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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Sex Differences in Neurocognitive Function in Adults with HIV: Patterns, Predictors, and Mechanisms

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Abstract

Purpose of Review Sex differences in cognitive function are well documented yet few studies had adequate numbers of women and men living with HIV (WLWH; MLWH) to identify sex differences in neurocognitive impairment (NCI) and the factors contributing to NCI. Here, we review evidence that WLWH may be at greater risk for NCI.

Recent Findings We conducted a systematic review of recent studies of NCI in WLWH versus MLWH. A power analysis showed that few HIV studies have sufficient power to address male/female differences in NCI but studies with adequate power find evidence of greater NCI in WLWH, particularly in the domains of memory, speed of information processing, and motor function.

Summary Sex is an important determinant of NCI in HIV, and may relate to male/female differences in cognitive reserve, comorbidities (mental health and substance use disorders), and biological factors (e.g., inflammation, hormonal, genetic).

Keywords Sex differences · Cognition · Neurocognition · HIV

Introduction

With the National Institutes of Health (NIH) mandate to consider sex as a biological variable [1], there is growing appreciation and recognition of sex differences in brain function and brain disorders [2]. Historically, very few studies included adequate numbers of women to sufficiently address key questions about possible sex differences in neurocognitive complications of HIV. From 1988 to 1997, females comprised only 9.3% of research participants in studies of HIV and cognition [3]. Since the introduction of effective antiretroviral therapy (ART), more neurocognitive studies focused on women living with HIV (WLWH), but sample sizes have remained modest [4–11]. The Women's Interagency HIV Study (WIHS)

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is the largest prospective cohort study in WLWH in the United States and has made fundamental contributions to understanding about neurocognitive function in WLWH. The WIHS neurocognitive studies have several strengths including a longitudinal design, a large sample (> 1500), a well-matched group of HIV-seronegative (HIV−) women [12, 13], and extensive comorbidity data (e.g., cardiovascular, mental health). Through its merge with the Multicenter AIDS Cohort Study (MACS) as the MACS/WIHS Combined Cohort Study (MWCCS), there is also now access to a well-matched group of men living with HIV (MLWH) and HIV− men [14••, 15].

Compared to MLWH, WLWH may be at greater risk for neurocognitive impairment (NCI) due in part to a disproportionate burden of poverty, low literacy levels, low educational attainment, substance abuse, poor mental health, barriers to health care services, and environmental exposures prevalent in predominantly minority urban communities [11, 13, 14••]. There is also evidence to suggest that WLWH may be more cognitively susceptible than MLWH to the effects of the same challenges [15]. In addition, biological factors such as sex steroid hormones (e.g., estrogen, progesterone, testosterone) and female-specific hormonal milieus (e.g., pregnancy, menstrual cycle, menopause transition) may contribute to sex differences in the pattern and magnitude of HIV-associated alterations in neurocognitive function. The goal of this review is to provide a systematic review of sex differences in the prevalence and patterns of neurocognitive function in HIV, identify key gaps in knowledge, and discuss some of the potential biological drivers.

Literature Search

To identify peer-reviewed studies on sex differences in the prevalence and patterns of neurocognitive function in people living with HIV (PLWH), we searched PubMED (May 2019) for titles/abstracts containing MeSH terms "sex," or "gender" combined with "cognition," "cognitive," "HIV-associated Neurocognitive Disorders (HAND)," "neurocognitive," "neurocognition," or "neuropsych," combined with "HIV," or "HIV-infected" with additional limits of "English Language," "Humans," and published in the last 5 years (2013 and after) per article instructions. Our search yielded 307 abstracts which were reviewed for the following inclusion criteria: (1) HIV sample size ≥ 100, (2) neurocognitive function determined based on two or more validated neuropsychological tests, and (3) prevalence or pattern of neurocognitive function by sex. Six articles met criteria. Five additional publications [14••, 16, 17, 18••, 19] meeting criteria but not generated by this search were also included, for a total of 11 publications (Table 1). Two of the eleven publications reflect different analyses (one cross-sectional, one on a longitudinal subset) from the same cohort (CNS HIV Anti-Retroviral therapy Effects Research-CHARTER) [18, 19] and both papers were included.

Characteristics of Included Studies and Study Participants

Of the eleven articles, nine produced cross-sectional results and two longitudinal results. Sample sizes ranged from 137 to 1361 (median = 266) for a total of 4456 PLWH. Six studies (54%) included HIV− controls in sample sizes ranging from 58 to 710 (median = 300), for a total of 2143 HIV− individuals. The percent of WLWH ranged from 15 to 62% (median = 43%) and HIV− females from 30 to 65% (median = 55%). The average age of participants was 40 years. Overall 58% of PLWH had undetectable HIV RNA (median = 62%). The articles spanned eight different countries, with 27% based in the US.

Of the eleven articles, two [16, 25] used raw neuropsychological test scores, three [14••, 21, 24] transformed raw scores into demographically adjusted (age, education, sex, race/ethnicity) T-scores based on the HIV− individuals from the same cohort, and six [17, 18••, 19, 20, 22, 23] transformed raw scores into demographically adjusted T-scores based on an external normative sample of HIV− individuals.

Findings Related to Sex Differences in Global Cognitive Function

Of the nine cross-sectional analyses, seven [17, 18••, 20–24] examined sex differences on a global neurocognitive measure in PLWH (Table 1). In unadjusted analyses, three [17, 18••, 24] of seven [20–23] analyses (43%) demonstrated that the prevalence of NCI was higher in WLWH. In the first of those three studies, global NCI (defined as a global deficit scores [GDS] score of at least 0.50) was found in 52% of WLWH versus only 41% of MLWH, for an 11% difference and an odds ratio (OR) of 1.53 (95% confidence interval [CI] 1.13–2.06, $P = 0.005$) [18••]. No sex difference was observed among the HIV− individuals (women = 27% vs. men = 26%). In the second study, the prevalence of NCI plus functional impairment (mild neurocognitive disorder + HAD) was 30% in WLWH versus 19% in MLWH, again for an 11% difference (OR = 1.79, 95% CI 1.10–2.87, $P = 0.02$) [17]. That study did not include a HIV− control group. In the third study, WLWH had a significantly lower GDS score (mean [M] = 0.38; standard deviation [SD] = 0.35) than MLWH ($M = 0.27$, SD = 0.30) ($P = 0.04$) [24]. Additionally, the mean sex difference in PLWH was greater than the mean difference in HIV− individuals. In adjusted analyses across seven analyses, the sex differences remained significant in three studies [18••, 22, 24], were attenuated in two [17, 20] with one just missing significance after adjusting for disease characteristics particularly current CD4 count ($P = 0.08$) [20], and were no

Table 1 Longitudinal and cross-sectional studies included in the literature review of sex differences in neurocognitive (NC) function in people living with HIV (PLWH) in the era of effective antiretroviral therapy (ART) and the association between sex and NC function in unadjusted and adjusted analyses

Study	PLWH *n*	WLWH *n* (%)	HIV− *n*	HIV− female *n* (%)	Country	Mean age (SD)	UD VL (%)	Number of cognitive domains assessed	Outcome	Sex-NC function association	
										Unadj	Adj
Longitudinal											
Maki (2018) [14]^{P}	858	429 (50)	562	429 (50)	US	41 (8)	48	5	T-score^{IN}	–	–
Heaton (2015) [19]	436	87 (20)	–	–	US	44 (8)	41	7	NCI^{EN}	♀ < ♂*	ns
Cross-sectional											
Sundermann (2018) [18]^{P}	1361	204 (15)	702	214 (30)	US	41 (11)	54	7	T-score; NCI^{EN}	♀ < ♂**	♀ < ♂**†
Gascón (2018) [17]	412	131 (32)	–	–	BR	45 (11)	84	7	NCI^{EN}	♀ < ♂*	♀ < ♂^{T}
Do (2018) [16]	329	141 (43)	510	284 (56)	TH	45 (13)	93	2	T-score^{NN}	–	–
Kabuba (2016) [20]	266	159 (60)	–	–	ZM	38 (13)	76	7	T-score^{EN}	ns	♀ < ♂^{T}
Burlacu (2018) [21]	250	129 (52)	72	31 (43)	RO	23 (3)	62	7	s-score^{IN}	ns	ns
Foca (2016) [22]	206	31 (15)	–	–	IT	40 (10)	0	7	NCI^{EN}	♀ > ♂*	♀ > ♂*
Vassallo (2015) [23]	200	156 (78)	–	–	FR	52 (10)	100	7	NCI^{EN}	ns	–
Royal (2016) [24]	149	92 (62)	58	38 (65)	NG	33 (7)	2	7	T-score^{IN}	♀ < ♂*	♀ < ♂*
Behrman-Lay (2016) [25]	137	44 (32)	91	49 (54)	US	39 (2)	79	7	T-score^{IN}	–	–

Note. **$P < 0.01$; *$P < 0.05$; † $P = 0.05$; ^{T} $P > 0.05$ to 0.09; *ns*, not significant; −, not assessed; ♀, women; ♂, men; † except when adjusting for reading level; *adj*, adjusted analyses; *WLWH*, women living with HIV; *HIV−*, HIV-seronegative; *NC*, neurocognitive; *NCI*, neurocognitive impairment (categorical outcome); *NP*, neuropsychological testing; *ns*, not significant; *P*, adequate power to test the sex difference; *s*, scaled score; *T-scores*, continuous outcome; *UD VL*, undetectable viral load; *unadj*, unadjusted analysis; *W*, women; *IN*, raw scores from the neuropsychological tests were demographically normed (e.g., sex, age, race/ethnicity, education) using HIV-uninfected individuals from the study; *EN*, raw scores from the neuropsychological tests were demographically normed (e.g., sex, age, race/ethnicity, education) using external norms; *NN*, raw scores that were from the neuropsychological tests were used for analysis

Country codes: *BR*, Brazil; *CN*, China; *IT*, Italy; *FR*, France; *NG*, Nigeria; *RO*, Romania; *TH*, Thailand; *US*, United States; *ZM*, Zambia

longer significant in three analyses [20, 21, 23]. Of the three analyses in which the sex differences remained significant [18••, 22, 24], one demonstrated that WLWH were less likely to have HAND (29%) then MLWH (50%); however, this study only had 31 WLWH [22].

Only one longitudinal study [19] to date has examined the risk of decline on a global measure of neurocognitive function between WLWH and MLWH. In univariate analyses, WLWH showed a 76% increased risk of decline over a 35-month follow-up versus MLWH (OR = 1.76, P = 0.01); however, sex no longer remained a significant predictor of risk of decline in the final multivariable model. This model controlled for demographic (years of education), disease, laboratory, treatment, and mental health factors (lifetime major depressive disorder [MDD] and substance use disorders).

Findings Related to Sex Differences in Specific Cognitive Domains

Across the eleven studies, six [16, 18••, 20, 21, 24, 25] cross-sectional and one [14••] longitudinal analysis examined sex differences in domain-specific cognitive performance in PLWH (Table 2). For learning and memory, two [20, 24] of five [18••, 21, 25] analyses (40%) demonstrated that WLWH were more likely have lower performance scores or greater impairment than MLWH. Only Royal et al. [24] included HIV− men and women as comparators. For speed of information processing (SIP), two [14••, 16] of seven [18••, 20, 21, 24, 25] analyses (28%) demonstrated that WLWH were more likely to perform lower or show higher impairment than MLWH. For motor skills, two [14••, 21] of seven [16, 18••, 20, 24, 25] analyses (28%) demonstrated that WLWH performed lower than MLWH. Among seven studies examining executive function [14••, 16, 18, 20, 21, 24, 25], only one [14••] analysis (14%) demonstrated that WLWH performed lower than MLWH. However, this pattern was only noted on a measure of mental flexibility and not behavioral inhibition [14••]. No sex differences were evident for fluency [16, 18••, 20, 21, 24, 25] or attention/working memory [16, 18, 20, 21, 24, 25]. The largest longitudinal study to date found that females performed worse on SIP and motor function, and that the magnitude of this sex differences did not change over time [14••]. Learning, memory, fluency, and the attention/working memory domains were not assessed [14••] and thus additional research is needed to determine if these other domains remain stable in HIV over time.

To determine the rigor and reproducibility of the eleven analyses, we ran a series of power analysis using both the T-score (continuous) and NCI (categorical). Figure 1 shows the power versus effect size (T-score difference) for different sample sizes when the sample size for men and women is (A) equal (50/50), (B) 60/40, (C) 70/30, and (D) 80/20. As the

Table 2 Sex differences in domain-specific cognitive performance in people living with HIV (PLWH) in the era of effective antiretroviral therapy (ART): longitudinal and cross-sectional analyses

Study	PLWH *n*	WLWH *n* (%)	HIV− *n*	HIV− female *n* (%)	Examined HIV × sex interaction	Cognitive domains						
						EF	FLU	ATT/WM	SIP	LRN	MEM	Motor
Longitudinal												
Maki (2018) [14]	858	429 (50)	562	429 (50)	Yes	♀ < ♂*†	–	–	♀ < ♂*	–	–	♀ < ♂**
Cross-sectional												
Sundermann (2018) [18]	1361	204 (15)	702	214 (30)	No; HIV-stratified	ns	ns	ns	ns	♀ < ♂T	♀ < ♂T	ns
Do (2018) [16]	329	141 (43)	510	284 (56)	No; HIV-stratified				♀ < ♂***			ns
Kabuba (2016) [20]	266	159 (60)	–	–	–	ns	ns	ns	ns	♀ < ♂**	♀ < ♂**	ns
Burlacu (2018) [21]	250	129 (52)	72	31 (43)	Yes	ns	ns	ns	ns	ns	ns	♀ < ♂*
Royal (2016) [24]	149	92 (62)	58	38 (65)	Yes	ns	ns	ns	ns	♀ < ♂*	♀ < ♂*	ns
Behrman-Lay (2016) [25]	137	44 (32)	91	49 (54)	Yes	ns	ns	ns	ns	ns	ns	ns

Note. ***P < 0.01; **P < 0.01; *P < 0.05; †P = 0.05; TP > 0.05 to 0.09; *ns*, not significant; –, not assessed; ♀, women; ♂, men; *ATT/WM*, attention and working memory; *EF*, executive function; *FLU*, fluency; *HIV−*, HIV-seronegative; *LRN*, learning; *MEM*, memory; *ns*, not significant; *SIP*, speed information processing; *WLWH*, women living with HIV; † Trail Making Test Part B was significant but Stroop Interference Trial was not

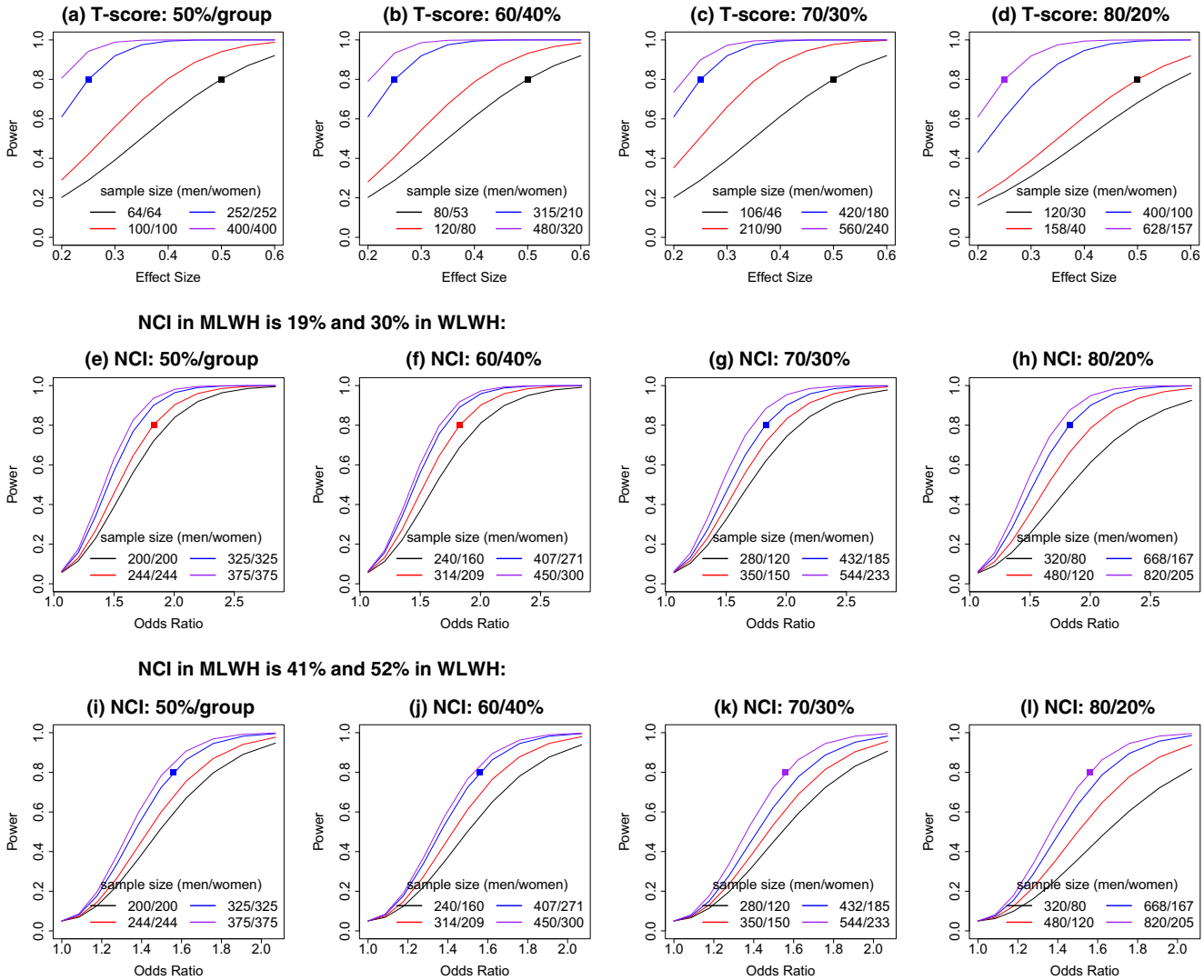

Fig. 1 Power simulations computed to determine the sample size needed/group to have 80% power to detect sex differences in T-scores (continuous) and neurocognitive impairment (NCI; categorical) in HIV. For T-scores, power versus effect size is plotted for different sample sizes (n) when the proportion of men and women living with HIV is **a** equal (50%/group), **b** 60/40, **c** 70/30, and **d** 80/20. For NCI, power versus odds ratio is plotted for different sample sizes when we assume 19% NCI in MLWH and 30% in WLWH and when the proportion of HIV-seropositive men and women is **e** equal, **f** 60/40, **g** 70/30, and **h** 80/20 women. Power versus odds ratio is plotted for different sample sizes when we assume 41% NCI in MLWH and 52% in WLWH and when the proportion of HIV-seropositive men and women is **i** equal, **j** 60/40, **k** 70/30, and **l** 80/20

proportion of MLWH and women in the sample diverge, larger sample sizes are needed to have adequate (e.g., 80% power). For example, to detect a T-score difference of 0.25 SD when the number of men and women are equal, a sample of 504 ($n = 252$/group) is needed whereas a sample of 525 is needed when the split is 60/40 (315 men; 210 women), 600 when the split is 70/30 (420 men, 180 women), and 785 when the split is 80/20 (628 men, 157 women). Of the studies examining sex differences in T-scores, only two [14••, 18••] of seven studies [16, 20, 21, 24, 25] were adequately powered; it is notable that these two studies had divergent findings, one with sex differences and one without.

We also examined the sample sizes needed to detect a significant increased odds (odds ratio) of NCI in WLWH than MLWH, using prevalence rates from studies reviewed above [17, 18]. Figure 1 panels E–G show the sample size needed to detect a significant odds ratio with sufficient power when NCI is set at 30% for WLWH and 19% for MLWH [17] and the sample size for men and women is (E) equal (50/50), (F) 60/40, (G) 70/30, and (G) 80/20. Figure 1 panels H–L show the sample size needed to detect a significant odds ratio with sufficient power when NCI is set at 52% for WLWH and 41% for MLWH where even larger sample sizes are needed (50/50 split; $N = 650$: 325 per group; 80/20 split; $N = 1025$:

820 men, 205 women). Of the studies examining sex differences with a categorical outcome (e.g., NCI, HAND), only one [18••] of seven studies [17, 19, 22–25] was adequately powered.

While powering for the sex difference in PLWH is pertinent, the optimal study design is to examine sex differences by HIV-serostatus on a T-score or NCI; this allows analysis of the sex by HIV infection interaction. We conducted a series of power simulations to determine the sample sizes needed per cell to have 80% power to detect an interaction effect size of 0.25 when we vary the proportion of men and women (50/50, 60/40, 70/30, 80/20) and the proportion of PLWH (66% or 75%) (Supplemental Materials). Of the studies examining an HIV-serostatus by sex interaction, only one [14••] of four [21, 24, 25] studies was adequately powered. For NCI, we also conducted a series of simulations to determine power needed to detect a significant odds ratio (Supplemental Materials). Only one [18••] of the two studies [24] was adequately powered.

In sum, although a number of recent studies have examined sex differences in neurocognitive function, few studies are adequately powered to detect a meaningful sex difference. The lack of statistical power appears to be an important consideration and likely contributes to inconsistent findings of sex differences in NCI. The strongest available evidence indicates a higher prevalence of NCI in WLWH compared to MLWH, with the largest differences in memory and learning followed by SIP and motor, and inconsistent findings in executive function. Adequately powered studies are needed to determine the reproducibility and longitudinal course of these findings. Adjusting for critical factors such as reading ability, education, mental health, and poverty reduces the magnitude of the sex difference, and elucidates factors that contribute to NCI in women. Given that neuropsychological testing in clinical practice adjusts for age and educational differences but not mental health and other factors, a higher prevalence of NCI in women in the clinical setting may be expected, and the consequent need for interventions may be higher in women.

Why Are There Sex Differences in the Prevalence and Patterns of Neurocognitive Function in HIV?

Sex Differences in Cognitive Reserve

A greater likelihood of NCI among WLWH versus MLWH may reflect differences in psychological risk factors (e.g., poverty, low education, substance use, depression, early life trauma, barriers to healthcare) which are more common in women versus men [26, 27]. These factors can additively or synergistically lower cognitive reserve before HIV infection and contribute to greater cognitive dysfunction following infection [28, 29]. Cognitive reserve is a key determinant of NCI because it sets a threshold level of brain insult that is necessary for NCI to manifest [30, 31]. Applied to HIV, women with low cognitive reserve would be less able to compensate for the myriad adverse neurobiological effects of HIV and, thus, would be more susceptible to NCI than those with high cognitive reserve. Accordingly, the higher rates of neurocognitive risk factors in WLWH versus MLWH and the resulting lower cognitive reserve may contribute to women's increased susceptibility to NCI.

Reading level, as assessed by word pronunciation tests such as the Wide Range Achievement Test (WRAT) and the North American Reading Test (NART), is a common proxy for cognitive reserve. Reading level is thought to better reflect educational attainment than years of education especially in lower socioeconomic, ethnically diverse populations due to factors that limit the effectiveness of schools serving these populations including less access to quality education, reading materials and school supplies, and teaching expertise [32]. Consistent with this notion, low reading level, but not low education (< 12 years), was a risk factor for neurocognitive decline in HIV cohort studies [13, 32]. Low reading level is also associated with a range of clinical outcomes including hospitalizations and outpatient doctor visits [33], and therefore could also indirectly influence neurocognitive performance through factors such as low health literacy, increased medical comorbidities, and medication non-adherence.

In the WIHS, reading level, years of education, income, and race were more strongly associated with neurocognitive performance than HIV-serostatus [13], indicating that adverse sociodemographic factors are key determinants of neurocognitive function in WLWH. An HIV Neurobehavioral Research Program (HNRP) study addressed whether the higher rates of psychosocial risk factors in WLWH account for their higher rates of NCI versus MLWH [18••] and for any sex differences in association between HIV-serostatus and NCI. NCI was more prevalent in WLWH versus MLWH, but not after adjustment for the lower reading level in WLWH. HIV-seropositivity was more strongly associated with NCI in women versus men and this association was attenuated but not eliminated after adjustment for reading level. Those results were driven by non-Hispanic Blacks [18••]. The greater prevalence of NCI in WLWH may therefore be due in part to their suboptimal educational experience, which may lower cognitive reserve and increase susceptibility to NCI. Further, study samples that are predominantly White and more educated may be less likely to yield a sex difference. It is notable that two studies in Africa did find evidence of worse NCI in WLWH compared to MLWH [20, 24].

Sex Differences in Mental Health Risk Factors and Disorders

Stress and early life trauma as well as mental health disorders including depression and post-traumatic stress disorder

(PTSD) may contribute to higher rates of NCI in WLWH versus MLWH. Stigma and social isolation associated with the diagnosis of HIV may contribute to progression of NCI. Mental health risk factors and disorders are strongly associated with neurocognitive function in WLWH. In a series of cross-sectional WIHS studies, we examined associations between PTSD, anxiety, perceived stress, depression, and neurocognitive function. PTSD, anxiety, perceived stress, and depression were each associated with deficits in learning, memory, and attention [13, 34–36]. High stress and elevated anxiety were associated with decreased learning and memory only among WLWH [35, 36]. In WLWH but not HIV− women, higher perceived stress and PTSD were associated with accelerated declines in fluency, learning, and memory [37]. Irrespective of time or HIV-serostatus, depression, perceived stress, and PTSD were associated with lower SIP, executive function, and global neurocognitive function. In a longitudinal study of South African WLWH, trauma exposure was related to less improvement in executive function and fluency [38].

Few large-scale HIV cohort studies assess sex differences in mental health risk factors and disorders on NCI. We examined the association of elevated depressive symptoms with NCI in the WIHS and MACS [15]. Although MLWH showed a higher frequency of elevated depressive symptoms than WLWH (perhaps due to sexual minority status), WLWH with elevated depressive symptoms had 5 times the odds of impairment in executive control/inhibition versus HIV− women with elevated depressive symptoms, and 3 times the odds of impairment on that measure versus MLWH with elevated depressive symptoms. Including comprehensive mental health measures particularly diagnostic measures in HIV cohort studies is warranted to better understand how mental health and sex differences in mental health contribute to HIV-associated NCI.

Sex Differences in Sex Steroid Hormones and Hormonal Milieus

Sex steroids, particularly estradiol, progesterone and testosterone, influence cognition in healthy individuals, contributing, for example, to sex differences in performance on verbal tasks (favoring females) and visuospatial tasks (favoring males). For women, changes in sex steroid hormones across the menstrual cycle, pregnancy, and the menopause contribute to changes in neurocognitive performance [39]. In HIV, sex has an influence on pretreatment viral load [40], the immune response to HIV itself [41], and on measures of viral persistence and immune activation during effective ART [42•, 43•]. Estradiol has been directly linked to HIV transcriptional activity [44, 45] and may further influence neurocognitive function through effects on viral suppression and replication. Both estradiol and progesterone also have immunomodulatory effects, impacting cytokines and chemokine levels [46], contributing to sex differences in immune function. The role of peripheral aromatization of testosterone to estradiol is understudied in relation to NCI in PLWH. In WLWH, there is initial evidence of an association between testosterone insufficiency and cognitive complaints [47]. The cognitive effects of testosterone deficiency in MLWH are unclear [48, 49]. As sex steroids have both direct effects on neurocognitive indices and can also modulate HIV viral activity, the contribution of sex steroids and relative deficiencies to changes in neurocognitive function in MLWH and WLWH warrants further investigation.

Sex Differences in Immune Function

Immune responses are modulated by biological sex with implications for infectious, inflammatory, and autoimmune diseases [50, 51]. Recent work highlighted the critical influence of sex on the immune system and the potential for sex-specific genetic determinants of immune function [52]. Early in the HIV epidemic, a sex difference in HIV viral load was identified, and importantly, despite lower viral loads in women, they were not protected against disease progression and CD4 decline. This sex difference had direct implications for treatment guidelines which were at the time based on viral load [40, 53, 54]. Sex differences in the immune response to HIV infection [41, 55] are likely contributors to these variations in pathogenesis. Chronic immune activation and inflammation predict HIV disease progression and mortality independent of viral load [56–61] and can trigger HIV-induced neurotoxicity and other comorbid diseases [62, 63].

A growing body of research demonstrates the importance of considering sex differences in monocyte-driven inflammatory biomarkers in PLWH. For example, sCD163 concentrations are higher in ART-naive WLWH versus ART-naive MLWH, both before and after 24 months of suppressive ART [64]. We found similar results in the WIHS and MACS (see analyses below). These differences may increase with aging. In a study of WLWH and MLWH with viremic control, sCD163 levels increased more with age among women versus men [65] (see also [66]). Other work indicates that WLWH show less of a decrease in sCD14 levels after cART initiation versus MLWH [56]. Hormonal factors appear to relate to sCD163 levels as women with lower ovarian reserve as measured by antimullerian hormone levels have higher sCD163 levels, independent of age [67]. Sex differences in monocyte-driven inflammatory biomarkers in HIV have been studied in relation to cardiovascular disease [65, 67].

We examined sex differences in markers of monocyte activation and inflammation in 778 WIHS (74% PLWH) and 503 MACS participants (65% PLWH) [68]. In unadjusted analyses, PLWH versus HIV− individuals had higher levels of the monocyte-driven inflammatory markers sCD163 and sCD14 (P's < 0.05; Fig. 2). Females had higher sCD163 levels than

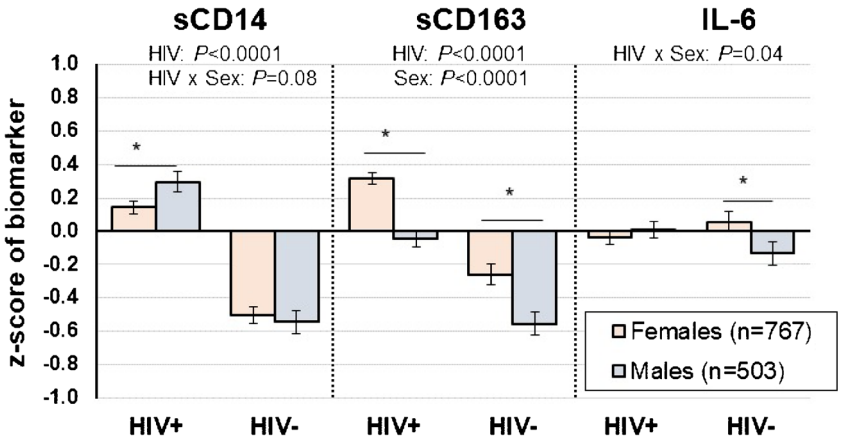

Fig. 2 Male/female differences in monocyte-associated inflammatory markers and less specific markers of inflammation among people living with and without HIV. HIV+, HIV-seropositive; HIV-, HIV-seronegative

males ($P < 0.05$). Moreover, there was a significant HIV × sex interaction on IL-6, a non-specific marker of inflammation ($P = 0.04$) with a trend for an interaction on sCD14 ($P = 0.08$). No sex differences in sCD14 were found among the seronegative controls, but MLWH had higher levels than WLWH. This pattern of results held after adjusting for age and race/ethnicity. These findings and other studies [64–67] demonstrate male/female differences in inflammatory biomarkers, setting the stage for future studies examining these factors in relation to NCI.

Neopterin, a marker of cellular immune activation, is produced by activated monocyte/macrophage cells. CSF neopterin levels were associated with NCI, while plasma neopterin levels were associated with NCI only in WLWH [69–72]. NCI was related to higher plasma neopterin levels in but not MLWH in a small cohort study from Thailand of individuals with chronic HIV who were about to initiate cART treatment [70]. A substantial proportion of the cohort met criteria for the most severe form of HAND, HAD. Individuals with HAD showed the highest neopterin levels versus individuals with normal cognition. The pattern of effects appeared more specific to women than men.

Altogether, findings suggest distinct patterns of immune response to HIV in women and men. Delineating the specific patterns of association between markers of inflammation and indices of neurocognitive function may help to identify sex-specific therapeutic targets and causal disease pathways.

Sex Differences in Hypothalamic Pituitary Adrenal Axis Function

The hypothalamic pituitary adrenal (HPA) axis is a key mediator of the stress response. A major player in this axis is cortisol, a glucocorticoid, which exerts actions after finding to glucocorticoid receptors which are abundant in the hippocampus and prefrontal cortex [73–77], two brain regions that are important for learning and memory. At a cellular level, increased glucocorticoids can disrupt suppress neuronal excitability, disrupt long-term potentiation, and casual apoptosis and atrophy in the hippocampus and dendritic shortening and atrophy in the prefrontal cortex [78–80]. The HPA axis response is initiated by release of corticotrophin releasing hormone (CRH) from the hypothalamus which stimulates release of adrenocorticotrophic hormone (ACTH) from the pituitary that subsequently triggers production of cortisol by the adrenal glands. The impact of CRH on neurocognitive function is highlighted by a recent finding that single nucleotide polymorphisms (SNPs) in CRH receptor 1 or the gene that encodes the CRH binding protein associates with NCI in WLWH. The SNP in CRH receptor 1 also moderated the association of childhood trauma and NCI [81].

The HPA axis may play an important role in NCI in PLWH given that the HPA axis may be perturbed in HIV [82–85]. In many but not all [86, 87] studies, PLWH versus HIV− individuals show elevated basal cortisol levels [88–92], increased cortisol over time [93], attenuated cortisol responsivity to behavioral [94] and CRH challenges [91], and alterations in the diurnal rhythm of cortisol secretion [95]. The relevance of those findings to WLWH may be limited as they are based primarily on small studies of men that predate effective ART. There are sex differences in HPA axis activity [96, 97] and neurocognitive function (e.g., memory) vulnerabilities to cortisol [98, 99]. Our recent work highlights a potential causal relationship between cortisol and neurocognitive function in HIV that differs by sex. In a double-blind, placebo-controlled, cross-over study, a single dose of hydrocortisone (10 mg) improved learning and memory 4 h following treatment in WLWH [100] but not in MLWH [101].

Sex differences in neurocognitive function may also be in part driven by the interplay between the HPA axis function and the immune system at the level of the glucocorticoid receptor. The immune response to an acute laboratory stressor, a threat of shock stressor, was altered in PLWH such that TNF-alpha responsivity was blunted for both sexes but IL-1β and cortisol responsivity were blunted in WLWH only [102]. It is unclear whether such differences are adaptive or maladaptive. Evidence of alterations at the level of the glucocorticoid receptor was found in the WIHS, where HIV and depressive

symptoms were independently associated with impaired glucocorticoid signaling [103]. How those alterations influence neurocognition is not yet elucidated but warrants further investigation.

Conclusions

Based on a systematic review of recent studies to assess whether WLWH are more cognitively vulnerable than MLWH, paired with a power analysis to guide the interpretation of existing studies, we found that few HIV studies are adequately powered to address male/female differences in the presence and pattern of NCI but that those with adequate power do find evidence of greater NCI in WLWH, particularly in the domains of memory, SIP, and motor function. Biological sex needs to be considered in neurocognitive studies in PLWH. Factors that may contribute to these sex differences include cognitive reserve, mental health and other comorbidities, and biological factors.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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