrieval (impaired delayed recall but spared recognition), with no effect on retention. Interestingly, that same pattern of effects was evident in follow-up analyses examining the impact of cocaine use specifically as well as frequency of crack cocaine use. Crack cocaine was the primary drug of choice among recent users. Moreover, analyses of recent drug use in HIV-infected women alone showed deficits in acquisition (total learning and learning slope) and retrieval (impaired delayed recall but spared recognition), with no effect on retention. This pattern of interactive effects differs from the pattern of main effects associated with HIV serostatus and recent drug use, which were characterized by deficits in acquisition only. The apparent pattern of interactive effects on acquisition and retrieval suggests that HIV and cocaine might interact to influence subcortical-prefrontal circuitry. Chronic cocaine use has been associated with anatomical changes, cerebrovascular defects, and functional alterations in the prefrontal cortex[88–92]. Given the known executive component, such as encoding strategies, on episodic memory performance, deficits in subcortical-prefrontal circuitry may contribute to deficits in verbal memory[93–95]. A neuroimaging study of delayed verbal memory in HIV-infected women demonstrated alterations in hippocampal function with

decreased activation during verbal encoding and increased during verbal retrieval[96]. Importantly, the magnitude of those alterations correlated with worse delayed recall on the HVLT[96]. Together these findings suggest that cocaine and heroin use in HIV-infected women may also lead to further alterations in hippocampal function during verbal encoding.

Our study had several limitations. First, self-report data was used to determine drug use categories. If women who had recently used illicit drugs reported never using cocaine, the impact of illicit drug use on cognition may be underestimated. Second, toxicology screens were not administered in conjunction with neurocognitive testing, so it is possible that the recent users could have been under the influence of drugs or experiencing drug withdrawal. WIHS staff are trained in detecting illicit substance use and reschedule women for cognitive testing if they appear to be under the influence of illicit substances. Third, given the use of multiple illicit substances in our cohort, we could not fully disentangle the effects of different substances on cognition. We found that cocaine use (with or without heroin) predicted worse total learning, learning slope, and delayed recall, and heroin use (with or without cocaine) predicted worse total learning and learning slope among HIV-infected women. Fourth, only two neurocognitive tests were administered, so we could not evaluate effects across a broader spectrum of cognitive domains. Fifth, although effect sizes are 0.11 or lower, the effect sizes for the interaction between serostatus and drug use are equal to or exceed the effect sizes associated with HIV serostatus alone or drug use alone. Lastly, the cross-sectional design of this study precludes the possibility of examining causality. We presume that illicit drug use leads to poor memory performance but it is possible that learning and memory deficits preceded drug use for at least some women. The last two limitations are being now addressed with the collection of longitudinal cognitive data in the WIHS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study Funding: Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC, Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590) and by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (UO1-HD-32632). The study is co- funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). V. Grauzas' effort on this project was supported by the National Institute on Drug Abuse (1F31DA028573). L. Rubin's effort was supported by grant number K12HD055892 from the National Institute of Child Health and Human Development (NICHD), and the National Institutes of Health Office of Research on Women's Health (ORWH). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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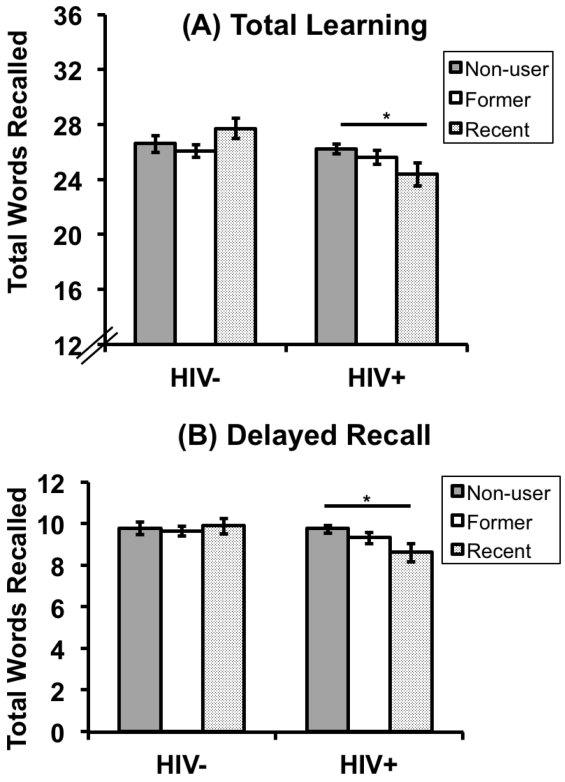

Figure 1.

Results from adjusted analysis examining the effect of serostatus, crack, cocaine, and/or heroin use, and their interaction on the HVLT total learning and delayed free recall.

Note. *p<0.01.There was a significant interaction between crack, cocaine, and/or heroin use (specifically current versus non-users) and serostatus on total learning (p<0.01) and delayed recall (p<0.01). Among HIV-infected women, recent illicit drug users performed worse than non-users on total learning (p=0.002) and delayed recall (p<0.001). All models are adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody.

Table 1

Demographic Characteristics as a Function of Serostatus and Crack, Cocaine, and/or Heroin Use.

	Groups					
	Infected (n=952)			Uninfected (n=443)		
Background Characteristics (%)	**Recent (n=91)**	**Former (n=463)**	**Non-users (n=398)**	**Recent (n=49)**	**Former (n=188)**	**Non-users (n=206)**
Age(M, SD)[D,S,DxS]	46.8 (7.7)	46.9 (6.9)	40.6 (9.7)	42.8 (8.0)	44.4 (8.9)	34.4 (9.1)
WRAT-R[D]	88.7 (17.4)	90.6 (17.2)	94.8 (18.3)	89.7 (15.5)	89.8 (17.9)	95.4 (16.5)
Years of Education[D]	11.5 (2.8)	11.9 (3.1)	13.1 (2.9)	12.2 (3.0)	12.0 (2.7)	13.2 (2.8)
Race/Ethnicity[S]						
African American, non-Hispanic	70%	64%	64%	61%	58%	63%
White, non-Hispanic	10%	16%	16%	12%	11%	8%
Hispanic	14%	18%	15%	21%	28%	24%
Other	6%	2%	5%	6%	3%	5%
Hepatitis C virus antibody[S,D]	56%	45%	6%	29%	28%	4%
Recent						
Depressive Symptoms, CES-D ≥16[D]	54%	35%	28%	50%	34%	19%
Antidepressant medication use[S,D]	20%	18%	9%	10%	11%	1%
Hazardous alcohol use[±S, D]	21%	5%	3%	35%	9%	6%
Crack cocaine use	78%	0%	0%	65%	0%	0%
Powder cocaine use[S]	24%	0%	0%	45%	0%	0%
Heroin use	29%	0%	0%	33%	0%	0%
Crack, cocaine, and/or heroin use prior to entry into WIHS	92%	98%	0%	92%	94%	0%
Proportion of WIHS visits where crack, cocaine, and/or heroin use was yes[S,D,DxS]	53%	7%	0%	52%	19%	0%
Smoking[S,D]						
Never	4%	10%	56%	0%	9%	50%
Former	85%	50%	19%	84%	60%	32%
Recent	11%	39%	25%	16%	31%	18%
Marijuana Use[S,D]						
Never	7%	9%	53%	2%	7%	40%
Former	51%	76%	38%	39%	70%	43%
Recent	43%	15%	9%	59%	23%	17%
Disease						
CD4 nadir (cells/mm3)[D]	208 (163)	230 (172)	254 (175)			
CD4 Count (cells/mm3)[D]						
> 500	29%	44%	51%	-	-	-

	Groups					
	Infected (n=952)			Uninfected (n=443)		
Background Characteristics (%)	**Recent (n=91)**	**Former (n=463)**	**Non-users (n=398)**	**Recent (n=49)**	**Former (n=188)**	**Non-users (n=206)**
≥ 200 and < 500	44%	43%	39%			
<200	27%	13%	10%			
Viral Load (HIV RNA, cp/ml)[D]						
Undetectable	27%	56%	57%	-	-	-
< 10,000	44%	30%	29%			
≥ 10,000	29%	14%	14%			
Medication Use[D]						
No cART	50%	33%	32%	-	-	-
cART <95% compliance	25%	15%	16%	-	-	-
cART ≥95% compliance	25%	52%	52%	-	-	-
ART duration (years)(M, SD)[ǂD]	8.1 (3.4)	9.6 (2.7)	8.6 (3.2)	-	-	-

Note.

"Recent" refers to within 6 months of the most recent WIHS visit. "Former" refers to any previous use, but not in the past 6 months. cART = combination antiretroviral therapy; ART = antiretroviral therapy.

[D] Main effect of drug use significant at p<.05;

[S] Main effect of serostatus significant at p<.05,

[DxS] Drug use × Serostatus interaction significant at p<.05;

[^] Hazardous alcohol use reflects >7 drinks per week or more than 4 drinks in one sitting.

[ǂ] Reflects the mean for 859 HIV-infected women (90%) who started ART prior to data collection (WIHS visit 25).

Table 2

Raw Neuropsychological Test Score Means and Statistical Comparisons by Serostatus and Crack, Cocaine, and/or Heroin Use.

Tests	n	Group					
		Infected (n=952)			Uninfected (n=443)		
		Recent (n=91) M (SD)	Former (n=463) M (SD)	Non-users (n=398) M (SD)	Recent (n=49) M (SD)	Former (n=188) M (SD)	Non-users (n=206) M (SD)
HVLT							
Trial 1	1395	5.23 (1.84)	5.47 (1.66)	5.83 (1.67)	6.12 (1.45)	5.59 (1.69)	5.95 (1.69)
Total learning	1395	19.46 (5.26)	21.17 (5.22)	22.44 (4.82)	23.47 (4.34)	21.92 (4.85)	23.26 (4.75)
Learning slope	1395	1.31 (0.34)	1.45 (0.35)	1.52 (0.31)	1.59 (0.26)	1.50 (0.29)	1.58 (0.30)
Delayed recall	1395	6.26 (2.40)	7.265 (2.60)	8.03 (2.46)	8.02 (2.18)	7.76 (2.45)	8.34 (2.34)
Percent retention	1395	81.13 (29.71)	83.73 (25.76)	88.40 (21.13)	85.36 (19.84)	87.11 (23.40)	88.36 (19.77)
Recognition	1390	9.59 (2.29)	10.08 (2.01)	10.24 (1.99)	10.29 (2.28)	10.49 (1.75)	10.75 (1.50)
Stroop Test							
Trials 1&2[a]	1313	67.79 (26.02)	63.83 (15.57)	60.71 (13.53)	61.49 (14.32)	61.91 (13.88)	58.46 (10.65)
Trial 3[a]	1247	140.34 (42.60)	132.35 (36.21)	126.09 (33.82)	126.37 (26.87)	125.50 (32.63)	120.37 (26.55)

Note. HVLT = Hopkins Verbal Learning Test.

[a]Unadjusted means are displayed, but log-transformed scores were used in the statistical comparisons.

Table 3

Results from Adjusted Analysis Examining the Effect of Serostatus, Crack, Cocaine, and/or Heroin use, and their Interaction on Cognitive Function.

	Multivariable Linear Regression Models							
	Model 1: No interactions in model					Model 2: Interactions included in model		
	Serostatus	Drug use						
	HIV+ vs. HIV−	Recent vs. Non-users	Former vs. Non-users	Recent vs. Former	Adjusted R^2	Recent vs. non-users × Status	Former vs. non-users × Status	Adjusted R^2
Tests	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**		**B (SE)**	**B (SE)**	
HVLT								
Trial 1	−.07 (.06)	−.04 (.10)	−.09 (.07)	.05 (.09)	.16	−.43 (.18) *	−.01 (.11)	.17
Total learning	−.14 (.05) **	−.16 (.09)	−.11 (.06)	−.05 (.09)	.25	−.58 (.17) **	.01 (.11)	.26
Learning slope	−.16 (.05) **	−.20 (.10) *	−.10 (.07)	−.10 (.09)	.19	−.60 (.18) ***	−.01 (.11)	.20
Delayed recall	−.11 (.05) *	−.27 (.10) **	−.12 (.07)	−.15 (.09)	.22	−.50 (.17) **	−.11 (.11)	.23
Percent retention	−.02 (.06)	−.15 (.11)	−.05 (.07)	−.09 (.10)	.03	-	-	-
Recognition	−.16 (.06) **	−.24 (.11) *	−.04 (.07)	−.20 (.09) *	.15	-	-	-
Stroop Test								
Trials 1&2 [a]	−.05 (.05)	−.04 (.10)	.02 (.07)	−.07 (.09)	.25	-	-	-
Trial 3 [a]	−.05 (.06)	.04 (.11)	.06 (.07)	−.02 (.10)	.21	-	-	-

Note.

B = Parameter estimates for each factor modeled individually. SE = standard error. HVLT = Hopkins Verbal Learning Test.

All models are adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody.

* p<0.05;

** p<0.01;

*** p<0.001.

[a] For Stroop, we also controlled for the number of times a woman was exposed to the test (range 1–3 times).

Table 4

Results from Adjusted Analysis Examining the Effect of Crack, Cocaine, and/or Heroin use in HIV-infected Women on Cognitive Function.

	Hopkins Verbal Learning Test (HVLT)			
	Trial 1	**Total learning**	**Learning Slope**	**Delayed Recall**
Models	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**
Adjusted for only non-HIV specific factors [a]				
Recent vs. non-users	−.16 (.13)	−.32 (.12)*	−.45 (.15)**	−.43 (.12)***
Former vs. non-users	−.10 (.08)	−.13 (.08)	−.14 (.10)	−.19 (.08)*
Recent vs. Former	−.05 (.11)	−.19 (.11)	−.31 (.13)*	−.24 (.11)*
Adjusted R^2	**.17**	**.27**	**.20**	**.25**
Adjusted for non-HIV specific factors and CD4, viral load, medication use, and duration on ART [b]				
Recent vs. non-users	−.14 (.16)	−.29 (.12)*	−.42 (.15)**	−.44 (.13)***
Former vs. non-users	−.10 (.08)	−.12 (.08)	−.12 (.10)	−.17 (.08)*
Recent vs. Former	−.04 (.11)	−.17 (.11)	−.30 (.13)*	−.27 (.11)*
Adjusted R^2	**.17**	**.27**	**.21**	**.25**

Note.

B = Parameter estimates for each factor modeled individually. SE = standard error.

*p<0.05;

**p<0.01.

[a]Adjusted for age, education, race/ethnicity, WRAT-R, site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, and Hepatitis C virus antibody

[b]Adjusted for site, depressive symptoms, self-reported use of antidepressant medication, marijuana use, smoking, hazardous alcohol use, self-reported dementia, Hepatitis C virus antibody, recent cd4 count and viral load, cd4 nadir, medication use, and duration on ART.