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Elevated depressive symptoms are a stronger predictor of executive dysfunction in HIV-infected women than men

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Abstract

Background: HIV-infected (HIV+) women appear to be more vulnerable to neurocognitive impairment than HIV+ men, perhaps in part due to mental health factors. We assessed the association between elevated depressive symptoms and NCI among HIV+ and HIV-uninfected (HIV-) women and men.

Setting: Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS).

Methods: 858 HIV+ (429 women; 429 men) and 562 HIV- (281 women; 281 men) completed the Center for Epidemiologic Studies Depression (CES-D; 16 cutoff) scale and measures of psychomotor speed/attention, executive, and motor function over multiple visits (or time points). WIHS and MACS participants were matched according to HIV status, age, race/ethnicity, and education. Generalized linear mixed models were used to examine interactions between biological sex, HIV-serostatus, and depression on impairment (T-scores<40) after covariate adjustment.

Results: Despite a higher frequency of depression among males, the association between depression and executive function differed by sex and HIV-serostatus. HIV+ women with depression had 5 times the odds of impairment on a measure of executive control and inhibition

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versus HIV- depressed women, and 3 times the odds of impairment on that measure versus HIV+ depressed men. Regardless of group status, depression was associated with greater impairment on processing speed, executive (mental flexibility), and motor function (P's<0.05).

Conclusions: Depression contributes to NCI across a broad range of cognitive domains in HIV+ and HIV- individuals, but HIV+ depressed women show greater vulnerabilities in executive function. Treating depression may help to improve cognition in patients with HIV infection.

Introduction

HIV-infected (HIV+) women may be more vulnerable to developing neurocognitive impairment (NCI) than HIV+ men[1,2]. Among HIV studies showing male/female NCI differences, some demonstrate greater impairments in females than males overall, whereas others demonstrate male/female differences in the pattern of NCI[1,3–8]. For example, in a large study (n=1420) combining the two longest-running U.S. multisite, longitudinal studies of HIV progression in the U.S., the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS), HIV was associated with alterations (via continuous T-scores) in the pattern of sex differences in executive function (mental flexibility), attention, psychomotor speed, and motor function[1]. Performance was consistently worse among HIV+ women versus HIV+ men even after adjusting for HIV-related characteristics. Greater impairments among HIV+ females is also evident in the context substance-dependence[8–10]. This female-specific vulnerability may be due to biological influences (e.g., hormonal), sociodemographics, mental health factors (e.g., trauma) or disorders (e.g., major depressive disorder-MDD)[2].

Here we examine whether associations between MDD and NCI differs between men and women as MDD is the most common neuropsychiatric complication among people with HIV (PWH)[11,12] and is more prevalent than in the general U.S. population[11–14]. The only nationally representative study among PWH reported an 18.5% 12-month prevalence of MDD[11,12] which is two- to three-times higher than the general U.S. population. Prevalence estimates in U.S. cohort studies are similarly high[14,15]. In the WIHS, current MDD via diagnostic interview was 20% and lifetime MDD was 32% versus 10% and 23% nationally[13]. In cognitive studies, about 30% of WIHS women report elevated depressive symptoms,[16–18] an estimate about 10% higher than other large-scale cohort studies of healthy midlife women[19–21]. Additionally, HIV+ women often have higher rates of depression[22] and more depressive symptoms than HIV+ men[7,23–25]. It cannot be assumed; however, that the magnitude of the male/female depression difference will be similar among PWH, due to greater depression severity in sexual minority men versus heterosexual men[26].

The presence and/or severity of depression may contribute to the greater cognitive vulnerability in HIV+ women versus HIV+ men. Among HIV-uninfected (HIV-) individuals, depression severity is commonly associated with poorer episodic memory, executive function, psychomotor speed, and attention[27]. Across cross-sectional studies in PWH, the domains most reliably associated with depression are psychomotor speed (50% of studies), executive function (45%), learning and memory (42%), and motor function (44%)[28] followed by attention and working memory (38%). Longitudinal WIHS studies demonstrate

associations between depression and psychomotor speed (Symbol Digit Modalities Test [SDMT], Stroop word-reading), executive function (Trail Making Test-[TMT-B], Stroop color-word [interference]), memory (Hopkins Verbal Learning Test), motor function (Grooved Pegboard [GP]), and fluency[29]. In the MACS, depression is also associated with psychomotor speed (SDMT) and executive function (TMT-B minus TMT-A); however, other domains have not been examined[30]. It remains unknown whether these associations differ by sex.

We examine combined and independent associations between three factors known to influence NCI—HIV, biological sex (sex), and depression. Associations were analyzed in the same large sample (n=1420; 50% female) of MACS men and WIHS women where we examined HIV by sex interactions on NCI[1]. Biological mechanisms that may contribute to sex differences in the depression-NCI relationship include, among others, sex differences in neuroinflammation[31–33], dopamine transmission[34], genetics[35] and the HPA axis[36,37]. Given our prior work demonstrating an HIV by sex interaction on NCI (attention/psychomotor speed, motor function)[1] and given that depression influences many of those domains (attention, executive function)[29,30], we hypothesized that depression would predict greater HIV-related NCI in females versus men, particularly in attention, executive function, and motor function.

Methods

Participants

Longitudinal data collected through September 2016 were extracted from WIHS and MACS in August 2017. In brief, the WIHS was established in August 1994 at 6 clinical sites (Brooklyn, New York; Bronx/Manhattan, New York; Washington, DC; Los Angeles, California; San Francisco, California; Chicago, Illinois). The MACS was established in 1984 at 4 clinical sites (Baltimore, Maryland; Pittsburgh, Pennsylvania; Los Angeles, California; Chicago, Illinois). MACS data were limited to participants recruited during the most recent enrollment period (2001–2003), as those participants more similar to WIHS participants in race and socioeconomic status[38].

For the present analysis, there were 3,766 WIHS participants (2,791 HIV+; 975 HIV-) who enrolled in the study during 1994–1996 (n=2,623) or 2001–2002 (n=1,143). Based on these numbers, we drew identical numbers of HIV+ and HIV- men from 1735 individuals enrolled in the MACS[1]. To be included, all participants completed four tests administered by both cohorts—TMT-A and TMT-B, SDMT, Comalli Stroop color-word test[39], and GP. We analyzed data collected by WIHS from May 2009-September 2016 and by MACS from October 2001-May 2014 of which 97% of all selected visits had complete data. We also limited the tests to the first five years of testing as men had more tests administered versus women, and the restricted time span limited the differences between cohorts in neuropsychological test exposure.

Participants were excluded based on history of toxoplasmosis, CNS lymphoma, cryptococcal meningitis (MACS) or cryptococcal infection (WIHS), progressive multifocal leukoencephalopathy, AIDS-defining or other dementia, transient ischemic attack/stroke, use

of antiseizure/antipsychotic drugs, head injury with loss of consciousness (>1 hour for MACS; >30 minutes for WIHS), and preference for Spanish as first language.

Neuropsychological outcomes

Neuropsychological tests included measures of: psychomotor speed/attention (TMT-A, Stroop color-naming and word-reading, SDMT); executive function (TMT-B, Stroop color-word [interference]); and motor function (GP). Outcomes for all tests was time to completion except SDMT which was total correct. All timed outcomes were log transformed to normalize distributions and reverse scored so higher values represented better performance. Demographically-adjusted (age, sex, black race) T-scores were derived for each outcome based on the entire HIV- population with impairment defined as T-score < 40.

Depression

The primary predictor was probable depression as assessed by the Center for Epidemiologic Studies Depression (CES-D) scale[40], a 20-item self-report measure of depressive symptoms. We utilized the standard 16 cutoff[41].

Covariates

A number of covariates were included based on prior WIHS and MACS studies[1,29,30] including age (also included as covariate as it is a strong predictor of NP performance and ensures it is not a residual confounder), race/ethnicity, income, education (only collected categorically in the MACS), sexual orientation, heavy alcohol use classified using NIAAA standards (≥15 drinks/week for men; ≥8 drinks/week for women), recreational drug use since the previous visit (cannabis, cocaine/crack), cigarette smoking, HIV RNA and CD4 T-cell counts, antiretroviral therapy, nadir pre-HAART CD4+ T-cell count, ever having clinical AIDS diagnosis, and count of neuropsychological test exposures.

Statistical analyses

Generalized linear mixed models (GLMM) were conducted (SAS, version 9.4; PROC GLIMMIX) to assess combined and separate associations of depression (time-varying), biological sex (sex), and HIV-serostatus on NCI. The GLMM include a random-subject effect which accounts for within-person correlation of the repeated assessments (i.e., neuropsychological test performance). Primary initial predictors included depression, HIV-serostatus, sex, all two-ways, and the three-way interaction. Of particular interest was the three-way interaction. A significant three-way interaction would indicate that depression exacerbates the interactive associations between HIV-serostatus and sex on NCI. Non-signficant three-way interactions were removed from the models so that we could assess whether depression exacerbates a general: 1) female versus male difference (depression by sex interaction) and/or 2) HIV-serostatus difference (depression by HIV-serostatus interaction) on NCI. If none of the two-way interactions were significant they were removed from the models so that we could examine whether depression, irrespective of HIV-serostatus and sex, predicts NCI. All models adjusted for race (black vs. non-black), ethnicity (Hispanic vs. non-Hispanic), education (≤ high school, some college, college/post-graduate degree) and time-varying factors including age, heavy alcohol, marijuana, cocaine/

crack use (each yes/no), smoking (never, former, current), income (<$20,000 in MACS; ≤ $18,000 in WIHS), time from enrollment, and number of prior neuropsychological testing administrations (continuous with an upper limit set to 8 as few individuals had more than 8 exposures). In HIV only analyses, models also adjusted for the following time-varying factors: antiretroviral use, log10-transformed HIV RNA, current CD4 count (per 100 cell increase), CD4 nadir <200, and prior AIDS diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) are presented and predicted probabilities from models including all two- and three-way interactions are plotted for visual interpretation.

Results

Participants included 858 HIV+ (429 women) and 562 HIV- (281 women) individuals, ranging in age from 20–66 years, with 67% non-Hispanic, African American and 20% Hispanic per group. Table 1 provides socio-demographic, behavioral, and clinical characteristics stratified by sex, HIV-serostatus, and depression status. Groups differed on numerous factors (e.g., heavy alcohol, cannabis, cocaine/crack use, smoking) during visits categorized as depressed versus not depressed. Depressed individuals had lower income levels and were more likely to have increased alcohol, marijuana, and cocaine use, and more likely to be current/former smokers.

Across study duration, depression was reported by HIV+ and HIV- women on fewer visits (20% and 15%) versus HIV+ and HIV- men (36% and 38%)(P<0.001). Similarly, men were more likely to ever be depressed regardless of HIV-serostatus than women (P<0.001, Figure 1). In the MACS, 50% of HIV+ men reported ever being depressed versus 47% of HIV- men; 3% difference (P=0.37). In the WIHS, 34% of HIV+ women reported ever being depressed versus 25% of HIV- women; 9% difference (P=0.01). Among PWH, the difference between men and women ever being depressed was 16% (P<0.001). Similarly, among HIV- individuals the difference between men and women ever being depressed was 22% (P<0.001). To ensure the reversal of conventional rates of depression in men and women was not due to the higher rates of crack/cocaine in men, we re-ran the frequency of depression among those who never used crack/cocaine. In this subgroup, depression remained higher in men than women (data not shown). Among PWH, depressed individuals were more likely to have higher plasma HIV RNA but the higher rates of depression among HIV+ men versus HIV+ women remained after controlling for HIV RNA (P<0.001).

Does depression exacerbate interactive associations of HIV-serostatus and sex on NCI?

The test of the primary hypothesis—the three-way interaction between depression, HIV-serostatus, and sex—was significant on Stroop color-word [interference] (P=0.02) but no other outcome (P's>0.34; Figure 2). The HIV-serostatus by sex interaction was significant only in the context of elevated depression (P=0.03). HIV+ depressed women had a more than 3-fold greater probability of impairment on Stroop color-word [interference] versus HIV+ depressed men (OR=3.29, 95%CI 1.25–8.69, P=0.02); however, HIV- women and men with depression showed a similar proability of impairment. HIV+ women with depression also had a greater probability of impairment versus HIV- depressed women (OR=5.03, 95%CI 1.36–18.61, P=0.01) and HIV- depressed men (OR=3.14, 95%CI 1.09–

9.06, P=0.03). A sensitivity analysis was conducted among those never using crack/cocaine to ensure substance use was not driving the pattern of effects. The pattern of effects were similar in analyses limited to those who never used crack/cocaine (data not shown). A second sensitivity analysis was conducted to ensure the male/female difference among HIV+ depressed individuals was not driven by HIV-related characteristics. After additional adjustments, women remained at a higher predicted probability of impairment versus men (OR=3.93, 95%CI 1.24–12.46, P=0.02).

Irrespective of HIV-serostatus, does depression and sex interact to predict NCI?

After removing the non-significant three-way interaction from the remaining models, the two-way interaction between depression and sex was significant on GP dominant hand (P=0.007). Irrespective of HIV-serostatus, depression was associated with higher odds of impairment among men (OR=2.73, 95%CI 1.64–4.54, P<0.001) but not women (OR=0.96, 95%CI 0.54–1.71, P=0.90).

Irrespective of sex, does depression and HIV-serostatus interact to predict NCI?

There were no significant HIV-serostatus by depression interactions on NCI.

Irrespective of sex and HIV-serostatus, does depression predict NCI?

Across all participants, depression was associated with a higher odds of impairment on SDMT (OR=1.54, 95%CI 1.04–2.28, P=0.03), Stroop color-naming (OR=1.66, 95%CI 1.11–2.48, P=0.01), TMT-B (OR=1.82, 95%CI 1.30–2.55, P=0.0005), and GP non-dominant hand (OR=1.76, 95%CI 1.22–2.55, P=0.002). Depression was not associated with TMT-A or Stroop word-reading (P's>0.16).

Discussion

These data add to the growing body of evidence that in the era of effective antiretrovirals, factors other than HIV are at least as important, and often more important determinants of NCI, than HIV serostatus among HIV+ men and women. In 1420 HIV+ and HIV- adults, we demonstrated that HIV+ women with elevated depressive symptoms are at 5-times the odds of impaired performance on Stroop color-word [interference] versus both depressed HIV+ and HIV- men and HIV- women. That trial is a measure of executive function requiring inhibition of a prepotent interfering behavioral response. This effect could not be attributed to differences in HIV-related clinical factors. There were no differences between HIV+ women and men with and without depression in tests of psychomotor speed/attention and motor skills.

The domain that was most vulnerable among HIV+ depressed women was a measure of executive function that relies on select areas of the cognitive control network (CCN), in particular the rostral anterior cingulate cortex (ACC) and the dorsolateral PFC (DLPFC) which are invoked during inhibitory tasks such as Stroop interference[42,43]. Neurobiological features of depression contributing to cognition include glucose metabolism in the PFC[44] and functional alterations of the ACC, during cognitive task performance[45–48]. An event-related functional magnetic resonance imaging study involving an in-scanner version of the

Stroop revealed hyperactivity in the rostral ACC and left dorsolateral PFC in patients with unipolar depression versus healthy participants, and those alterations in brain function correlated with Stroop infererence[49]. This pattern of regional hyperactivity can be induced by lowering serotonin levels with tryptophan depletion[50], and can be reversed with the antidepressant escitalopram[51]. Although causality cannot be determined in the present study, other work suggests that decreased levels of serotonin alter ACC and PFC function to influence performance on inhibitory tasks. These functional brain alterations partially overlap with the HIV-associated alterations in brain circuitry[52]. Multiple neurobiological features of HIV infection, including chronic neuroinflammation, reduction of trophic factors, and alterations in dopamine and other neurotransmitters can contribute to depression in HIV[53]. Mechanistically, neuroinflammation and impaired neurogenesis are key features of depression and HIV and are contributors to NCI[53–55]. Similarly, hypothalamic-pituitary-adrenal (HPA) axis function alterations can contribute to NCI in depression and HIV[56,57].

In our previous publication using this same sample, we demonstrated that although HIV+ women show cognitive vulnerabilities in several domains versus HIV+ men (e.g., TMT-A, TMT-B, SDMT, and GP), they show no vulnerability in Stroop. The current data show that it is only in the context of depression where they show greater vulnerability on Stroop color-word [interference], a task reliant on the CCN compared to depressed HIV+ men as well as depressed HIV- men and women. Biological explanations for this selective vulnerability may include females greater sensitivity to the negative effects of inflammation-induced depressed mood[31,32]. Inducing inflammation via endotoxin exposure (*e.g.*, IL-6, TNF-α) leads to increased depressed mood[31,32] and neural activity in the ACC in healthy females but not males[32]. Converging evidence from preclinical models also demonstrate that the adult female brain has more microglia with an activated phenotype versus the male brain[33]. Microglia play a critical role in maintaining homeostasis in the presence of a number of factors including infection or injury. Sexual dimorphisms in genetic variations in the dopaminergic system may also contribute to a female-specific vulnerability in cognitive control. The catechol-O-methyltransferase gene and the dopamine receptor D2 gene interact with sex on cognitive control behavioral measures[34]. Transcriptional signatures in brain regions in the CCN in MDD also differ by sex[35]. Lastly, sex differences in the HPA[36,37], and/or immune alterations[58–61] may contribute to these findings. For example, cortisol levels negatively relate to executive function in HIV- women but not men[62]. The tighter coupling of depression and HIV in women compared to men suggests a tighter coupling of these neural manifestations of HIV and depression in women than men, and consequently might explain the greater cognitive effect of these comorbidities in women than men.

There are also non-biological explanations for the decreased executive function among HIV + depressed women versus all other groups. Depressed HIV+ men could have had greater access and availability to mental health services (e.g., therapy, antidepressants, other psychiatric medications) versus depressed HIV+ women, and this treatment may have minimized the cognitive sequelae of depression in men. That explanation does not, however, account for the specificity of findings to Stroop color-word [interference] but not other tests. Second, depression among female HIV positive individuals may have the greatest adverse effects on cognitively demanding tasks regardless of domain. Of the tasks administered, Stroop color-word [interference] was the most difficult. Third, we used the same CES-D cut-

off for men and women though some argue in favor of a lower cut-off for men than women[63]. Whether a different pattern of findings would emerge with sex-specific cutoffs is unknown. Lastly, performance on Stroop color-word [interference] and possibly other outcomes may have been influenced by unusual patterns within the HIV- depressed men who showed lower performance than HIV+ depressed men in several tests (TMT-A, SDMT, GP). Even if these patterns did not lead to emergence of any other three-way HIV-serostatus X Sex X Depression interactions, they may have led to the lack of two-way HIV-serostatus X Depression interactions. HIV- depressed men were more likely than HIV+ depressed men to be heavy alcohol users, smoke, and use cannabis and cocaine/crack, but those factors did not account for the three-way interaction on Stroop color-word [interference]. HIV+ depressed men may also have had better engagement in care due to their HIV status versus HIV- depressed men.

We also found that elevated depression regardless of HIV status or biological sex was negatively associated with psychomotor speed/attention, executive function, and motor skills. Findings are consistent with studies in HIV- individuals demonstrating that primary NCI among depressed individuals are in psychomotor speed/attention (TMT-A, Stroop, Digit Symbol Substitution) and executive function (TMT-B)[64]; sex differences were not examined. In HIV, similar patterns are seen among mixed samples of HIV+ and HIV- individuals[16,30,65].

Overall, MACS men compared to WIHS women were more likely to report ever being depressed. Furthermore, HIV serostatus was associated with higher depression rates in women while in men depression rates did not differ by HIV-serostatus. This finding seems unexpected because the depression rate is twice as high in women than men[66]. Similarly in the few studies of sex differences in depression among PWH, HIV+ women have higher depression rates[22] and more severe depressive symptoms versus HIV+ men[23–25]. In most studies, the sample sizes were smaller (*e.g.,* range 60 to 267 women[23,24]) than in the present study so this study might provide more reliable estimates. However, men in the present study, had more opportunities to develop depression because they were followed for a longer period of time (HIV+ 1117 visits; HIV- 729 visits to become depressed) versus women (HIV +1071 visits; HIV- 698 visits to become depressed). When restricting our analysis to crack/cocaine non-users, men still had higher levels of depression versus women despite having fewer visits than women. A likely explanation for the higher frequency of depression in MACS men includes primarily sexual minority men whereas WIHS includes primarily heterosexual women. In both sexes, the prevalence of depression is higher among sexual minorities versus heterosexuals[67–70]. The high prevalence of depression in sexual minorities is associated with stress exposure resulting from stigma[71] and lack of social support[72]. In the MACS, men are predominately Black and all are gay or bisexual. Notably, even though depression was more frequent among HIV+ men, the increased frequency among HIV+ men did not increase NCI on any domain versus either depressed HIV+ women or HIV- men. Moreover, accounting for HIV RNA which was higher in depressed HIV+ men than nondepressed HIV+ men did not not account for the pattern of NCI correlates.

This study has a number of limitations including the limited cognitive battery (e.g., no common memory assessment between cohorts), unmeasured confounders (mental health

services, antidepressants, other specific non-antiretroviral treatments with adverse neuropsychiatric effects, early/late life trauma), and use of a self-report measure of depression. The preferred diagnostic interview to assess depression was unavailable in both cohorts. Additionally, we did not assess other diagnostic comorbidities commonly co-occuring with depression including anxiety (not assessed in MACS) and substance use disorders (although we statistically controlled). Finally, while there were differences in the data collection time frame in the two cohorts, it is unlikely that these differences led to a bias towards or against visits completed while a participant was depressed as depressive symptom trajectories are relatively stable in individuals[30]. Despite limitations, few studies have sufficient statistical power to examine whether the depression-NCI associations differ by HIV-serostatus and sex.

To our knowledge, this is the largest study in PWH examining sex and depressive symptoms as contributors to NCI in PWH. The importance of this topic is evident in the high frequency of depression and in the finding that overall depression is associated with impairment in psychomotor speed, executive function, and motor function. Focusing on sex differences is important because for women, the association between depression and executive function was particularly strong, increasing the odds of impairment 5-fold. This pattern was the case even though depression rates were higher in men regardless of HIV-serostatus. Findings indicate that depression is an important prevention and treatment target and that improved access to psychiatric and psychological services may help minimize the influence of this comorbidity on NCI.

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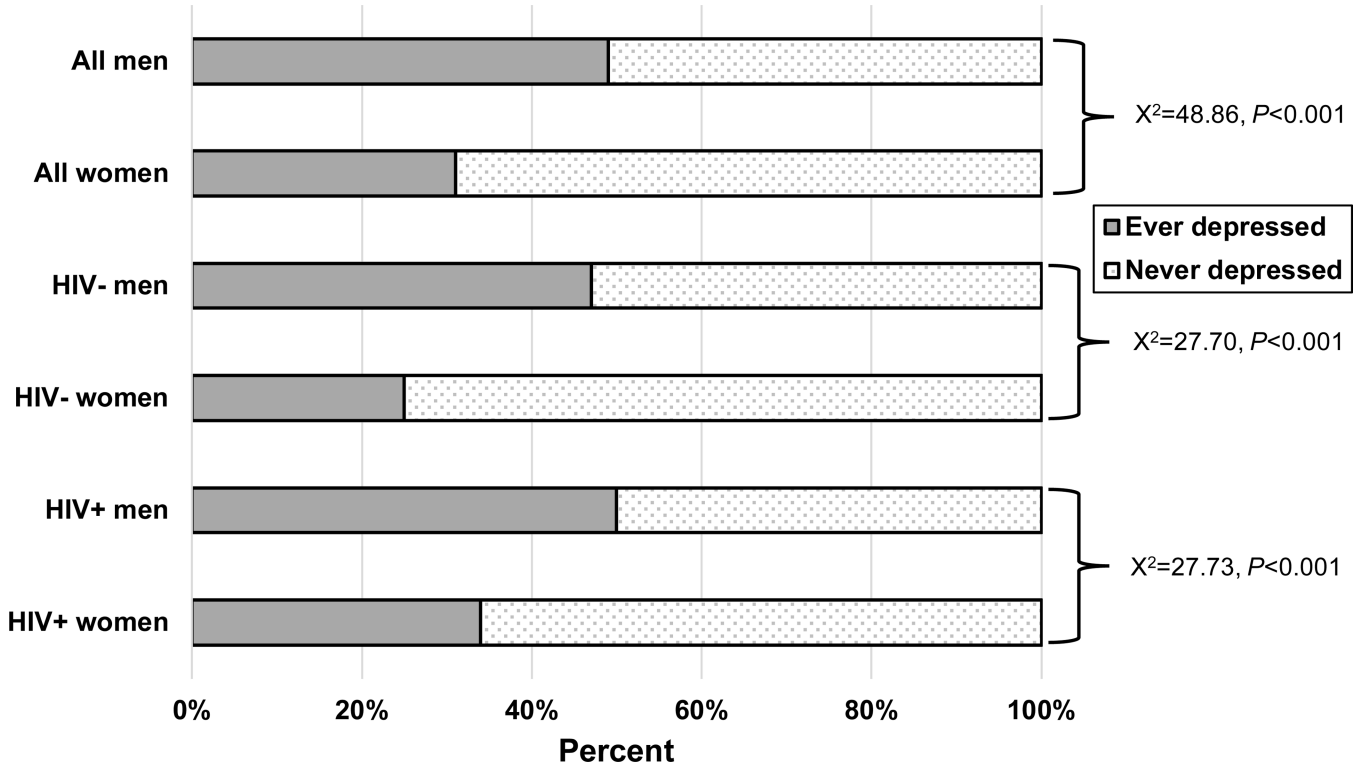
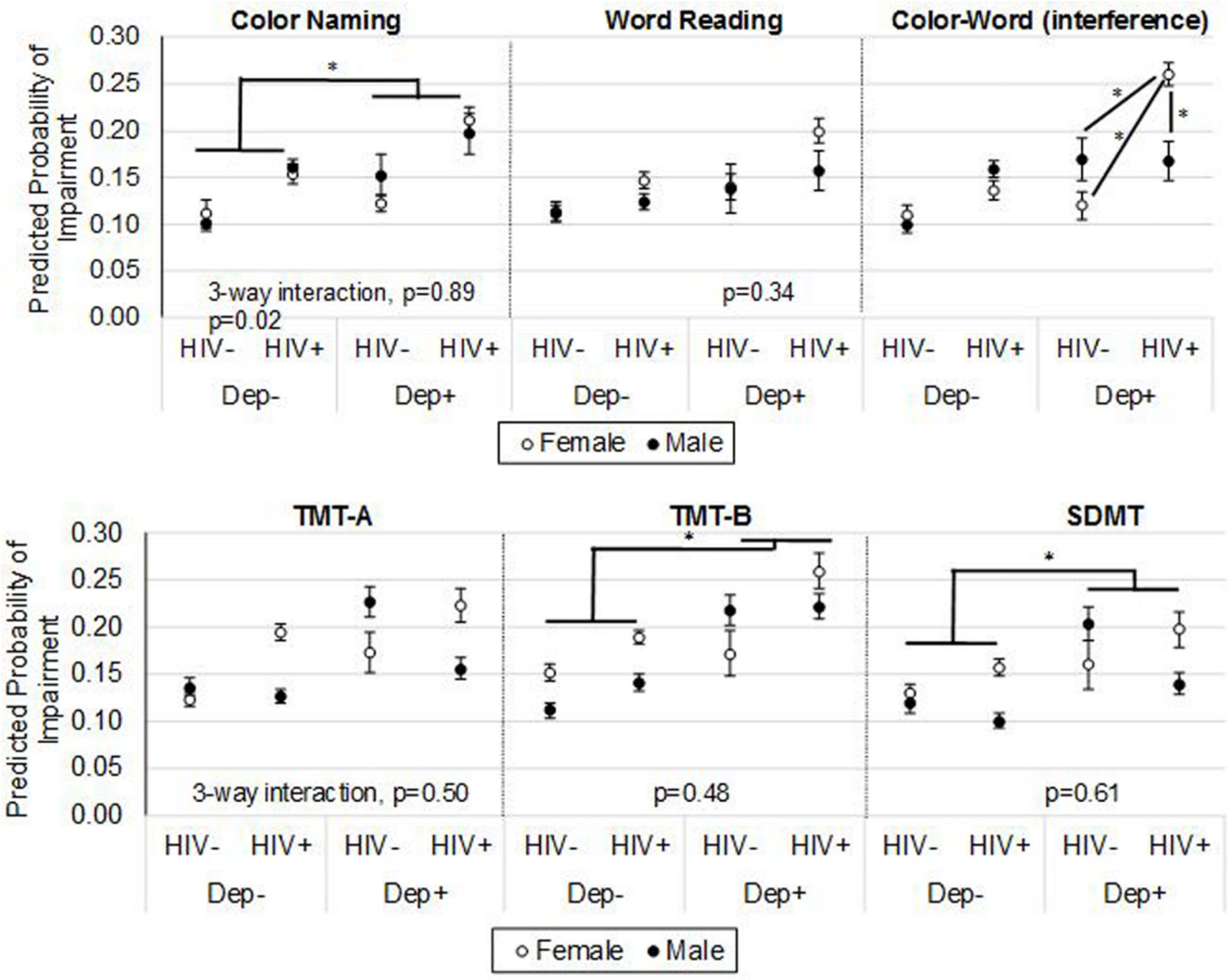


Figure 1.

Percent of visits that HIV+ and HIV- men and women were ever versus never depressed (Center for Epidemiological Studies Depression Scale, CES-D ≥16).

Note. 50% of HIV+ men reported ever being depressed versus 47% of HIV- men; 3% difference (X^2=0.77, *P*=0.37). 34% of HIV+ women reported ever being depressed versus 25% of HIV- women; 9% difference (X^2=5.95, *P*=0.01).



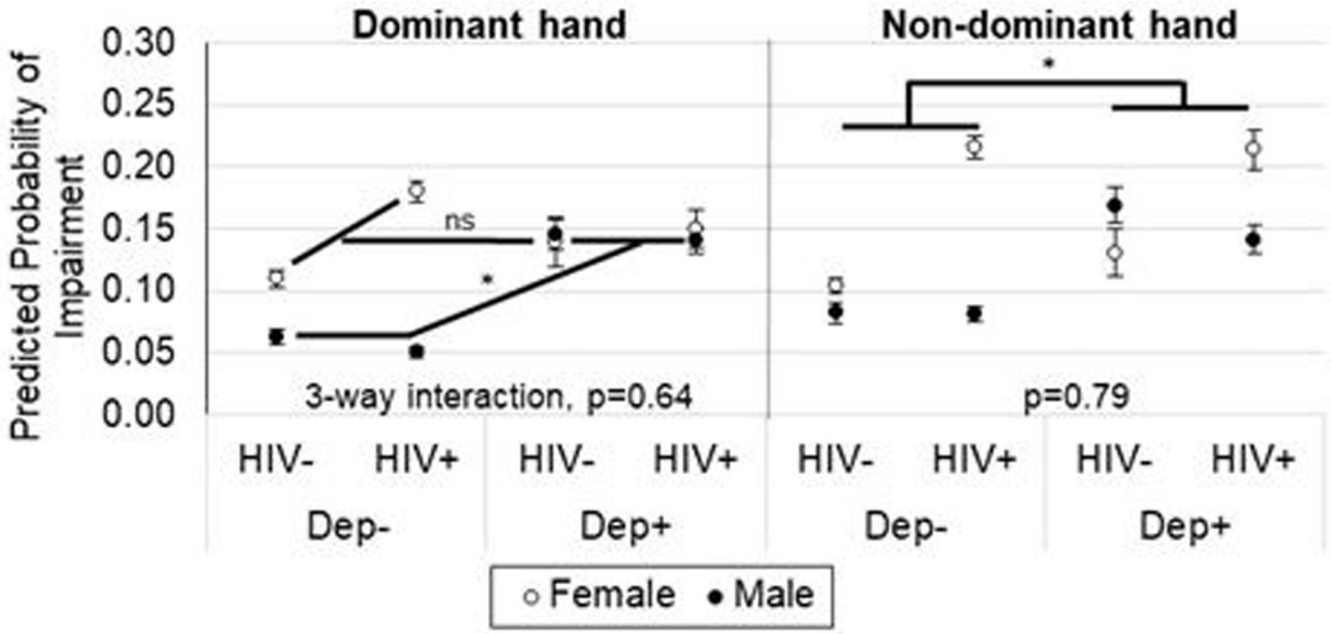


Figure 2.

Predicted probability of cognitive impairment (SE) for HIV+ and HIV- as a function of biological sex and depressive symptomatology.

(A) Stroop Test

(B) Trail Making Test (TMT) and Symbol Digit Modalities Test (SDMT)

(C) Grooved Pegboard

Note. Dep=depression. (–) is Center for Epidemiological Studies-Depression (CES=D) Scale <16; (+) is CES-D ≥16. **P*<0.05

Table 1.

Socio-demographic, behavioral, and clinical characteristics as a function of HIV status and sex across all visits.

	HIV+ (n=858)				HIV- (n=562)				
	Women (n=429)		Men (n=429)		Women (n=281)		Men (n=281)		
Characteristics	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**p-value**
Number of visits	858 (80%)	213 (20%)	714 (64%)	403 (36%)	590 (85%)	108 (15%)	448 (62%)	274 (38%)	
(# of unique participants)[‡]	388 (90%)	147 (34%)	324 (76%)	215 (50%)	266 (95%)	72 (26%)	216 (77%)	143 (51%)	
Socio-demographic									
Age, mean (SD)	45 (7.6)	43.7 (7.8)	43.0 (7.2)	41.4 (7.5)	42.0 (9.0)	42.9 (8.6)	41.8 (8.8)	41.1 (8.2)	<0.001
Black	75%	62%	68%	70%	74%	67%	71%	67%	0.002
Hispanic	17%	18%	22%	24%	21%	20%	15%	24%	0.002
Education									
High School or less	54%	57%	47%	60%	54%	65%	49%	57%	<0.001
Some college	34%	33%	38%	32%	37%	32%	39%	34%	
4 year degree or more	12%	10%	14%	7%	9%	3%	11%	8%	
Income[‖]	51%	58%	63%	85%	49%	58%	62%	79%	<0.001
CES-D, mean (SD)	4.7 (4.0)	25.4 (8.7)	6.4 (4.7)	26.1 (8.1)	4.6 (4.0)	27.1 (9.6)	7.2 (4.5)	25.5 (8.0)	<.0001
Sexual orientation									<0.001
Heterosexual/straight	92%	85%	-	-	81%	77%	-	-	
Lesbian/gay, bisexual, other	8%	15%	100%	100%	19%	23%	100%	100%	
Behavioral factors									
Heavy alcohol use[†]	9%	13%	4%	8%	19%	28%	6%	13%	<0.001
Cannabis use	12%	30%	28%	31%	24%	32%	31%	43%	<0.001
Cocaine/crack use	2%	2%	23%	32%	5%	7%	23%	43%	<0.001
Smoking									<0.001
Never	38%	25%	22%	18%	30%	22%	15%	14%	
Former	33%	38%	26%	25%	30%	26%	25%	22%	
Current	29%	37%	52%	57%	40%	52%	60%	64%	
HIV-related clinical factors									
CD4n, mean (SD)	578 (326)	562 (308)	528 (284)	486 (279)					<0.001

	HIV+ (n=858)				HIV- (n=562)				
	Women (n=429)		Men (n=429)		Women (n=281)		Men (n=281)		
Characteristics	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**Dep−**	**Dep+**	**p-value**
Therapy since last visit									<0.001
None	16%	14%	27%	34.1%					
Monotherapy	0.6%	0.7%	0.3%	0.2%					
Combination	0.4%		5%	4%					
HAART	83%	85%	68%	62%					
HIV RNA, Mean (SD)	9784 (44889)	12398 (47300)	37634 (232737)	34395 (139393)					<0.001
HIV RNA, Median (25, 75%ile)	48 (<20,290)	48 (<20,1449)	40 (40, 6980)	822 (40,17912)					<0.001
CD4 pre-HAART nadir, mean (SD)	264 (197)	267 (190)	419 (257)	400 (262)					<0.001
Count of test exposures mean (SD)									
TMT, SDMT	3.9 (1.6)	3.5 (1.7)	3.5 (3.5)	3.3 (3.6)	3.7 (1.6)	3.9 (1.6)	3.1 (3.2)	3.2 (3.2)	<0.001
Grooved Pegboard	0.9 (0.8)	0.9 (0.9)	1.3 (1.3)	1.2 (1.3)	0.9 (0.8)	0.9 (0.8)	1.2 (1.2)	1.2 (1.3)	<0.001
Stroop Test	2.2 (1.1)	2.1 (1.2)	1.3 (1.3)	1.2 (1.2)	2.2 (1.2)	2.1 (1.2)	1.2 (1.2)	1.2 (1.3)	<0.001

Dep-, Center for Epidemiologic Studies Depression Scale (CES-D) <16; Dep+, CES-D ≥16

‖MACS <$20000 average annual household income; WIHS; WIHS <=$18000 average annual household income

†Men and women's heavy alcohol use was classified according to the CDC definition. For men, 15 ≥ drinks per week and for women, 8 ≥ drinks/week was classified as heavy alcohol use. http://www.cdc.gov/alcohol/faqs.htm#heavyDrinking (page accessed 1/13/2016, Page last reviewed: November 16, 2015, Content source: Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention)

HAART=Highly active antiretroviral therapy

TMT=Trail Making Test; SDMT=Symbol Digit Modalities Test

ǂThere are 858 HIV+ (429 women, 429 men) participants and 562 HIV- (281 women, 281 men) participants in this study. The men and women were eligible to contribute visits as both depressed (Dep+) and not depressed (Dep-).