Degree of Polypharmacy and Cognitive Function in Older Women with HIV

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Abstract

The number of people with HIV (PWH) experiencing age-associated comorbidities including those treated with medications and cognitive impairment is increasing. We examined associations between polypharmacy and cognition in older women with HIV (WWH) given their vulnerability to this comorbidity. Cross-sectional analysis capitalizing on Women's Interagency HIV Study data collected between 2014 and 2017. WWH meeting the following criteria were analyzed: age ≥50 years; availability of self-reported non-antiretroviral therapy (ART) medications data; and neuropsychological data. The number of non-ART medications used regularly in the prior 6 months was summed. Polypharmacy was categorized as none/low (0–4), moderate (5–9), or severe (≥10). Multivariable linear regression analyses examined polypharmacy-cognition (T-score) associations in the total sample and among virally suppressed (VS; < 20 copies/mL)-WWH after covariate adjustment for enrollment site, income, depressive symptoms, substance use (smoking, heavy alcohol, marijuana, crack, cocaine, and/or heroin), the Veterans Aging Cohort Study index (indicators of HIV disease and organ system function, hepatitis C virus serostatus), ART use, nadir CD4 count, and specific ART drugs (efavirenz, integrase inhibitors). We included 637 women (median age = 55 years; 72% Black). Ninety-four percent reported ART use in the past 6 months and 75% had HIV RNA <20 copies/mL. Comorbidity prevalence was high (61% hypertension; 26% diabetes). Moderate and severe polypharmacy in WWH were 34% and 24%. In WWH, severe polypharmacy was associated with poorer executive function ($p = .007$) and processing speed ($p = .01$). The same pattern of findings remained among VS-WWH. Moderate polypharmacy was not associated with cognition. Moderate and severe polypharmacy were common and associated with poorer executive function and processing speed in WWH. Severe polypharmacy may be a major contributor to the persistence of domain-specific cognitive complications in older WWH above and beyond the conditions that these medications are used to treat.

Keywords: polypharmacy, cognition, HIV, women

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Introduction

Access and adherence to modern antiretroviral therapy (ART) has led people with HIV (PWH) to achieve life expectancies similar to those without HIV.[1] Consequently, ~50% of PWH in the United States are 50 years of age and older; this number is projected to exceed 70% by the year 2030.[2,3] The ''graying of the HIV epidemic'' has led to emergence of new public health and clinical care challenges associated with survival to older ages. One of the primary challenges has been addressing a marked increase in age-associated comorbidities and conditions in PWH 50 years of age and older, including multimorbidity,[4] polypharmacy, and cognitive and functional impairment.[5,6] Notably, the proportion of PWH with multimorbidity, defined as two or more comorbidities, has nearly tripled since 2000.[7] Accordingly, use of multiple medications is increasingly common among aging PWH,[8] particularly among those with multimorbidity.

Polypharmacy, often defined as use of five or more medications,[9] is associated with many adverse conditions in the general aging population, including mortality, falls, global cognitive impairment, and increased hospitalizations, length of stay, and number of readmissions.[10–14] In the geriatric literature, polypharmacy is a strong predictor of serious adverse drug events and drug–drug interactions. Moreover, increasing numbers of medications are associated with proportionally greater risks of harm,[15,16] leading some to further characterize use of ≥10 medications as ''excessive,'' ''major,'' or ''severe'' polypharmacy or ''hyperpolypharmacy''.[15,17–20]

Older individuals are at particularly high risk for adverse medication effects due to age-associated metabolic changes such as decreased renal and hepatic function and altered body composition, including increased body fat and loss of lean body mass.[21–23] These effects have even greater significance for older PWH, who are more likely to suffer from age-associated changes than people without HIV.[24] At present, little is known about the effects of polypharmacy on comorbidities in PWH ≥50 years of age.[25,26]

Among PWH, polypharmacy is highly prevalent (up to 96% among older PWH[27]) and often occurs prematurely, with greater lifetime exposure to multiple mediations. Among PWH and persons without HIV, a dose–response relationship was demonstrated between non-ART polypharmacy and adverse outcomes such as hospitalization and mortality with no interaction by HIV-serostatus.[28] However, few studies evaluating polypharmacy and its consequences including cognitive impairment in PWH focus on women. In the general population, women appear to be at higher risk for adverse drug-related events compared with men, and may require lower medication dosing due to pharmacokinetic and pharmacodynamic sex differences leading to lower clearance rates.[29–31] These sex differences may assume even greater importance as women age.

Cognitive impairment is a known adverse consequence of polypharmacy in the general aging population; yet relatively little is known about the impact of polypharmacy on cognition in PWH, and even less in older WWH. The few studies conducted to date have been in samples of mostly men with HIV, and indicate that polypharmacy is associated with lower global cognitive function[32,33] as well as with lower learning, memory, and verbal fluency.[33]

Thus, the primary aim of this analysis was to examine the potential cognitive burden of polypharmacy among older WWH (≥ 50 years of age). Our general hypothesis was that polypharmacy would have broad negative associations with cognitive performance above and beyond medical and psychiatric comorbidities. We further sought to determine whether the pattern of associations would parallel previous findings in older people (i.e., associate only with learning, memory, and executive function)[34,35] or findings seen in WWH across a wide age range (i.e., associate only with learning, fluency, speed, attention/working memory, and motor function).[36]

Methods

Participants

All participants were enrolled in the Women's Interagency HIV Study (WIHS), a prospective multisite cohort study of WWH and HIV-negative women (women without HIV).[37–39] In brief, study enrollment initially occurred at six U.S. sites (Brooklyn, NY; Bronx, NY; Chicago, IL; Washington DC; Los Angeles, CA; and San Francisco, CA) in three waves: 1994–95, 2001–02, and 2011–12. In 2013, the WIHS closed its Los Angeles site and added four southern U.S. sites: Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS. WIHS methods and cohort characteristics have been described previously.[37–39]

Participants completed semiannual visits, which included physical examinations, biospecimen collection, and a face-to-face interview for the collection of clinical, behavioral, and sociodemographic characteristics. Neuropsychological (NP) assessments were integrated into WIHS visits and collected every 2 years beginning in 2009 for the initial six study sites and beginning in 2013 for the southern sites.[40] Participants included in this analysis were WWH ≥50 years of age, who had available data on self-reported medication between 2014 and 2017, and completed one NP assessment during the 2014 and 2017 time period when polypharmacy was computed.

Measures

Medication assessments. At each WIHS visit, participants were asked to recall non-ART medications taken in the prior 6 months. These medications were summarized only for data collected between 2014 and 2017. Polypharmacy, the number of non-ART medications used regularly in the past 6 months was quantified and categorized as none/low (0–4 medications), moderate (5–9 medications), or severe (≥10 medications). In addition, non-ART medication data were reviewed with specific drugs categorized as neurocognitive acting effects (NC-AE) if there were known adverse cognitive effects.[36,41] NC-AE medications were quantified as none, one, or more than one.

These medications were also categorized (any vs. none) into specific drug classes (opioids, anticonvulsants, anticholinergics, antianxiety, antihistamine, gastrointestinal agents, beta-blockers, antidepressants, antipsychotics, and muscle relaxants). Finally, as in our previous study,[36,41] medications reported by participants were categorized by whether they had anticholinergic properties according to the Anticholinergic Risk Scale.[42] The purposes of this additional drug

categorization was to better understand the drug classes that participants were most commonly prescribed as well as to be used in secondary analyses when polypharmacy-cognition associations were present in WWH.

Cognitive function

Global and domain-specific NP cognitive function was assessed every 2 years. We chose the last NP assessment that occurred between 2014 and 2017 so it could be matched in time with the timeframe in which polypharmacy was determined. The comprehensive NP battery included the following: Hopkins Verbal Learning Test-Revised (HVLT-R), 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 the following seven domains: learning (total learning across HVLR-T trials), memory (delayed free recall on HVLT-R), attention/working memory (total correct on LNS control and experimental conditions), processing speed (total correct on SDMT, 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). All timed outcomes were log transformed to normalize the data distributions and reverse scored so that higher scores always reflected better performance.

As in our previous analyses,[40,43] demographically adjusted T-scores (M [mean] = 50; SD [standard deviation] = 10) were created for each test and these T-scores were then used to create domain-specific T-scores and a global T-score. Domains measured by more than a single test were derived by averaging the T-scores. If only one test in a domain was completed, the T-score for that test outcome was used. A global NP score was also derived for individuals with T-scores on at least four of the seven cognitive domains by averaging the T-scores across domains. Impairment on a domain or globally was defined using a T-score cutoff of 1 standard deviation ($T \leq 40$).

Covariables

The following variables were identified as confounders (related to polypharmacy and cognition but does not exist in the causal pathway): depressive symptoms assessed using the Center for Epidemiologic Studies Depression Scale (CES-D, score ≥16 indicating depressive symptoms),[44] smoking (current, former, and never), heavy alcohol use (>7 drinks per week[45]), recent marijuana use (yes vs. no), recent crack, cocaine, and/or heroin use (yes vs. no), and the Veterans Aging Cohort Study (VACS) index, which combines routinely monitored indicators of HIV disease (age, current CD4 count, and HIV viral load) and organ system function indicators (hemoglobin, Fibrosis-4, estimated glomerular filtration rate), as well as hepatitis C virus serostatus.[46,47]

HIV-specific variables included as confounders were nadir CD4 count (continuous), ART use (yes vs. no), and ART medications often associated with cognition, specifically efavirenz and integrase inhibitors dolutegravir, elvitegravir, and raltegravir.[48–50] Each ART medication was treated as a separate binary variable.

Statistical analyses

Univariable and multivariable linear and logistic regression analyses were used to examine the association between degree of polypharmacy (moderate vs. none/low and severe vs. none/low) and cognitive burden in the total sample and among virally suppressed (VS)-WWH (HIV RNA <20 cp/mL). Separate models were created for each cognitive domain and for global NP function. Linear regression analyses were used when absolute T-score was the outcome, whereas logistic regression analyses were used when impairment was the outcome.

All multivariable models adjusted for study site, annual household income, depressive symptoms, smoking, heavy alcohol use, current self-reported marijuana and crack, cocaine, and/or heroin use, the VACS index, nadir CD4 count, ART use, and efavirenz, dolutegravir, elvitegravir, and raltegravir use. Based on the pattern of polypharmacy-cognition associations, secondary multivariable linear regression analyses were conducted to determine whether the associations were strengthened when restricting the medication count to NC-AE medications including those with anticholinergic-acting properties. All statistical analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC). Results were considered significant at $p < .05$ (two-sided).

Results

A total of 637 women were included in the analysis. Table 1 includes sociodemographic, behavioral, and clinical characteristics of the sample. Among the total sample of WWH, 93% reported ART use and 75% had an undetectable HIV viral load. The overall prevalence of comorbidities was as follows: 61% with hypertension, 32% with depressive symptoms, and 26% with type 2 diabetes.

The prevalence of moderate and severe polypharmacy in the total sample of WWH was 34.5% and 23.9% and in VS-WWH 35.8% and 24.1%, respectively (Table 2). Approximately half of WWH (49%) were prescribed NC-AE medications with the most common being antidepressants (25%) followed by anxiolytics (13%) and opioids (12%). In addition, 31% of WWH were on NC-AE medications with anticholinergic properties. The mean T-scores in the sample were in the average range (means ~ 50).

Cognitive burden of polypharmacy

Overall, degree of polypharmacy was associated with domain-specific cognitive performance in WWH (Table 3). Specifically, in the total sample of WWH, severe but not moderate polypharmacy was associated with poorer performance on executive function, processing speed, and motor function in univariable analyses (p's < 0.05). However, in multivariable models in all WWH, severe but not moderate polypharmacy was only associated with poorer performance on executive function (B [unstandardized beta coefficient] = −2.95, SE [standard error] = 1.08, $p = .00\ 7$) and processing speed ($B = -2.46$, SE = 0.99, $p = .01$) (Fig. 1 left). The same pattern of associations were seen among VS-WWH in both univariable and multivariable models (Table 3 and Fig. 1 right).

When examining cognitive impairment in the total sample of WWH in multivariable models, severe polypharmacy,

Table 1. Demographic, Behavioral, Clinical, and Cognitive Characteristics in the Total Sample of Women with HIV and Among Virally Suppressed Women with HIV Only

Characteristic, N *(%)*	*Total sample* (N = *637*)	*VS* (N = *481*)
Age, years, median (IQR)	55 (52, 59)	55 (52, 58)
Education level high school or greater	444 (70)	336 (70)
Annual household income ≤$12,000/year	341 (54)	248 (52)
WIHS site		
Bronx/Manhattan	94 (15)	69 (14)
Brooklyn	93 (15)	67 (14)
Washington, DC	86 (13)	62 (13)
San Francisco	101 (16)	69 (14)
Chicago	85 (13)	76 (16)
Southern sites	178 (28)	138 (29)
Race/ethnicity		
White, non-Hispanic	108 (17)	86 (18)
Black, non-Hispanic	457 (72)	344 (72)
Hispanic/Other	69 (11)	49 (10)
Current smoker	225 (35)	178 (37)
Recent cocaine, crack, or heroin use	53 (8)	30 (6)
Recent marijuana use	103 (16)	77 (16)
Recent heavy alcohol use (>7 drinks/week)	56 (9)	33 (7)
Postmenopausal status[a]	583 (91)	434 (90)
Comorbidities		
Hepatitis C Virus infection[b]	191 (30)	135 (28)
Diabetes mellitus	168 (26)	134 (28)
Hypertension	388 (61)	293 (61)
Renal dysfunction (eGFR <60)	117 (18)	83 (17)
Depressive symptoms (CES-D ≥16)	199 (32)	140 (30)
Obesity (body mass index ≥30 kg/m^2)	273 (43)	220 (46)
VACS index, median (IQR)	33 (22, 40)	28 (22, 38)
HIV disease-related characteristics		
History of AIDS	246 (39)	171 (36)
Current CD4 cell count (cells/μL), median (IQR)	645 (429, 850)	664 (483, 880)
Nadir CD4 cell count (cells/μL), median (IQR)	258 (133, 442)	277 (158, 472)
Undetectable HIV RNA viral load (<20 copies/mL)	481 (75)	481 (100)
Current ART use[c]	602 (94)	465 (97)

[a]Postmenopausal status is defined by self-reported amenorrhea at two consecutive visits for women aged ≥45 years and no resumption of menses.

Recent is defined as in the past 6 months.

[b]Defined as antibody positive, RNA unknown and active infection, RNA+.

[c]Defined as therapy used since last visit (~ use in the past 6 months).

ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; CES-D, Center for Epidemiologic Studies Depression Scale; VS, virally suppressed.

Table 2. Non-Antiretroviral Therapy Medication Use and Neuropsychological Test Performance in the Total Sample of Women with HIV and in Virally Suppressed Women with HIV Only

N *(%)*	*Total sample* (N = *637*)	*VS* (N = *481*)
Polypharmacy (number of non-ART medications)		
None/low (0–4)	265 (42)	193 (40)
Moderate (5–9)	220 (34)	172 (36)
Severe (≥10)	152 (24)	116 (24)
Neurocognitively active non-ART medications	312 (49)	235 (49)
Opioids	76 (12)	54 (11)
Anticonvulsants	42 (7)	34 (7)
Anticholinergics	5 (1)	3 (1)
Antianxiety	81 (13)	62 (13)
Antihistamine	65 (10)	47 (10)
Gastrointestinal agents	28 (4)	21 (4)
Beta-blockers	20 (3)	16 (3)
Antidepressants	157 (25)	121 (25)
Antipsychotics	43 (7)	30 (6)
Muscle relaxants	36 (6)	22 (5)
Anticholinergic-acting non-ART medications	197 (31)	142 (29)
NP test performance (T-score), M (SD)		
Executive function	48.5 (10.3)	48.9 (10.4)
Processing speed	49.0 (9.6)	49.4 (9.5)
Attention/working memory	48.5 (9.7)	48.7 (9.8)
Learning	50.1 (9.9)	50.5 (9.7)
Memory	49.6 (10.2)	49.4 (10.3)
Motor	49.6 (10.8)	50.2 (10.6)
Fluency	49.3 (9.5)	49.7 (9.9)
Global NP function	49.2 (6.4)	49.6 (6.4)
NP impairment		
Executive function	121 (19)	90 (19)
Processing speed	96 (15)	68 (14)
Attention/working memory	119 (19)	87 (18)
Learning	94 (15)	67 (14)
Memory	108 (17)	85 (18)
Motor	103 (16)	72 (15)
Fluency	91 (14)	67 (14)
Global NP function	57 (9)	41 (9)

M, mean; SD, standard deviation.

compared with none/low medication use, was associated with a greater odds of having impaired executive function (adjusted odds ratio [AOR] = 1.71, 95% CI [confidence interval]: 0.99–2.94, $p = .05$] and processing speed (AOR = 1.98, 95% CI: 1.08–3.63, $p = .02$]. Among VS-WWH, severe polypharmacy, compared with none/low medication use, was associated with a greater odds of processing speed impairment (AOR = 2.10, 95% CI: 0.99–4.43, $p = .05$); executive function (AOR = 1.47, 95% CI: 0.77–2.81, $p = .24$).

When restricting non-ART medication count to NC-AE medications, in multivariable models women taking more than one medication but not one medication (vs. none) was associated with poorer performance on executive function ($B = -3.21$, SE = 1.06, $p = .002$) and processing speed ($B = -3.24$, SE = 0.97, $p < .001$) in the total sample of WWH (Table 4). The same pattern of associations was seen among VS-WWH. When specifically examining NC-AE medications

Table 3. Independent Univariable and Multivariable Linear Regression Associations Between Polypharmacy (Reference = 0–4 Non-Antiretroviral Therapy Medications) and Cognitive Performance T-Scores in the Total Sample of Women with HIV and Among Virally Suppressed Women with HIV Only

	Moderate polypharmacy (5–9 medications)				*Severe polypharmacy (≥10 medications)*			
	Total sample of WWH		*VS-WWH*		*Total sample of WWH*		*VS-WWH*	
Domain	*B (SE)*	p-*value*	*B (SE)*	p-*value*	*B (SE)*	p-*value*	*B (SE)*	p-*value*
Executive function								
Univariable	−1.3 (0.9)	.17	−1.5 (1.1)	.16	**−3.1 (1.0)**	**.003**	**−3.2 (1.2)**	**.008**
Multivariable	−0.9 (1.0)	.34	−0.9 (1.1)	.45	**−2.9 (1.1)**	**.007**	**−2.9 (1.3)**	**.02**
Processing speed								
Univariable	−0.3 (0.9)	.72	−1.1 (1.0)	.25	**−3.0 (1.0)**	**.002**	**−3.7 (1.1)**	**.001**
Multivariable	0.1 (0.9)	.92	−0.6 (1.0)	.56	**−2.4 (1.0)**	**.01**	**−2.7 (1.2)**	**.02**
Attention/working memory								
Univariable	−0.6 (0.9)	.52	−1.0 (1.0)	.34	0.2 (1.0)	.86	0.2 (1.1)	.77
Multivariable	−0.7 (0.9)	.47	−0.8 (1.1)	.44	0.1 (1.0)	.92	−0.1 (1.2)	.94
Learning								
Univariable	−1.1 (0.9)	.21	−0.4 (1.0)	.70	0.5 (1.0)	.64	1.4 (1.1)	.22
Multivariable	−1.1 (0.9)	.23	−0.1 (1.1)	.90	0.4 (1.0)	.70	1.0 (1.2)	.40
Memory								
Univariable	0.4 (0.3)	.69	0.8 (1.1)	.47	1.9 (1.0)	.07	1.9 (1.2)	.11
Multivariable	0.3 (0.9)	.72	0.7 (1.1)	.51	1.8 (1.1)	.10	1.4 (1.3)	.27
Motor								
Univariable	−0.4 (1.0)	.66	0.2 (1.1)	.88	**−2.5 (1.1)**	**.02**	**−2.6 (1.2)**	**.03**
Multivariable	0.2 (1.0)	.87	0.9 (1.1)	.41	−1.7 (1.1)	.13	−1.6 (1.3)	.23
Verbal fluency								
Univariable	−0.1 (0.9)	.89	0.1 (1.0)	.93	−1.4 (1.0)	.13	−1.1 (1.1)	.33
Multivariable	0.2 (0.9)	.79	0.7 (1.1)	.52	−1.7 (1.0)	.08	−1.4 (1.2)	.26
Global NP function								
Univariable	−0.5 (0.6)	.39	−0.4 (0.7)	.53	−1.1 (0.6)	.09	−1.0 (0.7)	.19
Multivariable	−0.3 (0.6)	.64	−0.0 (0.7)	.99	−0.9 (0.6)	.15	−0.9 (0.8)	.25

Multivariable linear models were adjusted for WIHS study city, income, depression, smoking, heavy alcohol use, recent marijuana use, recent crack, cocaine, and/or heroin use, the VACS index score, nadir CD4 count, ART use, and ART medications often associated with cognition—efavirenz and the following integrase inhibitors-dolutegravir, elvitegravir, and raltegravir. Findings significant at $p < .05$ are bolded.

B, unstandardized beta coefficient; NP, neuropsychological; SE, standard error; WWH, women with HIV.

with anticholinergic properties, these medications were associated poorer performance on executive function ($B = -2.26$, SE = 0.91, $p = .01$) and processing speed ($B = -2.07$, SE = 0.84, $p = .01$) in the total sample of WWH. In VS-WWH, NC-AE medications with anticholinergic properties were only associated with poorer performance on executive function ($B = -2.39$, SE = 1.09, $p = .03$).

Of the most commonly used NC-AE medications, antidepressants and anxiolytics but not opioids were associated with these cognitive domains in multivariable models (Table 4). Specifically, antidepressants were associated with poorer executive function in the total sample of WWH ($B = -2.29$, SE = 0.08, $p = .02$); similar trend in VS-WWH ($B = -2.09$, SE = 1.17, $p = .07$). Similarly, anxiolytics were associated with poorer executive function in the total sample of WWH ($B = -2.99$, SE = 1.29, $p = .02$) and among VS-WWH ($B = -3.48$, SE = 1.51, $p = .02$). Antidepressants and anxiolytics were not associated with processing speed.

Discussion

The overall prevalence of polypharmacy (≥5 medications) was high (59%) in this cohort of predominantly low-income WWH of color aged ≥50 years; however, only severe, not moderate, polypharmacy was associated with cognitive function after covariate adjustment, which included the VACS index. Among WWH, severe polypharmacy was associated with poorer executive function and processing speed. The same pattern of associations was present among VS-WWH.

The key finding in this study was that severe, but not moderate, polypharmacy was associated with poorer cognitive function in WWH. This finding is consistent with some,[51,52] but not all,[53,54] studies examining the degree of polypharmacy and cognition. Of note, whereas moderate (18.1%) and severe (4.7%) polypharmacy were related to poorer cognition in Rawle *et al.*,[55] severe polypharmacy was more strongly related to poorer cognition than was moderate polypharmacy. Differences in the pattern of associations across studies could be due to differences in characteristics of the study population (e.g., age, race/ethnicity, and sex), proportion of individuals using NC-AE medications including those with anticholinergic properties, cognitive status (e.g., cognitively intact, mild, dementia), and/or in the assessments used to measure cognitive function.

Although WWH in the present analyses were aged ≥50 years, 50% of the participants were between 52 and 59 years

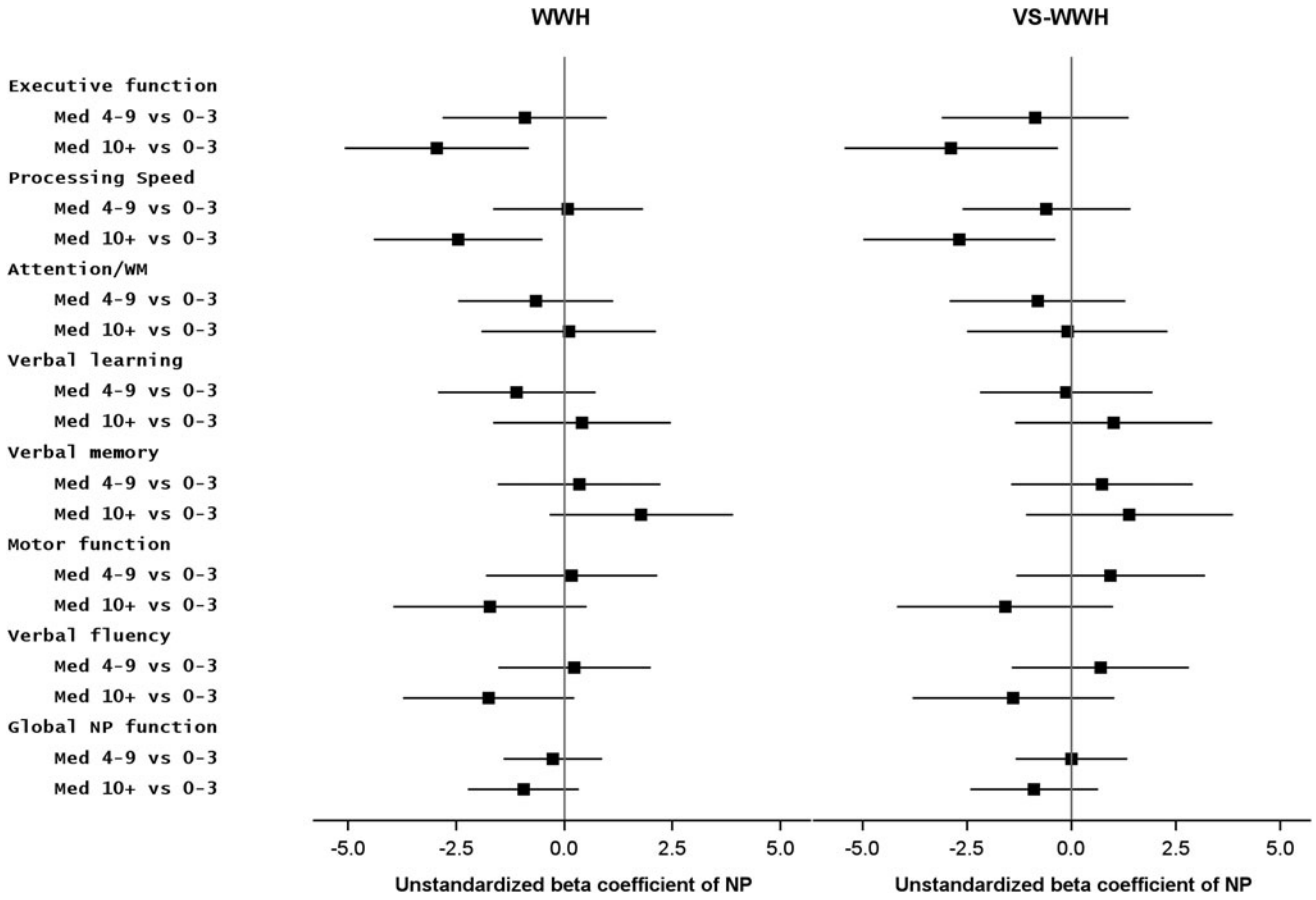

FIG. 1. Multivariable associations of polypharmacy and severe polypharmacy with cognitive performance in the total sample of older women with HIV (WWH; *left*) and among older VS-WWH only (*right*). VS, virally suppressed; WWH, women with HIV.

of age, which is younger than other studies in which the mean is often ≥65 years of age.[53,55] One possible explanation is that a greater degree of polypharmacy is needed to see any potential adverse effects on cognition among women in their 50s compared with their 60s. In addition, our study used a comprehensive NP test battery to assess global and domain-specific cognitive function, whereas others[32,33] only measured cognition using a minimal number of standard NP tests or simply a cognitive screener such as the Mini-Mental Status Examination (MMSE).

Severe polypharmacy was related to specific cognitive domains (vs. global NP function) in WWH. In particular,

TABLE 4. MULTIVARIABLE LINEAR REGRESSION ASSOCIATIONS BETWEEN NON-ANTIRETROVIRAL THERAPY MEDICATIONS WITH NEUROCOGNITIVE ACTING EFFECTS AND COGNITIVE PERFORMANCE T-SCORES IN THE TOTAL SAMPLE OF WOMEN WITH HIV AND AMONG VIRALLY SUPPRESSED WOMEN WITH HIV ONLY

	Executive function				*Processing speed*			
	Total sample		*VS-WWH*		*Total sample*		*VS-WWH*	
	B (SE)	p-*value*	*B (SE)*	p-*value*	*B (SE)*	p-*value*	*B (SE)*	p-*value*
NC-AE								
1 (vs. none)	−1.3 (1.0)	.21	−1.5 (1.2)	.23	−1.2 (0.9)	.19	−1.3 (1.1)	.23
1+ (vs. none)	**−3.2 (1.1)**	**.002**	**−3.4 (1.2)**	**.007**	**−3.2 (1.0)**	**<.001**	**−3.0 (1.1)**	**.008**
With anticholinergic properties								
Any (vs. none)	**−2.3 (0.9)**	**.01**	**−2.4 (1.1)**	**.03**	**−2.1 (0.8)**	**.01**	−1.5 (0.9)	.11
Antidepressants (vs. none)	**−2.3 (1.0)**	**.02**	−2.1 (1.1)	.07	−1.7 (0.9)	.06	−1.1 (1.0)	.30
Anxiolytics (vs. none)	**−3.0 (1.3)**	**.02**	**−3.5 (1.5)**	**.02**	**−1.4 (1.2)**	.24	−1.2 (1.4)	.38
Opioids (vs. none)	−0.3 (1.4)	.80	0.4 (1.6)	.79	1.1 (1.2)	.38	1.4 (1.4)	.32

Multivariable linear models were adjusted for WIHS study city, income, depression, smoking, heavy alcohol use, recent marijuana use, recent crack, cocaine, and/or heroin use, the VACS index score, nadir CD4 count, ART use, and ART medications often associated with cognition—efavirenz and the following integrase inhibitors-dolutegravir, elvitegravir, and raltegravir. Findings significant at $p < .05$ are bolded.

B, unstandardized beta coefficient; NC-AE, neurocognitive acting effects.

severe polypharmacy was associated with poorer executive function and processing speed. These findings are in contrast to a recent cross-sectional analysis of primarily white men with HIV in which polypharmacy was found to relate to learning, memory, and verbal fluency as well as global cognitive function.[33] Although differences in sociodemographics may in part contribute to the observed differences between studies, the specific medications are associated with cognition may also differ between studies. Although this study was focused on polypharmacy, we did find that the associations were strengthened when restricting to NC-AE medications, including those with anticholinergic properties.

In addition, antidepressants and anxiolytics, two of the most commonly prescribed NC-AE medications, were also associated with executive function. These findings may be specific to older WWH, as in our previous WIHS study, which included WWH ranging from 25 to 87 years of age (mean = 46.99, SD = 8.76), we did not find NC-AE medications or anxiolytics to relate to executive function or processing speed.[36] Antidepressants were not examined and opioids were not associated with these cognitive domains, which parallels our findings in older WWH. This is in contrast to a cross-sectional study of white men with HIV whereby anxiolytics, antipsychotics, opioids, and antimicrobials were the most common medication classes relating to poorer cognition.[33]

Despite the ability to examine the degree of polypharmacy on cognition in a large sample of WWH and women without HIV aged ≥50 years, there were a number of limitations. The primary limitations were that the study was cross-sectional, precluding any inferences of causality, and that non-ART medication data was self-reported. However, studies have demonstrated high correlations between self-reported measures of medication with pharmacy prescription records in low-income older adults.[56] In addition, it is difficult to disentangle the effect of medications on cognition from the diseases that those medications are used to treat. Although we adjusted for a number of factors including the VACS index, adjustment may only partially mitigate this potential bias.

Conclusions

In sum, moderate and severe polypharmacy were common in this cohort of aging WWH and were associated with poorer executive function and processing speed. Thus, as PWH age, it will become increasingly important to protect their cognitive function potentially through careful monitoring of their non-ART medications. Further research is warranted to better understand the longitudinal effects of polypharmacy on cognition above and beyond the comorbidities they are used to treat in aging WWH as well as potential medication interactions in these populations.

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Authors' Contributions

Conceptualization by L.H.R; data curation by Q.S., D.R.H, and B.T.; formal analysis by Q.S. and D.R.H; writing—original draft by L.H.R., A.N., and A.S.; writing—review and editing by all authors.

Author Disclosure Statement

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