Differences in Cognitive Function Between Women and Men With HIV

Pauline M. Maki, PhD,† Leah H. Rubin, PhD,*‡§ Gayle Springer, MLA,§ Eric C. Seaberg, PhD,§ Ned Sacktor, MD,‡ Eric N. Miller, PhD,‖ Victor Valcour, MD, PhD,¶ Mary A. Young, MD,# James T. Becker, PhD,** and Eileen M. Martin, PhD,†† for the Neuropsychology Working Groups of the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study*

Background: Women may be more vulnerable to HIV-related cognitive dysfunction compared with men because of sociodemographic, lifestyle, mental health, and biological factors. However, studies to date have yielded inconsistent findings on the existence, magnitude, and pattern of sex differences. We examined these issues using longitudinal data from 2 large, prospective, multisite, observational studies of US women and men with and without HIV.

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

Methods: HIV-infected (HIV+) and uninfected (HIV−) participants in the Women's Interagency HIV Study and Multicenter AIDS Cohort Study completed tests of psychomotor speed, executive function, and fine motor skills. Groups were matched on HIV status, sex, age, education, and black race. Generalized linear mixed models were used to examine

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From the Departments of *Psychiatry; and †Psychology, University of Illinois at Chicago College of Medicine, Chicago, IL; ‡Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; §Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; ‖Departments of Psychiatry & Behavioral Sciences, University of California Los Angeles, Los Angeles, CA; ¶Department of Neurology, University of California San Francisco, San Francisco, CA; #Department of Medicine, Georgetown University, Washington, DC; **Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA; and ††Department of Psychiatry, Rush University Medical Center, Chicago, IL.

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Correspondence to: Pauline M. Maki, PhD, Neuropsychiatric Institute MC/913, 912 S. Wood Street, Chicago, IL 60612 (e-mail: pmaki1@uic.edu).

group differences on continuous and categorical demographically corrected T-scores. Results were adjusted for other confounding factors.

Results: The sample (n = 1420) included 710 women (429 HIV+) and 710 men (429 HIV+) (67% non-Hispanic black; 53% high school or less). For continuous T-scores, sex by HIV serostatus interactions were observed on the Trail Making Test parts A & B, Grooved Pegboard, and Symbol Digit Modalities Test. For these tests, HIV+ women scored lower than HIV+ men, with no sex differences in HIV− individuals. In analyses of categorical scores, particularly the Trail Making Test part A and Grooved Pegboard nondominant, HIV+ women also had a higher odds of impairment compared with HIV+ men. Sex differences were constant over time.

Conclusions: Although sex differences are generally understudied, HIV+ women vs men show cognitive disadvantages. Elucidating the mechanisms underlying these differences is critical for tailoring cognitive interventions.

Key Words: HIV, cognition, sex difference, cognitive impairment

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Approximately 50% of HIV-infected (HIV+) individuals develop cognitive impairment.[1,2] Cognitive function in HIV+ men has been well characterized because most HIV+ individuals living in the United States and participating in cohort studies are men.[1–3] Women comprise approximately 25% of HIV cases[4] in the United States and half of global cases.[5] HIV+ women in the Women's Interagency HIV Study (WIHS)[6] show small but significant deficits in cognitive function, particularly in verbal learning and memory, and processing speed.[6,7] Few studies have directly compared cognitive function of HIV+ women and men, even though cognitive profiles of HIV+ women cannot be assumed to be the same as HIV+ men.[8] Including HIV-uninfected (HIV−) controls in such comparisons is important to determine the expected pattern of sex differences.

Women may be more vulnerable to HIV-associated cognitive impairment compared with men because of biological differences (eg, hormonal and pharmacokinetic) as well as poverty, low literacy, low education, substance abuse, poor mental health, early life stressors, trauma, and barriers to health care. Some studies suggest greater cognitive vulnerabilities in HIV+ women compared with HIV+ men,[3,9,10] whereas others suggest no difference[11] or show differences only in the pattern of impairment.[12]

We compared cognitive test performance in a matched subset of HIV+ and HIV− women from the WIHS and HIV+ and HIV− men from the Multicenter AIDS Cohort Study (MACS) who were comparable in age, education, and black race. Given previous findings,[13–15] we predicted that HIV+ women would perform worse than HIV+ men.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

Previous reports detail the WIHS and MACS recruitment, retention, and study procedures.[16–19] Both studies received institutional review board approval at each WIHS and MACS sites. All participants provided written informed consent before any research procedures.

Participants

The WIHS is a longitudinal study of the natural and treated history of HIV in women that was established in August 1994 at 6 clinical sites in Brooklyn, New York; Bronx/Manhattan, New York; Washington, DC; Los Angeles, California; San Francisco/Bay Area; and Chicago. WIHS participants in this cognitive analysis were enrolled from 1994 to 1996 (n = 2623) or 2001 to 2002 (n = 1143) for a total of 3766 (2791 HIV+ and 975 HIV− women). An identical number of HIV+ and HIV− male participants were drawn from 6972 individuals enrolled in the MACS, an ongoing longitudinal study of HIV+ and HIV− self-identified men who have sex with men. The MACS was initiated in 1984 with study sites in Los Angeles, Chicago, Baltimore, and Pittsburgh. The MACS has recruited 3 cohorts of participants.[18] From 1984 to 1985, 4954 men were enrolled, from 1987 to 1991, 668 men were enrolled, and from 2001 to 2003 another 1350 men were enrolled. Men included in this analysis were from that third enrollment, which more closely approximate the WIHS ethnic and educational composition. Men and women who completed the 4 tests that overlap in the WIHS and MACS—the Trail Making Test A and Trail Making Test B (TMTA and TMTB), Symbol Digit Modalities Test (SDMT), Stroop, and Grooved Pegboard (GP)—were eligible for inclusion in the analysis. Exclusion criteria included history of toxoplasmosis, brain lymphoma, cryptococcal meningitis (MACS) or cryptococcal infection (WIHS), progressive multifocal leukoencephalopathy, dementia, transient ischemic attack or stroke, use of antiseizure or antipsychotic drugs, loss of consciousness (>1 hour for MACS and > 30 minutes for WIHS), preference for Spanish as first language, and American Indian/Alaskan Native (WIHS only) because of lack of matching participants in the MACS.

Procedures

We examined performance on overlapping tests in the WIHS and MACS, including TMTA and TMTB (time to complete), GP (time to complete), SDMT (number of boxes correctly completed within 90 seconds), and Stroop (time to complete). All timed measures were right skewed and therefore log transformed. Similar to our previous publications,[6,20–22] demographically adjusted T-scores were created for each outcome. Impairment was examined with continuous and categorical T-scores (scoring in the impaired range, T < 40). T-scores were derived for each individual outcome adjusting for sex, age, years of education, race (African American vs not), ethnicity (Hispanic vs not), and number of previous test administrations (second, third, or later). The T-scores attenuate the expected sex differences in HIV− individuals.

In the WIHS, an abbreviated cognitive battery, including the TMTA, TMTB, and SDMT, was implemented in 2004

at core visits at the 6 original WIHS sites to 1142 HIV+ women and 511 controls. Participants completed the tests every 6 months over a 2-year period. During 2005–2006, the Stroop test was simultaneously administered to 1426 women as part of a cross-sectional WIHS study.[23] In 2009, a more comprehensive cognitive battery was administered once every 2 years to 1604 WIHS participants at the original 6 sites. That battery included 4 tests used by the MACS, including the TMTA and TMTB, SDMT, GP, and Stroop.[6] WIHS and MACS investigators worked together to maximize comparability of tests, and test administration and scoring procedures. At WIHS core visits, participants underwent physical and gynecological examinations, medical and psychosocial interviews, assessment of current medications and adherence, and a blood draw. This study used WIHS data collected from May 2009 to September 2016.

Neuropsychological testing in the MACS has been summarized.[18] From 1988 onward, the MACS semiannual clinical assessment included the TMT and SDMT. From 1988 to 2005, approximately 80% of the men also participated in a more extensive neuropsychological examination that also included the GP and Stroop Tests. In 2005, all MACS participants completed the more extensive battery at least every 2 years.[18] The MACS semiannual core visits include an interview covering physical health, medical treatments, and sexual and substance use behaviors, a physical examination, and blood draw. Cognitive batteries from October 2001 to May 2014 were included in the analysis.

Matching

Participants were matched at the first cognitive visit with valid TMTA and TMTB, SDMT, Stroop, and GP data. Participants were matched on HIV serostatus, age (±5 years), and education groups of high school or less, some college, and 4 years college (excluding those with postcollege education). We matched on race (black vs nonblack) with priority given to Hispanic, other race, and non-Hispanic white within the black, nonblack classification. Analyses were limited to tests occurring in the 5 years after the initial matching visit and where the complete neuropsychological battery was administered.

Covariates

Time-varying covariates included HIV serostatus (for 7 seroconverters), age, alcohol use, recreational drug use, cigarette use, and depression, and for HIV+ participants, also included medication use, log10-transformed HIV RNA, and CD4 (per 100 cell increase), CD4 nadir <200, and ever had an AIDS diagnosis. Because income level is captured differently in the WIHS (household income) and MACS (individual income), having Medicaid health insurance was used as a surrogate income measure. For men, heavy alcohol use was classified as ≥15 drinks/week and for women, ≥8 drinks/week. Education was categorized by high school or less, some college, and college degree or more. Illicit drug use since the previous visit was captured for marijuana, cocaine or crack, heroin or other opiates, and other street/recreational drug use. Cigarette smoking was categorized as current, former, or never. Depression was defined as Centers of Epidemiology Study-Depression (CES-D)[24] scores ≥16. Additional adjustments were made for previous test exposure, with counts of ≥8 administrations collapsed into 1 category.

Statistical Analysis

We examined differences in sociodemographic, clinical, and behavioral characteristics by HIV status and sex with χ^2 for categorical variables, analysis of variance for continuous normally distributed variables (ie, age, CD4 current, and CD4 nadir), and the Wilcoxon–Mann–Whitney U test for continuous variables that were not normally distributed (ie, HIV RNA). A series of generalized linear mixed models (random intercept) were conducted to assess interactions between HIV status and sex on cognitive outcomes. Primary predictors included HIV status, sex, time, and all possible 2- and 3-way interactions. Higher-order interactions were removed from the models when $P > 0.05$. Of primary interest were the 2-way interaction between HIV status and sex and the 3-way interaction between HIV status, sex, and time. The models controlled for relevant sociodemographic, behavioral, and clinical characteristics (see above). All models were conducted using the proc mixed procedure in SAS, version 9.3.

RESULTS

Participants included 710 (429 HIV+) women and 710 men (429 HIV+) 20 to 66 years old, with 67% non-Hispanic African American and 20% Hispanic in each group (Table 1). The 4 groups were similar in HIV serostatus, years of education age, and black race. Significant HIV status × sex differences were noted in depressive symptoms, Medicaid, smoking, and alcohol use as well as the use of cannabis, crack/cocaine, opiate, and intravenous drug use (P's < 0.001). Although each group had a similar representation of African Americans (67%), groups differed in other race/ethnicity categories ($P < 0.001$). Among HIV+ groups, women had a higher current mean CD4 count and were more likely to be on highly active antiretroviral therapy (HAART) (P's < 0.05), but had a lower CD4 pre-HAART nadir compared with men ($P = 0.03$). Table 2 shows average cognitive test performance by HIV status and sex at baseline.

There were no significant 3-way interactions between sex, HIV, and time interactions, so we examined HIV by sex interactions on average performance across all time points. For continuous T-scores, the sex difference varied by HIV status on TMTA ($P = 0.002$), TMTB ($P = 0.006$), SDMT ($P = 0.02$), and GP dominant ($P = 0.02$) and nondominant hand ($P = 0.009$) (Fig. 1). As shown in the figure, the T-score adjustment attenuated sex differences in HIV− individuals. A female disadvantage was seen among HIV+ individuals, but not among HIV− individuals (P's > 0.19), on the TMTA [B (unstandardized beta weight) = −2.92, SE = 0.63, $P < 0.0001$], TMTB (B = −2.65, SE = 0.64, $P = 0.01$), SDMT (B = −1.42, SE = 0.63, $P = 0.02$), GP dominant (B = −2.23, SE = 0.72, $P = 0.002$), and GP nondominant hand (B = −3.17, SE = 0.72, $P < 0.0001$). For categorical T-scores, the

TABLE 1. Sociodemographic, Behavioral, and Clinical Characteristics as a Function of HIV Status and Sex at the Matched Visit, Baseline

		HIV+		HIV−		*P*
Characteristics	**Overall Sample, n (%)**	**Women (n = 429), n (%)**	**Men (n = 429), n (%)**	**Women (n = 281), n (%)**	**Men (n = 281), n (%)**	**Sex × HIV Status**
Sociodemographic						
Race						<0.001
White, non-Hispanic	160 (11)	59 (14)	41 (10)	28 (10)	32(11)	
White, Hispanic	134 (9)	44 (10)	34 (8)	39 (14)	17 (6)	
Black, non-Hispanic	950 (67)	287 (67)	287 (67)	188 (67)	188 (67)	
Black, Hispanic	42 (3)	18 (4)	7 (2)	13 (5)	4 (1)	
Asian or Pacific Islander	14 (1)	7 (2)	—	5 (2)	2 (1)	
Other	12 (1)	1 (0)	4 (1)	2 (1)	5 (2)	
Other Hispanic	108 (8)	13 (3)	56 (13)	6 (2)	33 (12)	
Education						0.80
High school or less	758 (53)	227 (53)	227 (53)	152 (54)	152 (54)	
Some college	500 (35)	148 (34)	148 (34)	102 (36)	102 (36)	
4 year degree or more	162 (11)	54 (13)	54 (13)	27 (10)	27 (10)	
Age, mean (SD)	41.2 (8.1)	43.1 (7.5)	40.9 (7.6)	40.5 (8.7)	39.6 (8.7)	<0.001
Income†	811 (57)	202 (47)	291 (68)	135 (48)	183 (65)	<0.001
Has Medicaid	568 (40)	251 (59)	143 (33)	124 (44)	50 (18)	<0.001
Behavioral characteristics at matched visit						
Elevated depressive symptoms*	404 (28)	92 (21)	163 (38)	44 (16)	105 (37)	<0.001
Heavy alcohol use‡	149 (10)	35 (8)	32 (7)	53 (19)	29 (10)	<0.001
Cannabis use	399 (28)	63 (15)	147 (34)	64 (23)	125 (44)	<0.001
Cocaine/crack use	250 (18)	6 (1)	121 (28)	15 (5)	108 (38)	<0.001
Opiate use	83 (6)	—	32 (7)	4 (1)	47 (17)	<0.001
Other drug use	118 (8)	2 (0)	58 (14)	10 (4)	48 (17)	<0.001
Smoking						<0.001
Never	381 (27)	153 (36)	96 (22)	89 (32)	43 (15)	
Former	370 (26)	135 (31)	98 (23)	80 (28)	57 (20)	
Current	661 (47)	140 (33)	230 (54)	112 (40)	179 (64)	
Intravenous drug use	88 (6)	1 (0)	50 (12)	3 (1)	34 (12)	<0.001
CD4n, mean (SD)	539.6 (306.3)	561.9 (314.1)	516.8 (296.8)			<0.05
Therapy since last visit						<0.001
None	216 (25)	80 (19)	136 (32)			
Monotherapy	4 (0)	3 (1)	1 (0)			
Combination	26 (3)	2 (0)	24 (6)			
HAART	611 (71)	344 (80)	267 (62)			
HIV RNA, mean (SD)	20,639 (105,425)	9868.4 (41,837)	31,513 (142,686)			0.23
HIV RNA, median (25, 75%ile)	48.5 (40, 4925)	<48 (<48, 639)	239 (<40, 12,071)			
CD4 pre-HAART nadir, mean (SD)	347.9 (284.6)	319.3 (207.0)	375.8 (341.7)			<0.01

*The Center for Epidemiologic Studies Depression Scale (CES-D) ≥16 cutoff.

†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 were classified as heavy alcohol use. http://www.cdc.gov/alcohol/faqs.htm#heavyDrinking (page accessed January 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).

sex difference varied by HIV status on the TMTA ($P = 0.003$) and GP nondominant hand ($P = 0.007$). Specifically, HIV+ women were more likely to score in the impaired range compared with HIV+ men on both TMTA [odds ratio (OR) = 2.54, $P = 0.0006$] and GP nondominant hand (OR = 5.12, $P < 0.0001$), but no sex differences were observed in HIV− participants.

In subanalyses in HIV+ individuals only, significant sex differences persisted on continuous measures of TMTA, TMTB, SDMT, and GP dominant and nondominant hand,

TABLE 2. Cognitive Test Performance (Raw Mean and SD) and Number of Test Exposures as a Function of HIV Status and Sex at the Baseline Matched Visit

		HIV+		HIV−	
	Overall Sample, Mean (SD)	Women (n = 429), Mean (SD)	Men (n = 429), Mean (SD)	Women (n = 281), Mean (SD)	Men (n = 281), Mean (SD)
Test performance					
TMT*					
Part A (s)	32.2 (13.5)	34.7 (14.4)	30.4 (12.4)	32.3 (13.7)	30.8 (12.7)
Part B (s)	80.2 (40.7)	81.0 (42.3)	82.1 (43.5)	74.0 (34.1)	82.2 (39.3)
Grooved Pegboard					
Dominant (s)	77.4 (21.3)	81.5 (23.5)	74.3 (17.5)	78.5 (23.8)	75.0 (19.4)
Nondominant (s)	87.5 (25.8)	94.3 (28.2)	82.6 (21.5)	89.5 (28.9)	82.3 (22.1)
Symbol Digit (# correct)	46.9 (11.4)	47.3 (11.1)	45.5 (11.0)	50.0 (11.9)	45.6 (11.4)
Stroop test					
Color (s)	66.0 (14.9)	66.4 (15.4)	67.6 (15.2)	63.4 (13.3)	65.5 (14.7)
Word (s)	50.7 (12.2)	51.3 (11.7)	51.0 (13.9)	49.8 (10.0)	50.4 (12.2)
Interference (s)	123.2 (29.8)	123.7 (27.7)	125.8 (31.6)	118.7 (27.0)	123.2 (32.2)
Count of test exposures					
TMT, Symbol Digit	3.4 (3.0)	2.3 (1.6)	4.4 (3.6)	2.2 (1.6)	4.1 (3.3)
Grooved Pegboard	0.7 (1.1)	0.2 (0.5)	1.1 (1.2)	0.2 (0.5)	1.1 (1.2)
Stroop test	1.0 (1.2)	0.8 (1.1)	1.1 (1.2)	0.8 (1.2)	1.1 (1.2)

*Higher values indicate worse performance for the TMT, Grooved Pegboard, and Stroop test.
Lower values indicate worse performance on Symbol Digit.

after controlling for HIV-related clinical characteristics (current CD4 count, CD4 nadir <200, ever had an AIDS diagnosis, viral load, and medication use) ($P < 0.05$). On categorical measures, HIV+ women showed a higher odds of impairment compared with HIV+ men on the TMTA (OR = 2.27, $P = 0.015$) and GP nondominant hand (OR = 7.93, $P < 0.001$).

DISCUSSION

Cognitive function was examined in a large sample women from the WIHS (n = 710) and men (n = 710) from the MACS—the 2 longest-running longitudinal studies of HIV disease progression in the United States. We found evidence to support the hypothesis that HIV+ women compared with HIV+ men show cognitive vulnerabilities in aspects of psychomotor speed, attention, processing speed, and motor skills. To determine whether those differences were clinically significant, we also examined sex differences in the odds of scoring in the impaired range. We found that compared with HIV+ men, HIV+ women had a higher odds of scoring in the impaired range in psychomotor speed and attention (TMTA) and motor skills (GP).

For comparison with previous studies of sex differences in HIV+ individuals alone (ie, no controls), we note that HIV + women in the current study performed worse than HIV+ men on 4 of 5 tests, including the TMTA, TMTB, SDMT, and GP, but not the Stroop. Overall, those findings are in agreement with those from a study of 149 HAART-naive HIV+ adults and 58 HIV− controls from Nigeria.[9] Compared with HIV+ men, HIV+ women were more impaired in speed of processing, as well as verbal fluency, learning and memory, and global impairment. In that study, sex differences

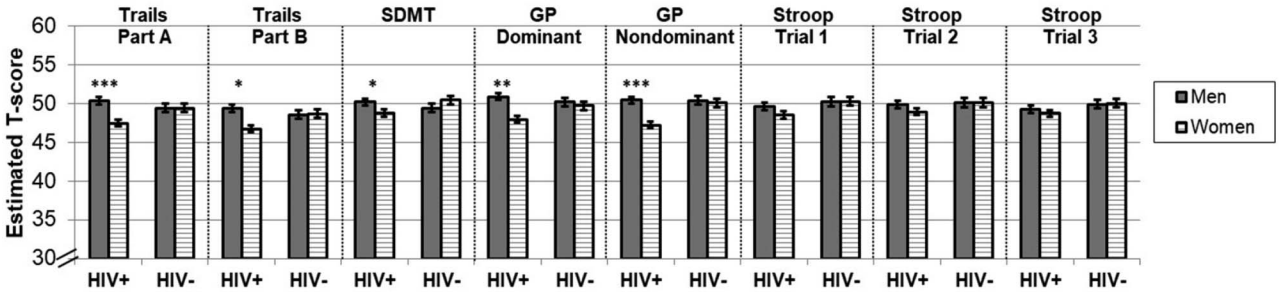

FIGURE 1. Average cognitive test performance, a function of HIV status and sex, at the matched visit. For all outcomes, lower values = worse performance. ***$P < 0.001$, **$P < 0.01$; *$P < 0.05$.

were influenced by women's higher plasma levels of HIV and higher circulating levels of monocyte-driven inflammatory markers (sCD14 and sCD163). In the current study, most HIV participants were treated, and the sex differences remained after controlling for HIV RNA and CD4 counts, which did not differ by sex. Current findings are also in general agreement with findings from 436 HIV+ individuals (80% men) enrolled in CHARTER (CNS HIV Antiretroviral Therapy Effects Research cohort). Compared with HIV+ men, HIV+ women showed a 76% increased risk of decline in a global estimate of cognitive function over a 35-month follow-up.[3] We found that the lower performance of HIV+ women compared with HIV+ men did not worsen over a 30-month follow-up.

Previous studies demonstrate some of the factors that may contribute to these findings of a female disadvantage across cognitive measures. We controlled for depression in this study, but other mental health factors that are not available in the MACS have been shown to negatively influence cognitive function in HIV+ women, including stress and post-traumatic stress disorder.[21,22,25] Previous studies show that these psychological factors affected cognitive function in HIV+ women more than HIV− women.[21,22] Although we controlled for recent substance use in this study, a more thorough examination of substance use is warranted. In the WIHS, cocaine and heroin use had a greater influence on cognition in HIV+ women compared with HIV− women, an effect that was associated with alterations in prefrontal function. Recent work shows an interactive effect of sex and HIV on cognition among substance-dependent individuals, with HIV+ women showing poorer cognitive function compared with other groups.[26–28] Finally, these effects may also reflect the influence of menopause[20] and sexual dimorphism in immune function,[29] pathogenesis,[30] and/or antiretroviral pharmacokinetics.[31] These possibilities will be addressed in the ongoing studies of WIHS and MACS. Overall, our results show that cognitive findings from HIV+ men cannot be uncritically generalized to HIV+ women, and that instead sex should be considered in studies of the pathogenesis, clinical presentation, and treatment of cognitive dysfunction in HIV.

Limitations of this study include no comparison of sex differences in verbal learning and memory because different measures were used (the Rey Auditory Verbal Learning Test in the MACS and the Hopkins Verbal Learning Test in the WIHS), and the magnitude of sex differences may differ between these tests given differences in test construction (eg, ability to semantically cluster on the Hopkins Verbal Learning Test but not the Rey Auditory Verbal Learning Test). Non-Hispanic blacks comprised 67% of the total sample here compared with 40% of individuals living with HIV in the United States,[4] so results may not generalize to the broader population of HIV+ individuals. Given differences in definitions of certain covariates between the WIHS and MACS (ie, income, education, and substance use), we determined covariates that could be applied across studies. For strengths, our study has the largest sample size to date of HIV+ men and women and controls. We had a longitudinal design with a follow-up time of 2.45 years with an average of 2.6 assessments per participant. Continued follow-up of this cohort is needed to examine these sex differences with advancing age.

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