

Cognitive Burden of Common Non-antiretroviral Medications in HIV-Infected Women

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Objective: The aging HIV population has increased comorbidity burden and consequently non-antiretroviral medication utilization. Many non-antiretroviral medications have known neurocognitive-adverse effects (“NC-AE medications”). We assessed the cognitive effects of NC-AE medications in HIV+ and HIV– women.

Methods: One thousand five hundred fifty-eight participants (1037 HIV+; mean age 46) from the Women’s Interagency HIV Study completed a neuropsychological test battery between 2009 and 2011. The total number of NC-AE medications and subgroups (eg, anticholinergics) were calculated based on self-report. Generalized linear models for non-normal data were used to examine the cognitive burden of medications and factors that exacerbate these effects.

Results: HIV+ women reported taking more NC-AE medications vs. HIV– women ($P < 0.05$). NC-AE medication use altogether was not associated with cognitive performance. However, among NC-AE medication subgroups, anticholinergic-acting medications, but not

opioids or anxiolytics/anticonvulsants, were negatively associated with performance. HIV status moderated the association between these NC-AE medication subgroups and performance (P 's < 0.05). HIV-serostatus differences (HIV– $<$ HIV+) in global, learning, fluency, and motor function were greatest among women taking >1 anticholinergic medications. HIV-serostatus differences in performance on learning and psychomotor speed were also greatest among women taking 1 or more anxiolytics/anticonvulsants and 1 or more opioids, respectively.

Conclusions: HIV+ women have increased cognitive vulnerabilities to anticholinergic, anxiolytic/anticonvulsant, and opioid medications. Potential synergy between these medications and HIV may explain some HIV-related cognitive impairments. It may be important clinically to consider these specific types of medications as a contributor to impaired cognitive performance in HIV+ women and assess the cost/benefit of treatment dosage for underlying conditions.

Key Words: anticholinergic, cognition, HIV, women
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INTRODUCTION

Increasing effectiveness and adherence to antiretroviral (ARV) therapies has led to an aging of the HIV population. To date, approximately 50% of all individuals with HIV are 50 years or older^{1,2} and about 90% of individuals older than 50 years have been living with HIV for the majority of their life.³ Two consequences of aging in the HIV-infected population are increases in: (1) prevalence of HIV-associated non-AIDS comorbidities; and (2) prescription and utilization of non-ARV medications to treat these comorbidities. Both consequences may cause detrimental effects on brain structure and function.

One common HIV-associated non-AIDS comorbidity is cognitive impairment, which is reported to occur in approximately 30%–60% of people with HIV at some point during their lifetime.⁴ The clinical features of HIV-associated cognitive impairment commonly include alterations in executive function, complex attention, processing speed, learning, and memory^{5–9} and these deficits are associated with dysfunction of frontostriatal networks¹⁰ and altered integrity of hippocampal and prefrontal brain regions.^{11–13} Interestingly, the utilization of non-ARV medications with known cognitive adverse effects may in part explain some of the cognitive complications among HIV-infected (HIV+) individuals, particularly among those individuals aged 50 years and older. Many of the non-ARV medications used among HIV+ individuals have known cognitive adverse effects (termed “NC-AE medications”), especially agents with anticholinergic properties^{14–18} as well as opioids,¹⁹ anxiolytics,²⁰ and anticonvulsants.²¹ This is particularly concerning because older adults in general have an increased vulnerability to medication side effects due to the pharmacokinetic and pharmacodynamic changes that occur with aging.²² For example, with age, metabolism and drug elimination slows, the blood–brain barrier changes, and there are age-related deficits in neurotransmission.²³ As a result, many medications with higher side effect burden are not routinely recommended in older patients.^{24–26}

The primary aim of the present analysis was to examine the potential cognitive burden of NC-AE medications (total number) and to determine whether HIV exacerbates potentially negative effects. We were interested in both the more general, diffuse effects of NC-AE medications²⁷ as well as the effects of commonly used non-ARV medications with known pharmacodynamic mechanisms including those with anticholinergic properties, opioids, anticonvulsants, and anxiolytics. Our overarching hypothesis was that the effects of NC-AE medications would be broad, negative influences on cognitive performance, and that HIV would exacerbate these effects. Furthermore, consistent with previous studies in older adults,^{16,18} we expected more specific associations with medications with known anticholinergic properties on measures of learning, memory, and attention.

METHODS

Participants

All participants were enrolled in the Women’s Inter-agency HIV Study (WIHS), a longitudinal, multisite study

(Chicago, Bronx, Brooklyn, Washington DC, San Francisco, and Los Angeles) between the period of 1994 and 2011 (enrollment varied by site). Study methodology, data collection, interviewer training, and retention have been previously reported.^{28–30}

Participants in this cross-sectional analysis completed a cognitive assessment during the first wave (April 2009–April 2011) of a comprehensive neuropsychological test battery administered every 2 years in combination with the WIHS semiannual study visits, which includes a physical examination, blood draw, and medical and psychosocial interviews. Briefly, all active English-speaking WIHS participants completing any of the 4 semiannual WIHS visits ($n = 1908$) were asked to undergo neuropsychological testing and 1595 consented to participate.³¹ Of the 1595, we included 1558 (98%) in our analyses. Thirty-seven women were excluded because they were missing non-ARV NC-AE medication data.

Measures

Medication Assessments

At each WIHS visit, participants were asked to recall ARV and non-ARV medications taken currently and since the last visit (~6 months). Medication data were reviewed with specific drugs categorized as NC-AE if there were known adverse cognitive effects.²⁷ Medication categories²⁷ were modified to include those medications or drug categories known to adversely impact performance on neuropsychological tests (for drug list, see Table 1, Supplemental Digital Content, <http://links.lww.com/QAI/B173>). In addition, medications reported by participants were categorized by whether they possessed anticholinergic properties according to the Anticholinergic Risk Scale.³² Our primary exposures of interest were: (1) the total number of NC-AE medications (0, 1, or >1), (2) anticholinergic burden, defined here as the total number of non-ARV medications with anticholinergic properties (0, 1, or >1), (3) taking opioid medications (yes vs. no), and (4) taking anticonvulsant/anxiolytics (yes vs. no) (see Table 1, Supplemental Digital Content, <http://links.lww.com/QAI/B173>). Categorization of each of the primary exposures was based on the data distributions. The focus on anticholinergic, opioid, and anticonvulsant/anxiolytic medications was based on the known adverse effects of these medication categories on cognitive performance and relative high-frequency use of these medications in this cohort allowing for subgroup analyses.

Neuropsychological Performance

Participants completed a test battery that comprised 8 tests: Hopkins Verbal Learning Test-Revised (HVLTR), Letter-Number Sequencing, Trail Making (TMT), Stroop Test, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Category Fluency Test (Animals), and Grooved Pegboard (GPEG). Performance on these tests were used to assess 7 domains: learning (total learning across HVLTR trials), memory (delayed free recall on HVLTR), attention/working memory (total correct on Letter-Number Sequencing control and experimental

conditions), psychomotor speed (total correct on SDMT and time to completion on Stroop Trial 2), executive function (time to completion on TMT Part B and Stroop Trial 3), fluency (total correct on COWAT and category fluency), and motor skills (total time to completion for each hand on GPEG). Timed outcome was log-transformed to normalize distributions and reverse-scored, so that higher values equated to better performance.

Demographically adjusted T-scores were derived for each outcome and these T-scores were used to create domain scores consistent with previous large-scale HIV cohorts including the WIHS.^{9,31,33–36} For each domain, a composite T-score was derived by averaging the T-scores for domains with ≥ 2 outcomes. If only one test in a domain was completed, the T-score for that test was used. A global neuropsychological score was derived for individuals who had T-scores for at least 4 of 7 cognitive domains.

T-scores were converted into clinical ratings, which ranged from 1 to 9 with 1 = reflecting above average performance (T-score ≥ 55), 2 = average performance (T-score ≥ 45 and < 55), 3 = low average (T-score ≥ 40 and < 45), 4 = borderline (used for only domain and global summary ratings not individual test scores), 5 = definite mild impairment (T-score ≥ 35 and < 40), 6 = mild to moderate impairment (T-score ≥ 30 and < 35), 7 = moderate impairment (T-score ≥ 25 and < 30), 8 = moderate to severe impairment (T-score ≥ 20 and < 25), and 9 = severe impairment (T-score < 20).³⁷ For each domain rating, a rating was derived based on the test (s) in the domain. If a single test was completed, we used the rating for the domain. If 2 or more tests in the domain were completed and all test ratings are (1–3) or (5–9), we averaged the ratings. If one or more test were scored 1–3 and one or more of the tests was 5 or greater, the domain was scored as the worst test score minus 1 (higher is worse, eg, a test score of 6 would result in a domain score of 5).

Statistical Analyses

Generalized linear models for non-normal data (PROC GENMOD, distribution = Poisson) were performed using SAS version 9.4 (Cary, NC) to examine associations between non-ARV NC-AE medications and cognitive performance. Similar generalized linear models were used to assess whether the association between medication burden and cognitive performance was modulated by HIV-serostatus. In the first set of models, non-ARV NC-AE medication use (0, 1, and > 1) was the primary predictor. Models controlled for HIV status, WIHS site, current employment status (employed vs. unemployed), a clinically relevant depressive symptom burden (CES-D ≥ 16), current smoking status (yes vs. no), heavy drinking (≥ 4 drinks in 1 sitting or ≥ 7 drinks/wk vs. not), marijuana use in the past 6 months (yes vs. no), recent crack, cocaine, and/or heroin use in the past 6 months (yes vs. no), and hepatitis C (HCV) RNA. Subsequent models included the interaction between NC-AE medications and HIV-serostatus. Similar sets of models were conducted to include non-ARV medications with anticholinergic properties, opioids, and anxiolytics/anticonvulsants. Results were considered significant at $P < 0.05$ (2-sided). The Benjamini–Hochberg procedure was used to control for the

false discovery rate, which was set at 0.10 for each set of analyses.

RESULTS

Table 1 includes demographic, behavioral, clinical, and cognitive characteristics of the HIV+ (n = 1037) and HIV– women (n = 521) included in the present analysis. Compared with HIV– women, HIV+ women were significantly older (47 vs. 43 years), were less likely to be Hispanic, were more likely to have positive HCV serology, and were less likely to be employed and engaged in smoking, heavy alcohol, marijuana, or crack, cocaine, and/or heroin use (P 's < 0.05). Eighty-three percent of HIV+ women reported combination ARV therapy use with greater than or equal to 95% adherence, 62% were taking low Central Nervous System (CNS)-penetrating ARV medications (CNS penetration effectiveness score $< 8^{38}$), and 52% of women had an undetectable plasma HIV RNA (below the limits of detection at < 48 cp/mL).

HIV+ women reported using more antidepressants, and more non-ARV NC-AE medications including anxiolytics, and medications with known anticholinergic properties vs. HIV– women (P 's < 0.05). Reported opioid and anticonvulsant use was the same among HIV+ and HIV– women. Among HIV+ women using non-ARV NC-AE medications (n = 405), the most common NC-AE medication reported by drug class were: anxiolytics alone (n = 46, 11%), opioids alone (n = 45, 11%), antihistamines alone (n = 31, 8%), antidepressants alone (n = 31, 8%), beta-blockers alone (n = 23, 6%), and antipsychotics alone (n = 21, 5%). In HIV– women who reported using NC-AE medications (n = 144), the most common drug classes used were: opioids alone (n = 22, 15%), antipsychotics alone (n = 14, 10%), antihistamines alone (n = 9, 6%), beta-blockers alone (n = 8, 5%), and antidepressants alone (n = 8, 5%). With respect to cognitive performance, HIV+ women performed lower than HIV– women on global function, memory, attention/working memory, and executive function.

Total Non-ARV NC-AE Medication Burden on Cognitive Performance

Table 2 presents cognitive performance by NC-AE medication use in the overall sample.

Non-ARV NC-AE medication use was not associated with cognitive performance (P 's > 0.07) and non-ARV NC-AE medication use did not moderate the association of HIV and performance ($P > 0.10$, Fig. 1).

Total Anticholinergic Burden on Cognitive Performance

Table 3 presents cognitive performance by non-ARV medications with anticholinergic properties in the overall sample. Total anticholinergic burden was negatively associated with learning and executive function. Regarding executive function, women taking at least 2 medications with anticholinergic properties demonstrated lower performance than women taking no medications, potentially indicating

TABLE 1. Demographic, Behavioral, Clinical, and Cognitive Characteristics as a Function of HIV-Serostatus

Variable	HIV+ (n = 1037), n (%)	HIV- (n = 521), n (%)	P
Age, M (SD)	46.99 (8.76)	42.83 (9.97)	<0.001
Years of education	12.45 (2.99)	12.50 (2.93)	0.75
WRAT-3 reading subtest	92.23 (18.33)	91.50 (17.50)	0.45
Race/ethnicity			0.01
Black, non-Hispanic	664 (64)	323 (62)	
White, non-Hispanic	142 (14)	50 (10)	
Hispanic	192 (18)	126 (24)	
Other	39 (4)	22 (4)	
Annual household income ≤12,000/yr	452 (44)	232 (44)	0.93
Currently employed	370 (36)	228 (44)	0.002
Clinically relevant depressive symptoms†	322 (31)	163 (31)	0.94
Currently smoking	425 (41)	243 (47)	0.03
Recent use			
Heavy alcohol	145 (14)	114 (22)	<0.001
Marijuana	161 (15)	117 (22)	<0.001
Crack, cocaine, and/or heroin use	60 (6)	44 (8)	0.04
Opioids	121 (12)	49 (9)	0.18
Antianxiety	136 (13)	38 (7)	<0.001
Anticonvulsants	59 (6)	20 (4)	0.12
Either antianxiety or anticonvulsants	173 (17)	52 (10)	<0.001
NC-AE medications			<0.001
0	632 (61)	377 (72)	
1	223 (22)	78 (15)	
>1	182 (18)	66 (13)	
Anticholinergic-acting medications			0.01
0	792 (76)	431 (83)	
1	171 (17)	66 (13)	
>1	74 (7)	24 (4)	
Hepatitis C RNA positive	238 (23)	66 (13)	<0.001
HIV RNA			
Undetectable (<48 cp/mL)	542 (52)	—	
Detectable, median (IQR)	1207 (14,793)	—	
≥10,000 cp/mL	141 (14)	—	
CD4 count, median (IQR)			
Current	505 (407)	—	
Nadir	189 (201)	—	
cART and ≥95% adherence	667 (83)	—	
ART duration (yrs), median (IQR)	13.05 (5.40)	—	
CPE exposure			
Low (<8)	648 (62)	—	
Medium (8–9)	224 (22)	—	
High (>9)	165 (16)	—	
Previous AIDS diagnosis	459 (44)	—	

TABLE 1. (Continued) Demographic, Behavioral, Clinical, and Cognitive Characteristics as a Function of HIV-Serostatus

Variable	HIV+ (n = 1037), n (%)	HIV- (n = 521), n (%)	P
NP test performance			
Clinical rating score, mean (SE)*			
Global	3.62 (0.13)	3.39 (0.14)	0.01
Learning	2.85 (0.11)	2.69 (0.12)	0.07
Memory	2.71 (0.11)	2.53 (0.12)	0.04
Attention/working memory	2.34 (0.11)	2.17 (0.11)	0.02
Executive function	3.10 (0.13)	2.88 (0.13)	0.02
Speed	2.89 (0.12)	2.72 (0.12)	0.05
Fluency	2.67 (0.11)	2.61 (0.11)	0.45
Motor	2.62 (0.12)	2.62 (0.13)	0.97

Variables reported as n (%) were analyzed with χ^2 tests. Variables reported as M (SD) were analyzed with independent t tests. Variables reported as median/IQR were analyzed with Wilcoxon–Mann–Whitney test.

*Higher is worse, and scores are from models adjusting for anticholinergic-acting medications, HCV status, depressive symptoms, heavy drinking, smoking, marijuana, crack, cocaine, and/or heroin use.

†CES-D, Center for Epidemiological Studies Depression scale ≥16 cutoff; current, refers to within the past week; recent, refers to within 6 months of the most recent WIHS visit; heavy alcohol use reflects >7 drinks/wk or ≥4 drinks in one sitting.

ART, antiretroviral therapy; cART, combination antiretroviral therapy; CPE, CNS penetration effectiveness; IQR, interquartile range; NP, neuropsychological; WRAT-3, wide range achievement test standard score.

a threshold effect of anticholinergic burden on these domains. There were incremental increases on learning impairment with anticholinergic burden (0 > 1 medication > more than 1 medication).

In models including the 2-way interaction between total anticholinergic burden and HIV status, the interaction was significant for global function, learning, attention/working memory, fluency, and motor function (P 's < 0.05), and trend for speed ($P = 0.05$) (Fig. 1). Follow-up analyses indicated that the magnitude of performance differences between HIV+ and HIV- women on global function, learning, fluency, and speed depended on the reported number of medications with anticholinergic properties. For these 4 domains, the greatest performance differences between HIV+ and HIV- women were among women taking 2 or more medications with anticholinergic properties ($P < 0.05$). Differences in performance on attention and working memory tasks were only observed between HIV+ and HIV- women who were not taking medications with anticholinergic properties ($P = 0.002$). Motor function performance differed between HIV+ and HIV- women among women taking one or more medications. Among women taking one medication, HIV- women demonstrated lower performance than HIV+ women ($P = 0.002$). However, among women taking more than 1 medication, HIV+ women demonstrated lower performance than HIV- women ($P = 0.04$).

To ensure that the pattern of medication effects on cognitive outcomes was not driven by uncontrolled viremia in a subset of HIV+ women, we reconducted the analyses only among HIV+ women with suppressed plasma HIV RNA

TABLE 2. Cognitive Performance by NC-AE Medication Use in the Women’s Interagency HIV Study

Outcome	Obs	Total NC-AE Medications			Generalized Linear Model*			
		0	1	>1	Overall	1 vs. 0	>1 vs. 0	>1 vs. 1
		(n = 1009)	(n = 301)	(n = 248)	P	P	P	P
Global NP	1556	3.2 (0.10)	3.4 (0.13)	3.5 (0.14)	0.08	0.07	0.07	0.86
Memory	1553	2.4 (0.09)	2.4 (0.11)	2.6 (0.12)	0.23	0.86	0.09	0.18
Learning	1553	2.5 (0.08)	2.6 (0.11)	2.6 (0.12)	0.16	0.11	0.13	0.95
Attention/WM	1398	2.3 (0.09)	2.4 (0.11)	2.2 (0.11)	0.24	0.58	0.16	0.10
Executive function	1540	2.8 (0.10)	2.9 (0.13)	3.0 (0.13)	0.07	0.04	0.11	0.59
Speed	1555	2.6 (0.09)	2.7 (0.11)	2.8 (0.13)	0.58	0.46	0.36	0.82
Fluency	1550	2.6 (0.09)	2.6 (0.11)	2.6 (0.12)	0.90	0.85	0.97	0.75
Motor	1531	2.4 (0.09)	2.6 (0.12)	2.6 (0.13)	0.19	0.13	0.16	0.98

*Controlling for HIV status and HCV status, site, current employment status, depressive symptoms, heavy drinking, smoking, marijuana, crack, cocaine, and/or heroin use. M, estimated mean T-score; NP, neuropsychological; WM, working memory.

(n = 542) and HIV– women. The same results were observed for global function, learning, attention/working memory, speed, and motor function. We also examined whether there were any differences in other HIV-related clinical characteristics, including the prevalence of different ARV regimens (see Table 2, Supplemental Digital Content, <http://links.lww.com/QAI/B173>) that could account for the pattern of associations. The only measured HIV-associated factor that differed among HIV+ women taking none, one, or more than one medication with anticholinergic properties was having a previous AIDS diagnosis. Reanalysis of these data indicated incremental increases in impairment for global, learning, and motor function specifically among women taking 2 or more medications with anticholinergic activity (HIV+ with previous AIDS diagnosis > HIV+ without previous AIDS diagnosis > HIV–, *P*'s < 0.05).

Opioid and/or Anxiolytic/Anticonvulsant Use on Cognitive Performance

Overall, neither opioid nor anxiolytic/anticonvulsant use was significantly associated with cognitive performance (*P* > 0.05 after controlling for the false discovery rate) (see Table 3, Supplemental Digital Content, <http://links.lww.com/QAI/B173>). However, both opioid and anxiolytic/anticonvulsants use moderated the association between HIV status and cognitive functioning. Opioid use moderated the association between HIV status and processing speed (*P* = 0.03), whereas anxiolytic/anticonvulsants moderated the association between HIV status and learning performance (*P* = 0.04; Fig. 1). Specifically, among women taking anxiolytic/anticonvulsants, HIV+ women performed worse on learning compared with HIV– women (*P* = 0.01). Similarly, among women taking opioids, HIV+ women performed worse on psychomotor speed compared with HIV– women (*P* = 0.01). There were no differences between HIV+ and HIV– women not taking these medications for either outcome (*P* > 0.27). To test whether these interactions were driven by uncontrolled viremia, we reconducted these analyses among the subset of HIV+ women with suppressed

plasma HIV RNA and HIV– women. Among the latter group of women, the interaction between anxiolytic/anticonvulsants medications and HIV-serostatus on learning and between opioid use and HIV-serostatus on psychomotor speed was not significant (*P* > 0.46).

DISCUSSION

To the best of our knowledge, this is the first study to examine the general effects of non-ARV NC-AE medications as well as the effects of commonly used non-ARV classes of medications such as anticholinergics, opiates, anticonvulsants, and anxiolytics with known neurocognitive effects on cognitive performance in a sample of HIV+ and HIV– women. Although we demonstrated that non-ARV NC-AE medications are more commonly used among HIV+ compared with HIV– women, differential usage of these non-ARV medications does not seem to explain greater cognitive impairment among HIV+ compared with HIV– women. However, greater use of non-ARV medications with anticholinergic properties as well as anxiolytics/anticonvulsants and opioids among HIV+ vs. HIV– women may in part explain some of the greater cognitive impairment among HIV+ compared with HIV– women, particularly on global function, learning, fluency, psychomotor speed, and motor function.

In this study, there were no overall influences of non-ARV NC-AE drugs on cognitive performance in women irrespective of HIV-serostatus. Typically, there are generalized latency effects, as well as sedative effects, of many medications³⁹ that can result from influences on a number of neurotransmitter systems. The accumulated influence of these latency and sedative properties are likely reasons for the lower global cognitive function. However, non-ARV NC-AE burden was not associated with any cognitive outcome across all women.

Of the drug categories further examined, anticholinergic-acting medications may in part explain our

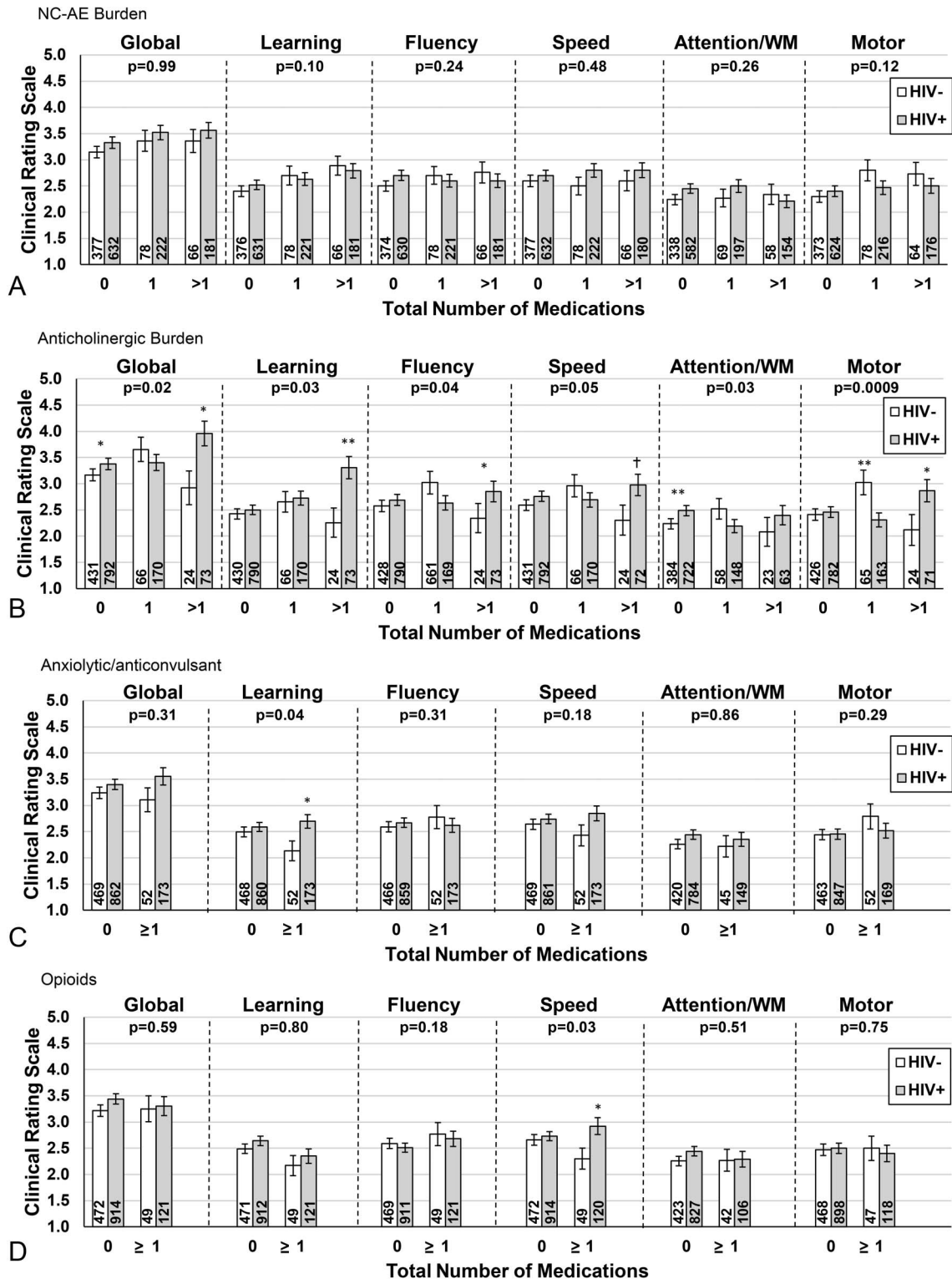


FIGURE 1. Association of (A) NC-AE burden, (B) anticholinergic burden, (C) anxiolytic/anticonvulsant, and (D) opioid use and cognitive performance as a function of HIV-serostatus. Higher clinical rating scale score = worse performance. WM, working memory. *P* is the *P*-value for the interaction between HIV status and total number of medications. Numbers in the bars represent the sample size. NC-AE, non-ARV medication with known general adverse cognitive effects. Executive function and memory were not included in the Figure as there were no interactions between total medications and HIV-serostatus on these 2 domains. ***P* < 0.01; **P* < 0.05; †*P* = 0.05.

TABLE 3. Cognitive Performance by Anticholinergic Burden

Outcome	Obs	Total Anticholinergic Burden			Generalized Linear Model*			
		0	1	>1	Overall	1 vs. 0	>1 vs. 0	>1 vs. 1
		(n = 1223)	(n = 237)	(n = 98)	P	P	P	P
Global NP	1556	3.3 (0.10)	3.4 (0.14)	3.6 (0.20)	0.07	0.21	0.03	0.26
Memory	1553	2.4 (0.08)	2.6 (0.12)	2.6 (0.17)	0.22	0.18	0.17	0.69
Learning	1553	2.4 (0.08)	2.7 (0.12)	3.0 (0.18)	<0.001†	0.03	0.0003	0.06
Attention/WM	1398	2.4 (0.09)	2.2 (0.11)	2.3 (0.17)	0.40	0.21	0.50	0.86
Executive function	1540	2.8 (0.09)	2.8 (0.13)	3.3 (0.20)	0.02	0.69	0.0003	0.02
Speed	1555	2.7 (0.09)	2.8 (0.12)	2.8 (0.17)	0.78	0.63	0.56	0.83
Fluency	1550	2.6 (0.09)	2.7 (0.12)	2.7 (0.16)	0.84	0.57	0.84	0.87
Motor	1531	2.4 (0.09)	2.5 (0.13)	2.7 (0.18)	0.34	0.57	0.15	0.35

Bold, significant at $P < 0.05$.

*Controlling for HIV status and HCV status, site, current employment status, depressive symptoms, heavy drinking, smoking, marijuana, crack, cocaine, and/or heroin use.

†After controlling the false discovery rate using the Benjamini–Hochberg procedure, the overall association remained significant.

M, estimated mean T-score; NP, neuropsychological; WM, working memory.

previous findings of a greater persistence of impairment observed in the learning domain and the gradual decline in motor function over time in HIV+ compared with HIV– women.⁸ Among women taking one anticholinergic-acting drug, HIV– women showed lower performance on motor function than HIV+ women. Detailed medication review in the each group revealed that the percentage of individuals taking antidopaminergic medications (ie, antipsychotics) was higher in HIV– women than in HIV+ women (36% vs. 25%) within women taking one anticholinergic-acting medication. Because motor performance is also robustly influenced by medications with antidopaminergic properties,¹⁶ similar anticholinergic exposure but higher antidopaminergic exposure in HIV– women compared with HIV+ women may in part explain these findings on motor function. In addition, on domains where we have not previously seen an HIV-serostatus difference over time such as fluency and psychomotor speed,⁸ anticholinergic-acting medications may have synergistic effects with HIV to yield performance differences. The general^{15–17} and more specific adverse cognitive effects^{16,18} of medications with anticholinergic properties are thought to result from suppression of cholinergic system by direct blockade of muscarinic acetylcholine receptors in the brain. Specific cognitive effects seem to depend on selectivity of the medication for 1 of the 5 muscarinic receptor subtypes (M1–M5).⁴⁰ Transgenic mouse models lacking the M1 receptor have impairments in learning, memory, and attention. Similarly, in humans, M1-selective antagonism decreases similar cognitive abilities.⁴¹

One possible explanation for medications with anticholinergic properties exacerbating HIV-serostatus differences on cognitive performance globally is that neurotoxic viral proteins may have additive or interactive effects with these medications. Effects on memory may be due to the neurotoxic effects of HIV viral proteins on brain regions important for learning such as the hippocampus.^{42,43} Envelope glycoprotein, gp120, is one example that may be important in HIV-induced cognitive impairment.⁴⁴ It has been suggested that gp120-mediated cognitive

impairment may, in part, result from impairing cholinergic function.⁴⁴ It was also shown that memory impairment induced by gp120 could be reversed by hippocampal cholinergic stimulation in mice.⁴⁴ Another neurotoxic viral protein that may contribute to adverse cognitive outcomes is Tat.⁴⁵ Tat protein selectively enhances acetylcholine release from human and rodent cortical synaptosomes.⁴⁶ The selectivity of Tat on the release of acetylcholine but not other neurotransmitters (ie, dopamine, glutamate, aspartate, GABA, serine, and norepinephrine) suggests that cholinergic neurons may be uniquely sensitive to HIV Tat proteins. These findings, taken together with this present work, suggest that there may be an additive adverse consequence of HIV neurotoxicity and anticholinergic medication burden. Although gp120 and Tat protein may be factors that contribute to these effects, there could be drug–drug interactions (eg, non-ARV drug by non-ARV drug; non-ARV drug by ARV drugs; non-ARV drugs by illicit drug use such as crack/cocaine⁴⁷), as well as pharmacodynamic effects such as anticholinergic-induced inflammation (eg, increases interleukin-1 β expression⁴⁸) that have not been accounted for in this study. Medication-induced inflammation compounded with HIV-induced inflammation⁴⁹ could adversely impact global cognitive performance.

Although HIV+ women reported using more anticonvulsants than HIV– women, unexpectedly, anticonvulsant medications were not negatively associated with cognitive performance in women. Although using these medications was associated with higher impairment among HIV+ vs. HIV– women on learning, these medications were not differentially related to cognitive performance by HIV-serostatus when accounting for uncontrolled viremia among the HIV+ women. Anticonvulsant medications (eg, phenytoin, carbamazepine, valproate, etc.) are typically associated with cognitive side effects.^{50,51} The adverse effects of anticonvulsant medications on cognition are thought to be related to their influence on glutamate transmission in the brain.⁵² Although the extent and type of cognitive adverse effects may vary among anticonvulsants, many induce impairments in attention, memory, and

mental speed.^{50,51} The lack of association in our analyses after accounting for uncontrolled viremia is likely due to the relatively higher utilization of some newer anticonvulsant drugs (ie, lamotrigine and pregabalin) that may not adversely influence cognition to a similar degree as older medications.^{53,54}

HIV+ and HIV– women reported similar rates of opioid use and, in our study sample, we did not identify associations between these drugs and cognitive performance. We did find that opioid use was associated with worse psychomotor speed among HIV+ vs. HIV– women. However, after accounting for uncontrolled viremia, this opioid use was not differentially related to performance on psychomotor speed by HIV-serostatus. These findings were also unexpected because opioid receptors are involved with pain as well as other central neuromodulatory systems including cognition, and are generally considered to have cognitive impairing effects.⁵⁵ Although there is no consensus on differential effects of opioids by cognitive domain, most previous studies have shown that opioid use is associated with decreased psychomotor speed.^{55,56} Opioids are commonly used for the short-term management of pain, often prescribed to take “as needed.” The doses and long- vs. short-term use of opioids in our study sample were not consistently available. Thus, the lack of association observed in our study may be partially related to inconsistent or “as-needed” use, which may be less likely to induce notable cognitive adverse effects than higher-dose or longer-term exposures.

Limitations of this study include the cross-sectional study design. Longitudinal studies are underway to examine the longer-term impact of non-ARV medications with adverse cognitive effects on cognitive performance among HIV+ and HIV– women as they age. In addition, medication dose or duration of use was not available and therefore could not be examined or accounted for in this study. Medication history interviews (eg, names, dose, times per day, route, and reason) and adherence assessments, even when conducted by trained research or medical professionals, are prone to recall bias in the absence of objective pill counts or pharmacy refill data. This may result in observed attenuation of drug-outcome relationships when there is inaccurate reporting of adherence, omission of medications, or reporting medications not actually taken.

In conclusion, HIV+ women seem to take a greater number of non-ARV NC-AE medications as well as non-ARVs with anticholinergic properties as well as anxiolytics and anticonvulsants compared with HIV– women. Despite these differences, non-ARV NC-AE medications seem to have no general effects on global or domain-specific cognitive performance among HIV+ and HIV– women. However, HIV+ women may have increased cognitive vulnerabilities to anticholinergic medications. Potential synergy between anticholinergic medications and HIV may explain some HIV-related cognitive impairments. It may be important clinically to consider anticholinergic medication use in HIV+ women.

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