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An investigation of menopausal stage and symptoms on cognition in HIV-infected women

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Abstract

Objective: We evaluated the separate and interactive associations of menopausal stage, menopausal symptoms, and HIV infection on cognition. We hypothesized that HIV-infected, perimenopausal women would show the greatest cognitive difficulties and that menopausal symptoms would be inversely associated with cognition.

Methods: This cross-sectional study included 708 HIV-infected and 278 HIV-uninfected, pre-, peri-, or postmenopausal women (64% African-American; median age 44 years) from the Women's Interagency HIV Study. Participants completed tests of verbal learning and memory,

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attention/processing speed, and executive function. We administered a menopausal symptom questionnaire that assessed anxiety, vasomotor, and sleep symptoms and obtained measures of depressive symptoms.

Results: In multivariable regression analyses controlling for relevant covariates, HIV infection, but not menopausal stage, was associated with worse performance on all cognitive measures (p's<0.05). Depressive symptoms were associated with lower cognitive performance on measures of verbal learning and memory, attention, and executive function (p's<0.05); anxiety symptoms were associated with lower performance on measures of verbal learning and memory (p's<0.05). Vasomotor symptoms were associated with worse attention (p<0.05). HIV and anxiety symptoms interacted to influence verbal learning (p's<0.05); elevated anxiety was associated with worse verbal learning in HIV-infected women only.

Conclusion: Vasomotor, depressive, and anxiety symptoms, but not menopausal stage, were associated with worse cognitive performance in both HIV-infected and uninfected women, although elevated anxiety symptoms were associated with verbal learning deficits more in HIV-infected women. Since cognitive problems can interfere with everyday functioning including treatment adherence, it may be important to screen and treat anxiety in HIV-infected women.

Keywords

HIV; Verbal Learning; Menopause; Mood; Anxiety; African American

INTRODUCTION

Approximately 52% of persons living with HIV/AIDS in the United States are aged 40-54 years[1]; for women, this coincides with the menopausal transition. Despite a growing literature on normative changes in cognition, depression, and anxiety associated with the menopausal transition, little is known about menopause in HIV-infected women, particularly with regard to cognitive function. Previous cross-sectional studies indicate that compared to HIV-uninfected women, HIV-infected women report more menopausal symptoms including vasomotor, sleep disturbances, and psychological symptoms[2-5] and may have an earlier age at menopause[3, 4, 6, 7]. In the United States, smoking, low socioeconomic status, and drug use are relatively common among women with HIV; these are all factors associated with depression, anxiety, and vasomotor symptoms[8, 9]. No study has yet focused on the effects of menopausal stage and menopausal symptoms on cognition in HIV-infected women. Determining how reproductive aging might impact cognitive function in HIV is important because: 1) women comprise the majority of HIV-infected individuals globally[10]; 2) with HIV therapies, HIV-infected individuals now survive to middle and older age; 3) menopausal stage and symptoms impact cognition in healthy women[11]; 4) cognitive impairment is associated with specific functional deficits (e.g., non-adherence to treatment regimen) in HIV-infected individuals[12]; and 5) menopause-related cognitive issues might require new therapeutic approaches to HIV care.

Findings from large-scale longitudinal cohort studies in healthy women suggest that menopause-associated cognitive deficits are modest, limited to the perimenopausal stage, and rebound to normal in postmenopause. Specifically, perimenopausal women demonstrate

greater cognitive impairment over time compared to premenopausal women[11, 13, 14]. For example in the Study of Women's Health Across the Nation (SWAN), the largest ongoing multisite, community-based cohort study in the United States (*n*'s=1903-2362), perimenopausal but not postmenopausal, women demonstrated greater impairment in processing speed and verbal memory than premenopausal women[11, 14]. Cross-sectional studies have also been conducted, but have yielded disparate results possibly due to differences in menopausal staging criteria and differences in cognitive test batteries.

Two general mechanisms have been postulated to contribute to cognitive changes in the menopausal transition. First, cognitive performance may reflect alterations in the function of brain structures and circuits due to changes in sex steroid hormones. Both animal and human studies indicate that the hippocampus and prefrontal cortex, brain regions necessary for cognitive abilities such as verbal learning and memory, are influenced by estrogen[15-17]. Secondly, cognitive changes may be due to the indirect effects of menopausal symptoms including sleep disturbances, mood, anxiety, and/or vasomotor symptoms[18, 19]. Thus, the extent of cognitive changes during perimenopause may depend on symptom severity. Conversely, data from SWAN indicated that menopausal symptoms did not account for the finding that perimenopausal women were impaired on cognitive performance compared to premenopausal women[11]. In SWAN, cognition was associated with anxiety and depression but not with sleep disturbance or vasomotor symptoms.

The purpose of this study was to examine associations between cognition, menopausal stage, and menopausal symptoms including mood, anxiety, vasomotor, and sleep disturbances in HIV-infected and uninfected women from the WIHS. Our first hypothesis was that there would be greater cognitive difficulties on measures of processing speed and verbal memory in perimenopausal women compared to premenopausal women. Our second hypothesis was that severity of menopausal symptoms would be inversely associated with cognitive performance. Specifically, consistent with SWAN[11], we predicted that depressive symptoms would be negatively associated with processing speed, whereas anxiety symptoms would be negatively associated with verbal memory. We also anticipated that sleep disturbances and vasomotor symptoms would be associated with worse overall cognitive performance, and the magnitude of these associations would be greater for HIV-infected compared to HIV-uninfected women.

METHODS

Study Population

All participants were enrolled in the WIHS, a national, multi-site study of women with and at-risk for HIV. Study methodology, standardized data collection, and training of interviewers have been previously reported[20, 21]. Briefly study visits are conducted every 6 months and include a detailed survey, brief physical exam and specimen collection. This study was approved by the IRB of all participating institutions and the WIHS Executive Committee with written informed consent provided by all participants. Analyses included WIHS participants who completed cognitive testing and survey measures of menopause and mood as part of their core assessment visits. Participants were enrolled at 6 sites (Chicago, Bronx, Brooklyn, Washington DC, San Francisco, Los Angeles) after institutional approval

at each site, approval of the WIHS Executive Committee, and written informed consent provided by all participants. Study methodology, data collection, and training of interviewers have been previously reported[20, 21].

Overall, 1901 women were assessed for some WIHS-related outcome and not necessarily for cognition during WIHS visit 25 (April 2007-April 2008). Of those women, 1329 met all of the following inclusionary criteria: a) valid and complete data on the Hopkins Verbal Learning Test-Revised (HVLT-R)(n=349 excluded); b) valid and complete data on menstrual cycle characteristics needed to stage menopause (n=254 excluded); c) valid and complete data on the SWAN menopausal symptom questionnaire (n=224 excluded); d) age 30 to 65 years (n=203 excluded); and e) valid and complete data on the Center for Epidemiologic Studies Depression Scale (CES-D)(n=22 excluded). Of the 1329 women meeting inclusion criteria (73% of the overall sample), 343 were excluded from the data analyses based on the following exclusionary criteria: a) primary language other than English (n=12); b) history of stroke/CVA (n=18); c) use of antipsychotic medication in the past 6 months (n=63); d) currently pregnant or breastfeeding (n=8); e) hysterectomy/ bilateral oophorectomy (n=164); and/or f) use of hormone therapy/oral contraceptives within the past 6 months (n=117). In the “Results” section, we compare the characteristics of the women included in the analysis (n=986) and those who were excluded (n=912).

Measures

Neuropsychological Outcome Measures

Participants completed the HVLT-R (primary outcome measure) and the Comalli Stroop test. The HVLT-R is a 12-item list-learning test used to measure verbal episodic memory[22, 23]. The HVLT-R includes three learning trials, a delayed recall trial (20-25 minute delay), and a yes/no delayed recognition trial. Outcomes include total words recalled on Trial 1 (single trial learning), total words recalled across each of three learning trials (total learning), learning slope across the three trials (average number of new words recalled across trials), number of words recalled after a 25-minute delay (delayed recall), and number of words correctly identified on a yes/no recognition test (recognition). 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[24] in which Trials 1 and 2 measure attention and processing speed; Trial 3 measures response inhibition/executive function. In Trial 1, participants name the colors of a series of squares; in Trial 2 they read a series of color names printed in black ink. In 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”)[24]. Completion times for all three trials were recorded. Outcomes included the average score on Trial 1 and 2 (r= 0.67, p<0.001) and Trial 3. All outcomes were right-skewed and therefore log-transformed. This was the first administration of the HVLT-R, the Stroop was administered previously to some participants (<1%: 0 exposures; 57%: 1 exposure; 40%: 2 exposures, 2%: 3 exposures).

Primary Predictors

Menopausal Stage—Questions pertaining to menopausal stage were administered during the interview. Responses were used to classify menopausal stage according to definitions used in the SWAN enabling us to compare our findings with those from the SWAN[25-28]. Definitions of menopausal stage were as follows: premenopausal (menses in the past 3 months with no changes in regularity); early perimenopausal (menses in the past 3 months with change in regularity); late perimenopausal (no menses within the past 3 months but some menstrual bleeding within the past 12 months); and postmenopausal (no menses within the past 12 months).

Depression and Anxiety Symptoms—Anxiety symptoms were ascertained using a questionnaire from the SWAN[11, 29-31]. Participants reported the frequency of four anxiety symptoms (irritability/grouchiness, tense/nervous, pounding/racing heart, feeling fearful for no reason) during the past two weeks on a scale from 1 (“not at all”, coded 0) to 5 (“every day”, coded 4). The anxiety score was the sum of the four symptom ratings[11, 29-32] and anxiety symptoms were categorized as elevated when scores were 7 or higher which is consistent with SWAN[11]. Items were considered elevated if the symptom was experienced on six or more days in the past two weeks. Depressive symptoms were assessed by the CES-D[33], a 20-item self-report measure of depressive symptoms over the past week. Depressive symptoms were considered elevated when they exceeded the scale’s established clinical cutoff of ≥16.

Vasomotor Symptoms and Sleep Disturbances—The frequency of three types of vasomotor symptoms (hot flashes, night sweats, cold sweats) during the previous two weeks were recorded as not at all, 1-5 days, 6-8 days, 9-13 days, or daily. Each of the three types of vasomotor symptoms were considered elevated if they occurred 6 or more days per week[11]. Overall vasomotor symptoms were categorized as elevated when women reported experiencing one or more of the three types of vasomotor symptoms as elevated. Given the high prevalence of sleep disturbances in our population[34], sleep disturbances were considered elevated if two or more of the following symptoms were reported for three or more nights per week: trouble falling asleep, waking up during the night, waking up early.

Covariates

Socio-demographic variables and risk factors for cognitive impairment were selected based on previous literature[14, 35-43] and included annual household income ≤$12,000; positive hepatitis C virus (HCV) infection (indicated by the presence of serum antibody to HCV); recent self-reported use (within 6 months) of marijuana, crack, cocaine, and/or heroin; smoking; heavy alcohol use (>7 drinks/week or ≥4 drinks in one sitting)[43]; antidepressants; past hormone therapy use (>6 months ago); and study site (of 6). Age, years of education, and race/ethnicity were covariates in a normative-based regression approach on each cognitive outcome (described below). Additional HIV-related clinical variables were combination antiretroviral therapy (cART) use (no cART therapy, cART therapy+<95% adherent, cART therapy+≥95% adherent); CD4 count <200cells/mm^3; HIV viral load >10,000cp/ml; CD4 nadir <200cells/mm^3; and duration of ART use.

Statistical analysis

Differences between HIV-infected and uninfected women in demographic characteristics were examined using independent sample t-tests for continuous variables and chi-square tests for categorical variables. A series of multivariable logistic regressions were conducted to assess and validate the influence of menopausal stage on menopausal symptoms adjusting for confounders shown to impact menopausal symptoms in prior studies including HIV status; age; race/ethnicity; education; marijuana use; crack, cocaine, and/or heroin use; smoking; heavy alcohol use; antidepressants; past hormone therapy use; HCV infection; income; and study site. There were no interactions between HIV status and menopausal stage.

In the absence of published cognitive tests norms for low-income minority women, we followed Heaton and colleagues[44] and prior work within the WIHS[38] by using a regression approach to estimate expected levels of function for the total sample based on scores of the comparison group (HIV-women) by regressing age, years of education, race/ethnicity, and the Wide Range Achievement Test–Reading (WRAT-R), a measure of reading ability[45] and proxy for educational quality[46], on each cognitive outcome. Next, the resulting unstandardized beta weights, constants, and standard errors were used to calculate predicted scores for each test that were then subtracted from each woman's actual score and transformed to more interpretable scores with means of 50 and standard deviations of 10 that had the advantage of being the same across all cognitive outcomes. In the total sample, we used multivariable regression analyses to examine the separate and interactive effects of our three independent variables of interest: HIV-infection group, menopausal stage, and menopausal symptoms (depression, anxiety, sleep, vasomotor). The model adjusted for confounders shown to affect cognition in prior studies including marijuana use; crack, cocaine, and/or heroin use; smoking; alcohol use; antidepressants; past hormone therapy use; HCV infection; income; and study site. We also adjusted for number of prior exposures to the Stroop, although they were not significantly associated with Stroop performance (p's>0.14). Interactions were retained in the final model (p's<0.10); only HIV status x anxiety was significant at p<0.05. For significant interactions, the final model was re-run for HIV-infected women and included additional HIV specific covariates (recent CD4 count and viral load, CD4 nadir, cART use and adherence). All p values are two sided at a p<0.05 level of significance; p's>0.05 and <0.10were considered trends. Analyses were performed using SAS (version 9.2, SAS Institute Inc, Cary, NC).

RESULTS

Sample Characteristics

Recent illicit substance use was reported significantly more frequently by HIV-uninfected than HIV-infected women, as was recent smoking, heavy alcohol use, and use of antidepressant medications (Table 1). HIV-infected women were older, less likely to report being Hispanic, and more likely to be HCV positive. All other differences were not significant. At the time of the cognitive assessment, SWAN staging indicated that 56% (n=550) of participants were premenopausal, 16% (n=158) early perimenopausal, 5% (n=46) late perimenopausal, and 24% (n=232) postmenopausal. As expected based on age

distribution, a larger proportion of HIV-uninfected women were premenopausal, whereas there was a larger percentage of HIV-infected postmenopausal women (*p's*<0.05). The prevalence of sleep disturbances, depressive, anxiety, and vasomotor symptoms ranged between 9% and 35% (Table 2). There was a trend for HIV-infected women to report more sleep disturbances compared to HIV-uninfected women (*p*=0.07).

Compared with the 912 women excluded from this analysis (see "Study Population"), the 986 women included in the analysis were more likely to be older (44.1 vs. 41.2 years, *p*<0.001); to be more educated (12.4 vs. 11.4 years, *p*<0.001);to be black non-Hispanic (64% vs. 51%, *p*<0.001); to smoke (47% vs. 40%, *p*=0.002); to recently use crack, cocaine, and/or heroin (12% vs. 8%, *p*=0.002); to be HCV positive (29% vs. 24%, *p*=0.01); and were less likely to have an annual income ≤12,000 (48% vs 53%, *p*=0.02).

Validation of Mood, Sleep, and Anxiety as Menopausal Symptoms

In multivariable analyses, early perimenopausal women were more likely to report depressive and anxiety symptoms compared to premenopausal women (*p*'s<0.05; Table 4). Postmenopausal women were more likely to report sleep disturbances and depressive symptoms compared to premenopausal women (*p*'s<0.05).

Hopkins Verbal Learning Test-Revised (HVLT-R)

Table 2 shows the unadjusted neuropsychological test scores as a function of HIV status and Table 3 shows the unadjusted scores as a function of menopausal stage. In multivariable analyses, HIV-infected women demonstrated significantly worse function than HIV-uninfected women on all outcomes (*p*'s<0.05; ~0.20 standard deviation (SD) units different; Table 5). The cognitive differences observed between HIV-infected and HIV-uninfected women were equivalent to differences observed in midlife women who were 5 years different in age[23]. Menopausal stage was not significantly associated with any of the cognitive outcomes on the HVLT-R (*p*'s>0.06; see Table 5 for trends). Depressive and anxiety symptoms were inversely associated with cognition (*p*'s<0.05). Specifically, women with elevated depressive symptoms performed worse than women without elevated depressive symptoms on all but one HVLT-R outcome —learning slope (~0.20 SD units different). Women with elevated anxiety symptoms also performed worse than women without elevated anxiety symptoms on all but one HVLT-R outcome—Trial 1 learning (~0.30 SD units different). Notably, anxiety symptoms interacted with HIV status to significantly influence Trial 1, learning slope, and total learning (Table 5/Figure 1). Among the HIV-infected women, those with elevated anxiety symptoms performed significantly worse than those without elevated anxiety symptoms on verbal learning outcomes (*p*'s<0.05). The cognitive differences observed between HIV-infected with and without elevated anxiety symptoms were equivalent to differences observed in midlife women who were 20 years different in age[23]. In contrast, among the HIV-uninfected women, there were no significant differences in cognitive performance between individuals with and without elevated anxiety symptoms. There were no significant interactions between menopausal stage or additional menopausal symptoms (depressive, vasomotor, sleep symptoms) and HIV status on any cognitive outcome.

In multivariable analyses limited to HIV-infected women, elevated anxiety symptoms were significantly associated with Trial 1, (B=−3.37, SE=1.38, p=0.01), total learning (B=−4.40, SE=1.42, p=0.002), and learning slope (B=−4.31, SE=1.57, p=0.006) even after controlling for HIV morbidity indicators. Analyses focused on individual anxiety items indicated that symptoms of feeling tense/nervousness were significantly associated with worse performance on total learning (B=−3.50, SE=1.22, p=0.004); trend on learning slope (B=−2.70, SE=1.41, p=0.05). Greater feelings of fearfulness for no reason were also significantly associated with learning slope (B=-4.50, SE=1.87, p=0.01).

Stroop Test

HIV-infection was associated with diminished performance on Stroop Trials 1 & 2 and Trial 3 (Table 5). Menopausal stage was not significantly associated with any Stroop outcome (p's>0.08; see Table 5 for trends). Depressive, but not anxiety, symptoms were associated with worse performance on each Stroop outcome (p's<0.05; ~0.20 SD units different). Elevated vasomotor symptoms were associated with slower performance only on Stroop Trials 1 & 2 (p<0.05; 0.25 SD unit different; see Table 5 for trend on Stroop Trial 3). This association was driven by hot flashes (B=−2.75, SE=1.25, p=0.03) and not night sweats. There were no significant interactions between menopausal stage or menopausal symptoms and HIV status on the Stroop.

DISCUSSION

This study examined associations between menopausal stage and menopausal symptoms and performance of measures of verbal memory, processing speed, and response inhibition in HIV-infected and uninfected women. We found no support for our first hypothesis that menopausal stage would be associated with worse performance in the cognitive domains of processing speed and verbal memory. We did, however, find support for our second hypothesis that menopausal symptoms would be related to worse cognitive performance. Specifically, after adjusting for HIV status, depression, anxiety, and vasomotor symptoms were each independently associated with worse cognitive performance. We also found some support for our third hypothesis that menopausal symptoms would differentially be associated with cognitive performance in HIV-infected women. Specifically, there was an interaction between HIV status and anxiety such that the association between elevated anxiety and worse verbal learning was only evident in HIV-infected women and remained significant even after adjusting for HIV-related clinical indicators.

In contrast to previous studies, we found no evidence that cognitive performance, particularly in the domains of processing speed and verbal memory, was lowered in the perimenopausal stage. At least two general factors might have contributed to the lack of an association between cognition and menopausal stage in the present study. First is the cross-sectional design of this investigation. Cross-sectional analyses reveal no significant association between menopausal stage and cognitive performance in the SWAN[47], whereas longitudinal analyses show significant associations[11]. Second, socio-demographic and mental health factors might have obscured an effect of menopausal stage in WIHS participants. The majority of women in WIHS are HIV-infected African Americans with

annual incomes below ≤12,000. Therefore, compared to SWAN, the WIHS cohort is less healthy, more economically disadvantaged, lower educated, and more often drug abusing. Similarly, the prevalence of elevated depressive symptoms was 35% in WIHS versus 23% in SWAN. It may be that the negative effect of socio-demographic factors and depressive symptoms on cognition obscured any smaller effect of menopausal stage.

Menopausal symptoms – vasomotor symptoms, depressive symptoms, and anxiety – were associated with lowered cognitive function across HIV-infected and uninfected women in the WIHS. Vasomotor symptoms were related to slower processing speed on simple processing tasks requiring reading words aloud and identifying the color of blocks. Simple processing speed predicts driving behaviors and medication adherence in HIV-infected individuals, though the magnitude of the association of vasomotor symptoms on simple processing speed was small in this study. Thus, the clinical significance of the effect is likely to be minimal given that an average t-score is 50 and the average t-scores for women with elevated vasomotor symptoms was 47.7 and for those reporting no elevated vasomotor symptoms was 50[12, 48]. Simple processing speed was not measured in the SWAN, but both SWAN and WIHS found no association between performance on a more complex measure of processing speed – the Digit Symbol Modalities Test – and vasomotor symptoms. Depressive symptoms in WIHS participants were associated with decreased verbal memory, simple processing speed, and executive function. SWAN similarly found that depressive symptoms were negatively associated with processing speed[11]; however, other studies have not reported an influence of depressive symptoms on cognition[49]. Consistent with SWAN, anxiety symptoms in WIHS participants were associated with lower verbal learning[11].

Of all of the symptoms investigated in this study, only anxiety was found to have a stronger association with lowered cognitive performance in HIV-infected compared to HIV-uninfected women, and this association was evident on measures of verbal learning. Notably, of all symptoms measured, anxiety had the largest association with cognitive performance across participants, and the magnitude of the association between anxiety and cognition was generally larger than the magnitude of the association between HIV and cognition. The test of the interaction between HIV status and anxiety symptoms (high versus low) on verbal memory revealed a significant association only among HIV-infected women, suggesting that the effects in the combined group were driven largely by the HIV-infected women. It is not the case that the association between elevated anxiety and cognition is due to a high prevalence of anxiety symptoms in the WIHS. In fact, elevated anxiety symptoms were less prevalent in WIHS (9%) compared to SWAN (~30%). Although the low rates of anxiety in the WIHS may be surprising, studies of HIV-infected individuals show that African-Americans are at a lower risk for anxiety and other psychiatric disorders compared to other ethnicities[50-52] perhaps due to reporting biases. One possible mechanism linking anxiety to decreased verbal memory in HIV-infected women is a female vulnerability to the negative effects of stress hormones on verbal memory. For example, in a community-based study of older adults, 12-hour free cortisol excretion was associated with poorer delayed verbal recall in women, but not in men[53]. Moreover, increases in cortisol over a 2.5-year period were associated with declines in memory in women, but not in men[53]. In studies involving laboratory-induced stress, stress-induced increases in cortisol levels correlated negatively with memory in women, but not in men[54].

Our study has several limitations. First, the cross-sectional design limited our ability to detect an effect of menopausal stage on cognition. The cross-sectional design also precludes the possibility of examining causality. We presume that anxiety and depressive symptoms lead to decreased cognitive functioning; however, it is possible that cognitive difficulties may precede anxiety and depressive symptoms for at least some women. A longitudinal investigation is underway in the WIHS. Second, elevated anxiety symptoms were measured using a widely-used menopause symptom inventory rather than a validated anxiety inventory. However, we used the same anxiety measure and cutoff as the SWAN allowing for comparisons with the largest investigation of menopause stage and symptoms on cognition[11]. Other studies also show that the anxiety scale used in this study is highly correlated with the Generalized Anxiety Disorder-7 scale (Spearman r = 0.71)[32]. Third, although depressive and anxiety symptoms increased in the menopausal transition in this study, these symptoms are not menopause-specific. Nevertheless, these symptoms are elevated in the perimenopause and relate to cognition in general[11]. Depressive symptoms have been shown to double the odds of cognitive impairment in a WIHS substudy[40]. Fourth, only two cognitive tests were administered so we could not evaluate associations across a broader spectrum of cognitive domains. Notably, however, we did include a test of verbal memory, a cognitive domain previously shown to be particularly sensitive to menopausal symptoms and stage[55].

CONCLUSION

At a general level, the present results extend findings from cohort studies of more economically-advantaged women to a sample of economically-disadvantaged women with a high prevalence of HIV. Our findings suggest that elevated depression, anxiety, and vasomotor symptoms are associated with lower cognitive function in HIV-infected and HIV-uninfected women. All three symptoms are elevated in the perimenopause. Anxiety was differentially associated with worse verbal learning in HIV-infected women only. Our results suggest that screening and treating anxiety symptoms in HIV-infected women might confer benefits to cognitive functions that are negatively impacted by HIV. Longitudinal studies of the menopausal transition and menopause-associated affective symptoms are underway using a more comprehensive cognitive test battery.

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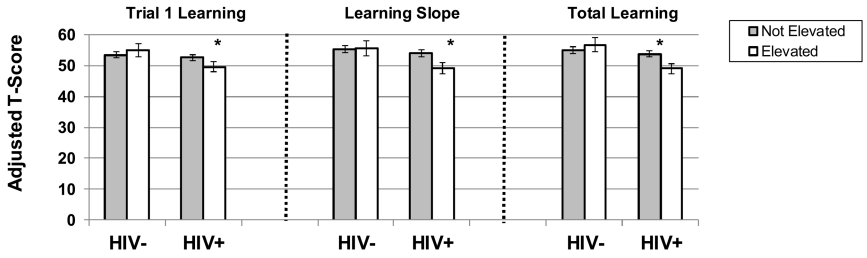

Figure 1.

Note. ***p<0.001; *p<0.05. HVLT-R=Hopkins Verbal Learning Test. There was a significant interaction between anxiety symptoms and HIV status on trial 1 learning (p<.05), learning slope (p<0.05), and total learning (p<0.01). Among the HIV-infected, individuals with elevated anxiety symptoms performed worse than those without elevated anxiety symptoms on trial 1 learning (p<0.05), learning slope (p=0.01), and total learning (p<0.001). All models are adjusted for site, depressive symptoms, vasomotor symptoms, sleep disturbances, crack, cocaine, and/or heroin use, marijuana use, smoking, heavy alcohol use, antidepressant medication use, past hormone therapy use, HCV status, and income.

Table 1

Background Characteristics of Study Sample by HIV Status and for Total Group.

Characteristics, n (%)	HIV Status		
	Infected n = 708	Uninfected n = 278	*p*-value
Background Characteristics			
Age, *M (SD)*	44.56 (7.35)	42.80 (7.51)	<0.001
WRAT-R, *M (SD)*	91.60 (17.89)	91.08 (17.20)	0.68
Years of Education, *M (SD)*	12.39 (2.94)	12.53 (2.96)	0.50
Race/Ethnicity			0.04
Black, non-Hispanic	455 (64)	173 (62)	
White, non-Hispanic	108 (15)	29 (11)	
Hispanic	118 (17)	65 (23)	
Other	27 (4)	11 (4)	
Site			<0.001
Bronx	120 (17)	68 (24)	
Brooklyn	179 (25)	47 (17)	
Washington DC	121 (17)	44 (16)	
Los Angeles	75 (11)	47 (17)	
San Francisco	100 (14)	45 (16)	
Chicago	113 (16)	27 (10)	
Hepatitis C virus antibody (HCV)	225 (32)	61 (22)	0.002
Recent[1]			
Annual household income, ≤$12,000	343 (48)	131 (47)	0.71
Crack, cocaine, and/or heroin use	81 (11)	42 (15)	0.08
Marijuana use	113 (16)	67 (24)	0.005
Smoking	309 (44)	153 (55)	0.02
Heavy alcohol use[†]	106 (15)	74 (26)	<0.001
Antidepressant medication use	112 (16)	28 (10)	0.02
Past[2]			
Crack, cocaine, and/or heroin use	351 (50)	139 (50)	0.44
Marijuana use	413 (58)	152 (55)	0.47
Smoking	207 (29)	61 (22)	0.55
Hormone therapy use	95 (13)	25 (9)	0.06
HIV-related Clinical Characteristics			
CD4 nadir (cells/μl), *M (SD)*	233 (178)	-	-
CD4 Count (cells/μl)		-	-
> 500	307 (43)		
≥ 200 and < 500	298 (42)		
< 200	103 (15)		
Viral Load (HIV RNA (cp/ml))		-	-
Undetectable	358 (51)		

Characteristics, n (%)	HIV Status		
	Infected n = 708	Uninfected n = 278	*p*-value
< 10,000	228 (32)		
≥ 10,000	122 (17)		
Medication Use		-	-
No cART	247 (34)		
cART+ < 95% medication compliance	122 (17)		
cART+ ≥ 95% medication compliance	339 (48)		
ART duration‡ (years), *M (SD)*	9.05 (3.02)	-	-

Note.

1"Recent" refers to within 6 months of the most recent WIHS visit;

2"Past" refers to any previous use but not within the past 6 months; WRAT-R = Wide Range Achievement Test Standard Score;

†The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommended limits for women are no more than three drinks per day and no more than seven drinks per week. Heavy alcohol use refers to amounts in excess of these limits or >7 drinks per week or ≥ 4 drinks at a sitting; cART = combination antiretroviral therapy; ART = antiretroviral therapy;

‡Reflects the mean for 458 HIV-infected women (89%) who started ART before current study.

Table 2

Menopausal Stage, Reported Symptoms, and Neuropsychological Test Scores as a Function of HIV Status.

		HIV Status			
Characteristics	**n**	**Infected n = 708**	**Uninfected n = 278**	***p*-value**	**Cohen's *d***
Menopausal stage, n (%)				0.009	
Premenopausal	986	378 (54)	172 (62)		
Early Perimenopausal	986	109 (15)	49 (18)		
Late Perimenopausal	986	35 (5)	11 (4)		
Postmenopausal	986	186 (26)	46 (16)		
Prevalence of elevated menopausal symptoms, n (%)					
Depression	986	249 (35)	95 (34)	0.77	
Anxiety	986	66 (9)	25 (9)	0.87	
Sleep disturbance	986	203 (29)	64 (23)	0.07	
Vasomotor	986	127 (18)	50 (18)	0.99	
Cognitive test (mean, SD)					
HVLT-R					
Trial 1	986	5.53 (1.64)	5.74 (1.73)	0.08	0.12
Total learning	986	21.31 (5.03)	22.27 (4.89)	0.007	0.19
Learning slope	986	1.45 (0.34)	1.52 (0.29)	0.007	0.22
Delayed recall	986	7.41 (2.55)	7.85 (2.38)	0.01	0.18
Recognition	984	10.09 (1.98)	10.47 (1.84)	0.006	0.20
Stroop Test (time in seconds)					
Trials 1&2[a]	919	63.15 (16.48)	60.48 (12.84)	0.02	0.18
Trial 3[a]	866	131.14 (36.14)	124.12 (29.50)	0.01	0.21

Note. HVLT-R = Hopkins Verbal Learning Test.

[a]Unadjusted means are displayed such that higher is worse, but log-transformed scores were used in the statistical comparisons. See methods section for operational definitions of menopausal stage and elevated symptoms. Stroop Trials 1 and 2 represent the average across the 2 trials. Cohen's d effect sizes: small effect = 0.2; medium effect = 0.5; large effect = 0.8.

Table 3

Neuropsychological Test Scores as a Function of Menopausal Status.

		Menopausal Stage					Tukey Post Hoc		
Cognitive Test	**n**	**Pre (n=550) M (SD)**	**Early Peri (n=158) M (SD)**	**Late Peri (n=46) M (SD)**	**Post (n=232) M (SD)**	**Omnibus *p*-value**	**Early Peri vs. Pre Cohen's *d***	**Late Peri vs. Pre Cohen's *d***	**Post vs. Pre Cohen's *d***
HVLT-R									
Trial 1	986	5.70 (1.66)	5.54 (1.66)	5.80 (1.84)	5.33 (1.65)	0.02	ns	ns	0.22*
Total learning	986	22.02 (4.87)	21.66 (5.22)	21.78 (5.30)	20.46 (4.95)	0.001	ns	ns	0.32*
Learning slope	986	1.50 (0.31)	1.48 (0.34)	1.46 (0.33)	1.40 (0.34)	<0.001	ns	ns	0.12*
Delayed recall	986	7.71 (2.43)	7.79 (2.56)	7.00 (3.04)	7.04 (2.47)	0.001	ns	ns	0.27*
Recognition	984	10.23 (1.95)	10.26 (1.92)	9.61 (2.66)	10.19 (1.80)	0.21	-	-	-
Stroop Test‡									
Trials 1&2[a]	919	59.95 (13.18)	63.74 (15.39)	62.77 (10.55)	67.27 (20.07)	<0.001	0.27*	ns	0.44*
Trial 3[a]	866	123.81 (31.71)	129.54 (32.76)	138.46 (42.01)	140.20 (37.61)	<0.001	ns	ns	0.47*

Note.

*p<0.05.

‡Time in seconds. Pre = Premenopause. Peri = Perimenopause. Post = Postmenopause. HVLT-R = Hopkins Verbal Learning Test. ns=not significant.

[a]Unadjusted means are displayed such that higher is worse, but log-transformed scores were used in the statistical comparisons. See methods section for operational definitions of menopausal stage and elevated symptoms. Cohen's d effect sizes: small effect = 0.2; medium effect = 0.5; large effect = 0.8. Stroop Trials 1 and 2 represent the average across the 2 trials.

Table 4

Results from Adjusted Analyses on the Impact of Menopausal Status on Elevated Menopausal Symptoms.

	Menopausal Stage		
Symptoms	**Early Peri (vs Pre) OR[a] (95% CI[b])**	**Late Peri (vs Pre) OR (95%CI)**	**Post (vs Pre) OR (95%CI)**
Depression	1.84 (1.23-2.74)**	0.97 (0.48-1.96)	1.61 (1.01-2.57)*
Anxiety	1.94 (1.01-3.71)*	1.27 (0.45-3.57)	1.60 (0.75-3.42)
Sleep disturbance	1.24 (0.80-1.91)	0.81 (0.38-1.74)	1.83 (1.13-2.97)*

Note.

***p<0.001;

** p<0.01;

* p < 0.05.

[a] OR=odds ratio.

[b] CI=confidence interval. Pre = Premenopause. Peri = Perimenopause. Post = Postmenopause. See methods section for operational definitions of menopausal stage and elevated symptoms. All analyses adjusted for: HIV status; age; race/ethnicity; education; marijuana use; crack, cocaine, and/or heroin use; smoking; heavy alcohol use; antidepressants; past hormone therapy use; HCV infection; income; and study site.

Table 5

Multivariable Linear Regression Analyses Predicting the Effects of HIV Status, Menopausal Stage, and Elevated Symptoms on Cognitive Test Performance.

	Cognitive Test						
	HVLT-R					Stroop Test	
	Trial 1	Total learning	Learning Slope	Delayed Recall	Recognition	Trials 1&2	Trial 3
	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)	B (SE)
Main Effects							
HIV Status							
HIV+ (vs. HIV−)	−1.56 (0.73)*	−2.31 (0.75)**	−2.18 (0.81)**	−1.74 (0.75)*	−1.97 (0.81)*	−1.98 (0.82)*	−1.82 (0.85)*
Menopausal Stage (vs. pre)							
Early Peri	−0.46 (0.88)	−0.06 (0.91)	−0.05 (0.98)	1.11 (0.92)	0.49 (1.02)	−1.70 (1.03)⁄	0.53 (1.07)
Late Peri	1.51 (1.52)	1.14 (1.56)	0.16 (1.68)	−1.69 (1.58)	−3.00 (1.74)‡	0.46 (1.74)	−0.44 (1.81)
Post	−0.56 (0.86)	−1.17 (0.88)	−1.72 (0.95)†	−0.59 (0.89)	0.97 (0.99)	−0.83 (1.00)	1.49 (1.05)
Elevated Symptoms							
Depression	−1.88 (0.74)*	−1.66 (0.75)*	−0.93 (0.81)	−1.79 (0.76)*	−1.97 (0.84)*	−2.19 (0.86)**	−2.47 (0.89)**
Anxiety	−1.74 (1.19)	−2.75 (1.22)*	−3.30 (1.32)**	−3.49 (1.24)**	−3.22 (1.36)*	−0.33 (1.40)	−2.42 (1.48)
Sleep Disturbance	0.27 (0.76)	0.11 (0.78)	0.33 (0.84)	1.21 (0.79)	1.07 (0.84)	−0.47 (0.89)	1.16 (0.92)
Vasomotor	−0.29 (0.86)	−0.23 (0.88)	0.17 (0.95)	0.85 (0.89)	0.91 (0.99)	−2.49 (1.01)*	−1.88 (1.06)‡
Interaction							
HIV Status x Anxiety	−4.72 (2.36)*	−6.48 (2.42)***	−5.22 (2.62)*	−4.02 (2.45)⁄			
HIV−: Persistent (vs. not)	1.54 (2.09)	1.76 (2.14)	0.34 (2.32)	−0.68 (2.17)			
HIV+: Persistent (vs. not)	−3.18 (1.35)*	−4.72 (1.39)***	−4.88 (1.50)**	−4.70 (1.40)***			

Note.

** p<0.01.

* p<0.05,

† p=0.07;

‡ p=0.08;

⁄ p=0.09. B = parameter estimates for each factor and SE = standard error from the multivariable linear regression analyses. HVLT-R = Hopkins Verbal Learning Test. Pre = Premenopause. Peri = Perimenopause. Post = Postmenopause. All models are adjusted for site, crack, cocaine, and/or heroin use, marijuana use, smoking, heavy alcohol use, antidepressant medication use, income, HCV status, and past hormone therapy use. For Stroop we also controlled for the number of times a woman was exposed to the test (range 0-3 times). See methods section for operational definitions of menopausal stage and elevated symptoms. Stroop Trials 1 and 2 represent the average across the 2 trials.