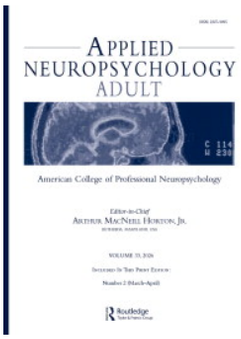

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Does cognitive intra-individual variability predict change in everyday functioning performance in women with and without HIV in the Women's Interagency HIV Study?

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ABSTRACT

This study examined the association between cognitive intra-individual variability (IIV), a non-mean-based indicator of underlying neuropathology, and self-reported everyday functioning of 1,086 women with HIV (WWH) and 494 socio-demographically similar women without HIV (WWoH). Objective cognitive performance across seven domains and the self-rated Lawton & Brody scale of Instrumental Activities of Daily Living (IADL) were assessed among participants of the Women's Interagency HIV Study. Two types of cognitive IIV were calculated by taking the standard deviation across seven cognitive domains to calculate dispersion: 1) intra-individual standard deviation (denoted as *sd*IIV) and 2) coefficient of variation (denoted as *cov*IIV). To account for the longitudinal nature of the data, generalized linear mixed effect models were conducted to examine associations between the dispersion coefficient of cognitive IIV (predictor (*sd*IIV and *cov*IV)) and functional outcomes (item level scores). Models were conducted in the overall sample (WWH + WWoH), WWH only, virally suppressed (VS)-WWH, and WWoH. *sd*IIV and *cov*IIV were not associated with any of the IADL items among WWoH but were for WWH and VS-WWH. In WWH *cov*IIV was predictive of poorer functional performance on twice as many IADL items (10 items—money and bills, buying groceries, getting where you need to go, using the phone, home repairs, dressing, laundry, taking/keeping track of medications, taking care of children, work) than *sd*IIV (5 items). In this study, cognitive IIV predicts functional impairment and different calculations of IIV produce differential predictive value, especially for WWH.

KEYWORDS

Activities of daily living; cognition; dispersion; HIV; instrumental activities of daily living

Introduction

A meta-analysis of 18 neurocognitive HIV studies showed that 44.9% of people with HIV (PWH) have HIV-Associated Neurocognitive Disorder (HAND) (Wei et al., 2020), although the diagnostic criteria for HAND are currently under re-consideration (Cysique et al., 2024). This is further characterized by varying levels of HAND severity with 26.2% of PWH characterized with Asymptomatic Neurocognitive Impairment, 8.5% with Mild Neurocognitive Disorders, and 2.1% with HIV-Associated Dementia (Wei et al., 2020). Fortunately, with advancements in antiretroviral therapy (ART), more severe forms of cognitive impairments (i.e., dementia) have decreased, but milder forms persist (Heaton

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et al., 2015). Among various subgroups, women with HIV (WWH) are particularly vulnerable to cognitive impairment (Rubin et al., 2019). Well-powered studies provide robust evidence that WWH exhibit greater deficits globally, especially in learning and memory domains, followed by processing speed and motor function when compared to women without HIV (WWoH) (Maki et al., 2018; Sundermann et al., 2018). As the population of PWH globally continues to reach older ages, concerns mount about the worsening of existing HIV-related cognitive impairments and their exacerbations in already vulnerable subgroups such as WWH impairing their everyday functioning (Goodkin et al., 2017; Thames, Becker, et al., 2011; Thames, Kim, et al., 2011).

PWH and their support system (i.e., family, friends) may experience psychological distress due to impairments in IADLs (Johs et al., 2019). These impairments can have serious emotional, physical, financial, and even cognitive consequences on caregivers (Lee et al., 2024; Mitchell et al., 2022; Vance, Lee, et al., 2022). With advancing age and cognitive decline, the severity and prevalence of IADLs increase (Marquine et al., 2018; Morgan, Iudicello, et al., 2012; Vance et al., 2013). In a sample of 277 PWH with HAND, IADL impairments were observed in employment, planning social activities, housekeeping, and understanding TV programs and reading materials (Obermeit et al., 2017).

While mean-based cognitive performance measures (e.g., Global *T*-scores) have been well studied in their association with everyday functioning, cognitive intra-individual variability (IIV) represents a less examined approach that may provide unique insights into IADL performance that are not evident in mean-based cognitive performance measures (Ettenhofer et al., 2010; Levine et al., 2008; Morgan, Woods, Grant, et al., 2012; Vance, Del Bene, et al., 2022). Cognitive IIV refers to the variation observed in cognitive performance when the same cognitive test is taken multiple times (referred to as inconsistency) or when different cognitive tests are administered (referred to as dispersion). Higher cognitive IIV has been suggested to indicate poor coordination of cognitive abilities, potentially indicating subtle cognitive decline. This variability in cognitive performance is associated with cognitive impairment and cognitive decline across various clinical populations including advanced age (Hilborn et al., 2009), traumatic brain injury (Hill et al., 2013), breast cancer survivors (Vance et al., 2023), and Parkinson's disease (Davis et al., 2023). A systematic review focusing on 13 cognitive IIV neuroHIV studies concluded that cognitive IIV shows promise as an approach to detect subtle cognitive impairments that may not be captured by traditional mean-based cognitive reporting (Vance, Del Bene, et al., 2022). In PWH, greater cognitive IIV has been associated with the following: 1) poorer cognitive performance and decline over time (Anderson et al., 2018), 2) cortical brain atrophy involving both gray and white matter (Hines et al., 2016; Jones et al., 2018), 3) increased mortality risk (Anderson et al., 2018), and 4) difficulties in everyday functioning (Morgan, Woods, Grant, et al., 2012) and medication adherence (Thaler et al., 2015).

Conceptually, everyday IADL performance does not rely on any single cognitive ability (e.g., speed of processing) but instead relies on a complex interplay between all cognitive abilities. For example, in cooking a meal, one must use executive functioning to plan what to prepare, long-term memory to recall the steps to prepare a dish, psychomotor skill in mixing and assembling ingredients, working memory, and attention to keep track of how much time remains for each dish to be heated without burning it, and visuospatial skills to plate the food. Likewise, the coordination of other cognitive domains is needed in other IADLs such as buying groceries, home repairs, managing money and bills, and so forth. While studies have shown that some cognitive domains may be more salient to certain IADLs (i.e., higher levels of visual speed of processing are associated with better performance in safe automobile driving; McManus et al., 2016), the coordination of these cognitive domains to perform everyday activities seems essential. As such, a metric that may serve as a proxy for this coordination is cognitive IIV (Morgan, Iudicello, et al., 2012; Morgan, Woods, Grant, et al., 2012; Vance, Del Bene, et al., 2022). Higher cognitive IIV suggests that cognitive domains may not function optimally together (Morgan, Iudicello, et al., 2012; Vance, Del Bene, et al., 2022). Thus, higher cognitive IIV may also serve as an indicator of poorer everyday functioning. In fact, the degree to which cognitive IIV is associated with an IADL task may suggest the degree to which everyday functioning relies more on a balance of cognitive abilities. This premise presents a largely unexplored area in applied neuropsychology in which to explore the impact of such a lack of cognitive coordination on everyday functioning.

Cognitive IIV has been shown to be related to everyday functioning tasks. In the aging literature, older adults with greater cognitive IIV have been observed to experience problems in everyday functioning task such as: 1) driving performance (Bunce et al., 2012); 2) falls (Graveson et al., 2016); 3) the ability to multitask between activities (Fellows & Schmitter-Edgecombe, 2015); and 4) early functional declines in adults without dementia (Bangen et al., 2019). A few examples in other clinical samples are noted as well: 1) in adults with hepatitis C, greater cognitive IIV was associated with poorer employment status (Morgan, Woods, Rooney, et al., 2012); 2) in breast cancer survivors, greater cognitive IIV was associated with poor language over time (Yao et al., 2017); and 3) in adults with Parkinson's disease, greater cognitive IIV predicts functional declines as measured by the Functional Ability Questionnaire (Davis et al., 2023). Interestingly, cognitive IIV was shown to be related to poorer flight maneuvers in a flight simulator of middle-aged and older pilots (Kennedy et al., 2013). As alluded to earlier regarding HIV, a few studies have found that higher levels of cognitive IIV are related to poorer medication adherence and everyday functioning in PWH. In a sample of mostly (90%) men with HIV, Morgan et al. (2012) found greater cognitive IIV was a significant predictor of greater dependence in basic and instrumental activities of daily functioning as well as medication adherence, even when controlling for other predictors of functional status (i.e., age, indices of disease status, profile of mood states). Likewise, in a sample of PWH, Mustafa et al. (2023) found that higher cognitive IIV predicted poor prospective memory (i.e., spontaneously remembering to do something that needs to be done), a

cognitive ability that is vitally important for performing everyday functioning tasks.

Given the relationship between cognitive IIV and everyday functioning, we explored this relationship among participants of the Women's Interagency HIV Study (WIHS). In this study, we calculated cognitive IIV from neuropsychological test performance in WWH and WWoH and examined its relationship to everyday functioning items (i.e., cooking, housekeeping, buying groceries) using the Lawton & Brody IADL scale. Based on prior literature demonstrating the predictive value that cognitive IIV exerts on several outcomes, including everyday functioning tasks (Morgan, Woods, Grant, et al., 2012; et al., 2011; 2014; Vance, Del Bene, et al., 2022), we hypothesized that greater cognitive IIV will be associated with poorer overall everyday functioning. Additionally, in this exploratory analysis, we examined whether being virally suppressed would alter these relationships between cognitive IIV and components of the IADL scale. Although it is assumed that being virally suppressed confers some neuroprotection and maintenance of IADLs, some studies suggest that this may not be the case (Rubin et al., 2017) and those who are virally suppressed may experience a different everyday functioning profile; and the impact of viral suppression has not been examined in relation to cognitive IIV. Furthermore, with regards to the underlying neuropathology among PWH, increases in cognitive IIV have been associated with decreased white matter integrity whereas cognitive mean scores have not (Jones et al., 2018). Altogether, our study represents a novel investigation of cognitive IIV within the neuroHIV literature with a focus on women.

Methods

The WIHS, now the MACS/WIHS Combined Cohort Study (MWCCS), is a prospective, multi-center study that focuses on the natural history and co-morbidities among women with HIV (WWH) and sociodemographically matched women without HIV (WWoH). The study's initial enrollment took place in three phases: a) between October 1994 and November 1995; b) between October 2001 and September 2002; and, c) between January 2011 and January 2013. These enrollments occurred at six sites located in Brooklyn, Bronx, Chicago, Washington DC, Los Angeles, and San Francisco. Subsequently, additional enrollment waves took place between October 2013 and September 2015 when new sites were established in high HIV prevalence areas of the southern United States, including Atlanta, Birmingham, Chapel Hill, Jackson, and Miami. Detailed information about the methodology of the WIHS, including ethical approval, consent procedures, recruitment processes, eligibility criteria, tester training, and quality assurance procedures, has been previously published (Adimora et al., 2018; Bacon et al., 2005; Barkan et al., 1998). The current analysis, using a longitudinal mixed-effects model, focused on women who had undergone a set of neuropsychological tests and a modified Lawton & Brody IADL scale. The implementation of the Lawton & Brody IADL scale in the WIHS started in April 2013 and was repeated at annual visits. The analysis included a total of 1,580 participants, accounting for 3,065 visits of IADL data.

Neuropsychological test battery

A panel of neuropsychology experts developed the WIHS neurocognitive test battery to facilitate the diagnosis of HIV-associated neurocognitive disorders (HAND) as specified in the Antinori et al. research nosology (i.e., Frascati Criteria). This selection also enables direct comparisons with findings from the Multicenter AIDS Cohort Study (MACS), which primarily examines HIV-positive men. Antinori nosology requires evaluating seven cognitive domains: executive function, attention/working memory, motor function, processing speed, verbal fluency, verbal learning, and memory. This approach aligns with methodologies employed in other HIV cohort studies, such as CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research), ensuring consistency in the assessment of neurocognitive outcomes. We developed demographically adjusted norms based on our large samples of women with and without HIV.

The battery of neuropsychological tests measured seven cognitive domains (Vance et al., 2016). ***Executive Function*** was evaluated with the Stroop test (outcome=time to complete 3 [color-word]) and the Trail Making Test (TMT; outcomes=time to complete Part B). ***Attention/Working Memory*** was evaluated with the Letter-Number Sequencing (LNS; outcomes=total correct on the attention and working memory conditions). ***Motor Function*** was evaluated with the Grooved Pegboard (GPEG; outcomes=time to completion, dominant and non-dominant hand). ***Processing Speed*** was evaluated with the Stroop Test (outcome=time to complete Trials 2 [color naming]) and the Symbol Digit Modalities Test (SDMT; outcome=total correct). ***Verbal Fluency*** was evaluated with the Controlled Oral Word Associations Test (COWAT; outcome=total correct words generated across three trials [F, A, S]) and Animal fluency (outcome=total correct animals generated). ***Verbal Learning*** and ***Memory*** were evaluated with the Hopkins Verbal Learning Test-Revised (HVLT-R; outcomes=total learning, delayed free recall) (Norman et al., 2011). To normalize distributions, timed outcomes were subjected to a log transformation because such times tests are often skewed; this helps reduce the influence extreme values can exert as well as normalize distributions (Hammouri et al., 2020); and reverse scoring was applied, such that higher scores corresponded to better performance. For each outcome, sociodemographically adjusted *T*-scores were computed as documented in our previous MWCCS publications (Maki et al., 2015; Rubin et al., 2017). These individual *T*-scores for these individualized T-scores were combined and utilized to generate seven cognitive domains. Having more than one test in certain domains meant that we could combine tests in that domain to make for a more stable estimate of that domain; this is reflective of other HIV cohort studies. The *T*-scores were standardized to have a mean of 50 and a standard deviation of 10.

Cognitive IIV

The estimate for each domain was used in the calculation for cognitive IIV. We did not use each individual test to calculate cognitive IIV because there was more than one test in certain domains, in which case this could bias the cognitive

IIV estimate to that domain. Using domain scores, cognitive IIV was calculated using two different calculations for cognitive IIV-dispersion: 1) intra-individual standard deviation (denoted as *sd*IIV) and 2) coefficient of variation (denoted as *cov*IIV) (Tractenberg & Pietrzak, 2011). Cognitive *sd*IIV is defined as the standard deviation of *Z*-scores for the seven domains mentioned above. Cognitive *cov*IIV is defined as the standard deviation divided by the mean overall Z-scores for each of the seven domains mentioned above. For our analyses, we used both *sd*IIV and *cov*IIV for comparison purposes as is often performed in the cognitive IIV literature; studies may use one versus the other. For thoroughness, we evaluated the predictive value of each.

Instrumental activities of daily living

In the WIHS, a minimally modified version of the Lawton & Brody IADL scale was used. This modified scale included items specifically tailored to women (i.e., child care responsibilities). The assessment was self-report and evaluated functional status across various IADLs including cooking, grocery shopping, housekeeping, handling money, and more (see Table 2 for complete listing). Participants were asked to rate their ability to perform these functions based on two factors: 1) their overall performance historically (ranging from "best ever" to "unable to perform" on a scale of 1–4, with 1 indicating the highest level of independence) (this "best ever" was asked only when participants entered the study); and 2) their current ability to perform in these domains over the past month (also on a scale of 1–4, with 1 indicating the highest level of independence) (this was asked when participants entered the study and at all follow up points and compared to their overall performance historically in to order to measure decline).

Following the methodology employed in the Multicenter AIDS Cohort Study (MACS) (Sacktor et al., 2016), descriptively a global classification system was used to assess the total level of IADL impairment. To determine the classification, at least 14 of 16 IADL items needed to be completed. Severe impairment was defined as having a major deficit in two or more items or a combination of major and minor deficits in four or more items. Mild impairment was defined as having a minor deficit in two or more items or a combination of major and minor deficits in two or more items, without meeting the criteria for severe impairment. Individuals who did not meet the criteria for either major or minor impairment were classified as normal. In this study, due to the low percentage of mild IADL impairment (9.15%), we combined mild and severe impairment categories; this resulted in 22% for the entire sample (Table 2).

More to the focus of this study, we specifically examined item-level IADL impairment by considering both the "best ever" score and the current score for each item. To calculate specific IADL deficits, we subtracted the ratings from the

Table 1. Sociodemographic, clinical, and behavioral variables in the total sample, in women without HIV (WWoH), in women with HIV (WWH), and in virally suppressed (VS)-WWH at their first visit completing the neuropsychological test battery and measure of instrumental activities of daily living.

Variables	Total sample *n* (%)	WWoH *n* (%)	WWH *n* (%)	VS-WWH *n* (%)	*p*-value[w]
Sample size	1580	494	1086	749	–
Number of contributing visits to the analysis	3065	994	2071	1430	–
Sociodemographic					
Age, M (IQR)	48 (13)	47 (13)	49 (12)	49 (13)	<0.01[w]
Years of Education, M (IQR)	12 (3)	12 (3)	12 (3)	12 (3)	0.86[w]
Race					
Black non-Hispanic	1224 (77)	380 (77)	844 (78)	577 (77)	0.78
Hispanic	187 (12)	76 (15)	111 (10)	79 (11)	<0.01
Other	50 (3)	17 (4)	33 (3)	24 (3)	0.79
White non-Hispanic	119 (8)	21 (4)	98 (9)	69 (9)	<0.01
Annual income <$12,000 per year	780 (49)	233 (47)	547 (50)	362 (48)	0.26
Employed	619 (39)	212 (43)	407 (37)	301 (40)	0.05
Insured	1480 (94)	419 (85)	1061 (98)	736 (98)	<0.01
Mental health and substance use					
Depressive symptoms	7 (14)	7 (13)	8 (14)	7 (14)	0.22[w]
Recent					
Crack	85 (5)	31 (6)	54 (5)	11 (1)	0.35
Cocaine	45 (3)	21 (4)	24 (2)	4 (1)	0.04
Heroin	16 (1)	9 (2)	7 (1)	7 (<1)	0.06
Marijuana	316 (20)	121 (24)	195 (18)	123 (16)	<0.01
Current smoker	656 (42)	220 (45)	436 (40)	273 (36)	0.11
HIV-related clinical characteristics					
Nadir CD4	–	–	294.5 (252.5)	301 (246.5)	–
Current CD4	–	–	621 (413.5)	676 (382)	–
Years of effective ART	–	–	9.48 (12.65)	9.19 (12.23)	–
Viral Load (log)	–	–	3.00 (25)	–	–
Antiretroviral adherence	–	–	827 (76)	636 (85)	–
Common ART drugs	–	–	741 (68)	541 (72)	–
Emtricitabine (FTC)					
Tenofovir (TDF)	–	–	590 (54)	413 (55)	–
Ritonavir (RTV)	–	–	341 (31)	219 (29)	–

P-value is for the comparison between WWH and HIV-uninfected women.
ART: antiretrovirals; IQR: interquartile range; M: median.
P-value with [w] is obtained under the Wilcoxon rank-sum test, and the other values are obtained by chi-square test.

last month from the corresponding historical "best ever" functioning rating. Higher negative scores indicated a decline in function from the "best ever" to the current state. Based on these values, a specific IADL was classified as impaired if: 1) the difference between the "best ever" score and the current score was less than −2, or 2) the difference between the "best ever" score and current IADL score was −1, and the current IADL score was already the lowest value on the scale (e.g., 2 or 3) for that specific IADL.

Antiretroviral adherence

To characterize the sample of WWH, ART adherence was reported; it was determined based on a self-reported item. This item assessed the frequency of ART intake as prescribed over the past 6 months. A 5-point Likert scale was utilized to quantify responses to the first item, which included the following options: 1= "100% of the time," 2= "95–99% of the time," 3= "75–94% of the time," 4= "<75% of the time," or 5= "I haven't taken any of my prescribed medications." Adherence was defined as self-reported ART adherence at the study visit and a minimum of 95% adherence was reported over the past 6 months.

Covariates

To account for potential confounding effects, several sociodemographic (e.g., age, years of education), behavioral, and clinical factors were considered in relation to the associations between cognitive performance and IADL outcomes, as is common in many of our WIHS cognitive analyses (Rubin & Maki, 2021; Vance et al., 2016). Based on our prior studies using the WIHS data in which we know these variables are associated with cognition, the following covariates were selected and statistically controlled for each visit in which data were collected for the participant in all models to derive a more precise evaluation of the relationship between cognition IIV and IADL outcomes: clinic site, age, years of education, annual household income, race (Black/non-Black), ethnicity (Hispanic, non-Hispanic), depressive symptoms measured by the Center for Epidemiological Studies Depression scale (CES-D), calculated body mass index, current smoking status, recent heavy alcohol use, and recent psychoactive substance use (specifically, marijuana as this is a commonly used substance). In the models focusing on WWH only, additional HIV-related covariates were incorporated, such as CD4 nadir and current CD4 cell count, prescribed type of ART therapy, and duration of ART.

Statistical analyses

A series of generalized linear logistic mixed-effects models with a random intercept were utilized to investigate the relationships between cognitive IIV as the predictor of both total and item-level scores of IADLs. Each model included the cognitive IIV scores as the predictor variable, along with the identified confounders, and the dependent variable of the individual IADL

Table 2. Percentage of the total sample, women without HIV (WWoH), women with HIV (WWH), and virally suppressed (VS)-WWH on instrumental activities of daily living (IADL) and cognitive performance at their first visit.

Variables	Total sample *n* (%)	WwoH *n* (%)	WWH *n* (%)	VS-WWH *n* (%)	*p*-value[w]
IADLs					
Total score	348 (22)	105 (21)	243 (22)	157 (21)	0.67
Housekeeping	138 (9)	39 (8)	99 (9)	56 (7)	<0.01
Money and bills	49 (3)	13 (3)	36 (3)	16 (2)	<0.01
Buying groceries	109 (7)	30 (6)	79 (7)	46 (6)	<0.01
Cooking	112 (7)	38 (8)	74 (7)	43 (6)	0.17
Planning social activities	192 (12)	63 (13)	129 (12)	89 (12)	<0.01
Understanding things read or watch on TV	61 (4)	17 (3)	44(4)	28 (4)	0.52
Getting where you need to go	81 (5)	27 (5)	54 (5)	31 (4)	0.02
Using the phone	13 (1)	5 (1)	8(1)	3(<1)	1
Home repairs	177 (11)	59 (12)	118 (11)	79 (11)	<0.01
Bathing	33 (2)	14 (3)	19 (2)	9 (1)	0.66
Dressing	11 (1)	7 (1)	4 (<1)	1 (<1)	0.95
Shopping	76 (5)	22 (4)	54 (5)	32 (4)	<0.01
Laundry	118 (7)	34 (7)	84 (8)	53 (7)	<0.01
Taking/keeping track of medications	36 (2)	11 (2)	25 (2)	13 (2)	0.01
Taking care of children/grandchildren	88 (6)	27 (5)	61 (6)	35 (5)	0.12
Working	458 (29)	129 (26)	329 (30)	220 (29)	<0.01
Cognitive function (T-scores)	*M* (*IQR*)	*M* (*IQR*)	*M* (*IQR*)	*M* (*IQR*)	
Verbal learning	49.24 (14.01)	50.46 (14.31)	48.74 (13.89)	48.99 (14.32)	<0.01[w]
Verbal memory	49.40(13.60)	50.03 (14.78)	48.98 (13.36)	48.78 (13.51)	0.03[w]
Verbal fluency	49.80 (11.45)	50.50 (11.06)	49.45 (11.38)	49.21 (11.77)	0.04[w]
Attention/Working memory	48.67 (12.33)	49.31 (12.03)	48.51 (12.59)	47.65 (12.51)	<0.01[w]
Processing speed	50.64 (11.59)	51.04 (11.57)	50.43 (11.70)	50.36 (11.74)	0.17[w]
Executive function	49.81 (12.62)	50.48 (11.73)	49.52 (12.88)	49.78 (13.02)	0.02[w]
Motor function	51.53 (11.66)	51.79 (10.37)	49.79 (9.84)	51.99 (11.89)	0.17[w]
*sd*IIV	7.21 (3.64)	6.98 (3.68)	7.33 (3.56)	7.36 (3.60)	0.04[w]
*cov*IIV	0.15 (0.08)	0.14 (0.08)	0.15 (0.08)	0.15 (0.08)	<0.01[w]

P-value is for the comparison between WWH and HIV-uninfected women.
M: median; IQR: interquartile range.
P-value with [w] is obtained under the Wilcoxon rank-sum test, and the other values are obtained by the chi-square test.

items. Initial models were conducted in the overall sample, WWH only, virally suppressed (VS)-WWH, and WWoH. All models were implemented using the lme4 package in R version 4.2.1. The significance level was set at $P<0.05$.

Results

Sample characteristics

In total, 1,580 participants were included in the study sample, comprised of 1,086 WWH (69% virally suppressed) and 494 WWoH (Table 1). Overall, 77% of women were non-Hispanic Black; with a mean age of approximately 48 years of age; an average of 12 years of education; and an annual household income of ≤$12,000 among 49%. Forty-two percent of participants were current smokers and 20% used marijuana. On average WWH were on ART for 9.48 years and 76% were highly ART adherent (≥95%). The most common ART used by WWH included emtricitabine (68%), tenofovir (54%), and ritonavir (a boosting agent, 31%).

With respect to cognitive function, individual domain *T*-scores approached 50. Although the differences were small, WWH demonstrated poorer performance compared to WWoH on several domains including attention/working memory, verbal learning and memory, and executive function (Table 2). With respect to IADLs, approximately 22% of the entire sample, WWoH and WWH, showed an overall total impairment in IADLs. Working (20%), planning social activities (12%), and home repairs (11%) were among the most common IADLs to be impaired in the overall sample of WWoH and WWH. Regarding the cognitive IIV values, WWoH had lower cognitive IIV scores (both *sd*IIV and *cov*IIV), reflective of less variability which is an indicator of better underlying neurological functioning.

Table 3. *sd*IIV and *cov*IIV associations with self-reported functioning in instrumental activities of daily living by group.

		WWoH	WWH	VS WWH
IADL	Type of IIV	Odds ratio (*p*-value)	Odds ratio (*p*-value)	Odds ratio (*p*-value)
Housekeeping	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Money and Bills	*sd*IIV	No	No	No
	*cov*IIV	No	0.337204 ($p=0.03070$)	No
Buying Groceries	*sd*IIV	No	No	No
	*cov*IIV	No	0.330138 ($p=0.012889$)	0.311519 ($p=0.035815$)
Cooking	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Planning Social Activities	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Understanding Things Read or on TV	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Getting Where You Need to Go	*sd*IIV	No	No	No
	*cov*IIV	No	0.29057 ($p=0.017759$)	No
Using the Phone	*sd*IIV	No	No	No
	*cov*IIV	No	8.100e-01 ($p=0.0322$)	No
Home Repairs	*sd*IIV	No	0.228 ($p=0.0038$)	No
	*cov*IIV	No	0.301538 ($p=9.82e-0$)	0.196914 ($p=0.03299$)
Bathing	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Dressing	*sd*IIV	No	8.433e-01 ($p=0.00032$)	0.74785 ($p=0.006167$)
	*cov*IIV	No	7.557e-01 ($p=0.000935$)	No
Shopping	*sd*IIV	No	No	No
	*cov*IIV	No	No	No
Laundry	*sd*IIV	No	0.2894 ($p=0.007$)	0.24260 ($p=0.039911$)
	*cov*IIV	No	0.32790 ($p=0.002020$)	0.239934 ($p=0.042677$)
Taking/Keeping Track of Medications	*sd*IIV	No	0.472806 ($p=0.02344$)	No
	*cov*IIV	No	0.57453 ($p=0.002480$)	0.521165 ($p=0.035092$)
Taking Care of Children	*sd*IIV	No	0.298702 ($p=0.02372$)	No
	*cov*IIV	No	0.380782 ($p=0.00202$)	No
Work	*sd*IIV	No	No	No
	*cov*IIV	No	0.196455 ($p=0.02902$)	No

Cognitive IIV predicting everyday functioning

To better explore and compare the association of *sd*IIV and *cov*IIV with IADL items, IADL group level data were examined (summarized in Table 3). In all groups, housekeeping, buying groceries, cooking, planning social activities, understanding things read or on TV, bathing, and shopping were not associated with either *sd*IIV and *cov*IIV. In fact, among WWoH, *sd*IIV and *cov*IIV were not predictive of any IADL items; however, *sd*IIV and *cov*IIV were predictive of several IADL items among WWH and VS-WWH. Among WWH, *cov*IIV was predictive of poorer functioning in 10 IADL items: money and bills (OR = 0.34, $p=0.031$, 95%CI = [0.03, 0.64]), buying groceries (OR = 0.33, $p=0.013$, 95%CI = [0.07, 0.59]), getting where you need to go (OR = 0.29, $p=0.018$, 95%CI = [0.05, 0.53]), using the phone (OR = 0.81, $p=0.032$, 95%CI = [0.07, 1.55]), home repairs (OR = 0.30, $p<0.001$, 95%CI = [0.15, 0.45]), dressing (OR = 0.76, $p=0.001$, 95%CI = [0.31, 1.20]), laundry (OR = 0.33, $p=0.002$, 95%CI = [0.12, 0.54]), taking/keeping track of medications (OR = 0.57, $p=0.002$, 95%CI = [0.20, 0.95]), taking care of children (OR = 0.38, $p=0.002$, 95%CI = [0.14, 0.62]) and work (OR = 0.20, $p=0.029$, 95%CI = [0.02, 0.37]). Among WWH, *sd*IIV was predictive of poorer functioning on only five IADL items: home repairs (OR = 0.23, $p=0.004$, 95%CI = [0.07, 0.38]), dressing (OR = 0.84, $p<0.001$, 95%CI = [0.38,1.31]), laundry (OR = 0.29, $p=0.008$, 95%CI = [0.08, 0.50]), taking/keeping track of medication (OR = 0.47, $p=0.023$, 95%CI = [0.06, 0.88]), and taking care of children (OR = 0.30, $p=0.024$, 95%CI = [0.04, 0.56]). Both *sd*IIV and *cov*IIV predicted the same five items; but overall, it appeared *cov*IIV was more sensitive to predict poorer functioning on these types of IADLs. Among VS-WWH, *sd*IIV was predictive of poorer functioning in two IADL items: dressing (OR = 0.75, $p=0.006$, 95%CI = [0.21, 1.28]) and laundry (OR = 0.24, $p=0.040$, 95%CI = [0.01, 0.47]); *cov*IIV was again predictive of poorer functioning in more (i.e., four) IADL items: buying groceries (OR = 0.31,

$p = 0.036$, 95%CI = [0.02, 0.60]), home repairs (OR = 0.20, $p = 0.033$, 95%CI = [0.02, 0.38]), laundry (OR = 0.24, $p = 0.043$, 95%CI = [0.01, 0.47]), and tracking/keeping track of medications (OR = 0.52, $p = 0.035$, 95%CI = [0.04, 1.00]).

Discussion

Less than 1% of neurocognitive HIV studies have examined the integral relationship between everyday functioning and cognition (Woods, 2021). Our study fills a gap in the literature while providing a unique examination of an array of IADL items and the predictive value of cognitive IIV on IADL items in WWH and WWoH who were participants in the WIHS. Approximately 22% of the total sample reported an overall impairment in IADLs, with working (20%), planning social activities (12%), and home repairs (11%) being the most commonly impaired IADLs. Compared to the AIDS Clinical Trails Group (ACTG) A5322 HAILO study ($N = 1{,}105$ PWH; median age = 51 years) which also used the Lawton & Brody IADL scale, the level of impairment in that sample was much higher, particularly in housekeeping (48%), transportation (36%), and shopping (28%) than that seen in the WIHS (Johs et al., 2017). Compared to the ACTG study, WIHS participants experienced less IADL impairment, likely due to the younger mean age of the participants and the fewer number of individuals with overall cognitive impairment. The cognitive differences between WWoH and WWH were quite small; this is consistent with an earlier study in the WIHS in which we observed that HIV status only accounts for 0.05–0.09 *SD* units of the cognitive domain variance between the serostatus groups with the effects of age, race/ethnicity, education, household income, and reading level having greater variance (Maki et al., 2015). Yet, such studies demonstrate that even subtle cognitive impairments may be associated with reduced everyday functionality.

In our prior study of IADL functioning in the WIHS (Vance, under review), we observed that the only cognitive domains to predict functional impairments were motor functioning and executive functioning. Moreover, for both serostatus groups, poorer motor functioning was related to greater impaired cooking, dressing, getting where you need to go, home repairs, housekeeping, and laundry. Specifically, for WWH, poorer motor functioning was related to greater impaired home repairs, housekeeping, and laundry while poorer executive functioning was related to more impaired social planning. Among VS-WWH, poorer motor function was associated with greater impairments in home repairs only, while poorer executive functioning was associated with more impaired social planning.

Compared to our prior IADL WIHS study, in this analysis, cognitive IIV seems to be more sensitive in predicting impaired IADL functioning. First, cognitive IIV (*sd*IIV or *cov*IIV) was not significant for any of the IADL items among WWoH, but it was for WWH and VS-WWH, indicating an ability to discriminate across serostatus groups. Second, in WWH neither *sd*IIV nor *cov*IIV were predictive of housekeeping, cooking, planning social activities, understanding things read or on TV, bathing, and shopping; however, *cov*IIV was associated with twice as many IADL items (10 items—money and bills, buying groceries, getting where you need to go, using the phone, home repairs, dressing, laundry, taking/keeping track of medications, taking care of children, work) than *sd*IIV (5 items—home repairs, dressing, laundry, taking/keeping track of medication, taking care of children). It is not clear why *cov*IIV would be more sensitive to detecting functional impairments than *sd*IIV. The calculations for both are similar; both are measures of dispersion. *sd*IIV is the intra-individual deviation of the *Z*-scores of the seven cognitive domains; *cov*IIV is the standard deviation of the *sd*IIV divided by the mean of the *Z*-scores for the seven domains. Because *cov*IIV provides additional information beyond standard deviation in the IIV calculation, by accounting for one's overall performance, this may stabilize this coefficient giving it more predictive value over the underlying concept of IIV. It is important to note that *sd*IIV and *cov*IIV are used interchangeably in the cognitive IIV literature but they may not have the same predictive value. Otherwise, the everyday functioning items that *cov*IIV detected beyond *sd*IIV do not seem to be qualitatively different IADLs (money and bills, buying groceries, getting where you need to go, using the phone, work) since they all appear to be higher level everyday tasks; but clearly *cov*IIV seems to provide more sensitivity. Finally, as seen in Tables 2 and 3, VS-WWH had fewer reported IADL impairments compared to the larger WWH sample supporting that viral suppression is associated with better overall health and functioning. Yet, the cognitive IIV values were actually higher in VS-WWH; this was surprising as being virally suppressed would also seem to provide some neurocognitive protection resulting in a lower cognitive IIV score, yet this may suggest legacy effects (Qu et al., 2022) or differences in size of viral reservoirs or the extent of HIV replication.

Strengths and limitations

This study demonstrates several methodological strengths. Firstly, the large number of women recruited from various sites across the United States enhances the generalizability of the findings to other WWH and similar WWoH. Secondly, the inclusion of a socio-demographically similar seronegative group allows for a meaningful comparison, revealing notable differences in the relationship between cognitive IIV and IADL scores. Thirdly, the utilization of an established neuropsychological battery ensures the reliability and validity of the cognitive assessment. Lastly, the use of the Lawton and Brody IADL scale for self-assessment of everyday functioning is well-regarded and widely accepted. These strengths collectively contribute to the robustness and credibility of the study's findings (Vance et al., 2023).

Several study innovations are likewise noted. To start, in the neuroHIV literature, this is the first of its kind to investigate the impact of cognitive IIV on everyday functioning within a large longitudinal cohort sample. Furthermore, this study offers other contributions, including: 1) comprehensive control for a wide range of covariates related to cognitive IIV and IADLs, 2) a comparative analysis that sheds light on

potential differences in the relationship between cognitive IIV and everyday functioning based on HIV viral suppression status, and 3) one of the first studies to compare competing calculations of cognitive IIV to examine how well they each perform in tandem.

Despite notable study strengths, certain study limitations remain. A statistical limitation is that we did not correct for alpha inflation as this was an exploratory study; yet, we reported the exact *p*-values to provide information for readers. Another limitation is that this self-reported IADL functional difficulty in this largely cognitively intact sample may not be explained solely by cognition. There are indeed several factors we did not investigate that could account for this such as comorbidity burden, peripheral neuropathy burden, frailty, level of physical activity, and so forth. Cognitively, we did not account for meta-cognition and the ability to accurately rate one's level of everyday functioning.

An instrumentation limitation pertains to the subjective (i.e., self-reported) nature of the Lawton & Brody IADL scale, which is susceptible to recall bias and does not capture objective performance-based measures of everyday functioning. Some studies have suggested that adults may underestimate or overestimate their IADL ability compared to their actual performance (Suchy et al., 2011). In fact, increased disparities between self-reported everyday functioning and performance-based measures of everyday functioning have been linked to lower cognitive abilities (Suchy et al., 2010). For instance, in a study of 236 PWH aged >40 years, both subjective (self-report) and objective performance-based measures of everyday functioning were employed (Jacob et al., 2024). The subjective measure included the Lawton & Brody IADL scale, while the objective measure involved the Timed IADL Test, a performance-based measure using time and accuracy. Discrepancy scores between subjective and objective measures were calculated. Nearly 58% demonstrated a discrepancy between subjective and objective performance, with many either under- or over-estimating their ability to perform IADLs. Compared to accurate reporters, inaccurate self-reporters were more likely to have poorer cognitive ability. These findings highlight the importance of considering both subjective and objective measures when evaluating everyday functioning.

The Lawton & Brody IADL scale has an additional limitation. It does not encompass the assessment of internet-based household IADLs, including tasks such as internet shopping, handling electronic financial transactions, and other digital activities commonly conducted online. Given the increasing significance of these computerized IADLs in everyday functioning, individuals with cognitive impairment may encounter new challenges in managing the complexity of such daily tasks. Woods et al. conducted a study examining performance on internet-based household IADLs, specifically internet shopping and banking, among 93 PWH, including 43 with HAND, and 42 cognitively normal individuals without HIV (Woods et al., 2017). They found that those with HAND experienced lower internet-based task scores and that such scores correlated with poorer numeracy, executive function, episodic memory, and motor skills. This research highlights the need to consider the association between cognition as well as cognitive IIV with internet-based household IADLs, particularly in PWH.

Future directions

There are subtle cognitive differences between women and men with HIV. For example, in a comparison between the WIHS and the Multicenter AIDS Cohort Study (MACS), a study of men with and without HIV, women tended to experience more impairment in motor function than men (Maki et al., 2018). As such, men and women with HIV may differ on cognitive IIV which may also differentially impact IADLs between them. Further studies should examine the association between cognitive IIV and IADL function by sex and gender.

Cognitive training may be used to improve everyday functioning in PWH. In a systematic review of 13 cognitive training studies in PWH, it was found that focused cognitive training could improve functioning in particular cognitive domains (i.e., speed of processing training improves speed of processing) (Vance et al., 2019). Some studies also show that cognitive training can improve everyday functioning. For instance, in a randomized sample consisting of 46 PWH, who were divided into either a no-contact control group or a speed of processing training group, participants undergoing this cognitive training showed enhanced performance on the Timed IADL test (Vance et al., 2012). Although it is possible that personalized cognitive domain training may improve everyday functioning by improving particular cognitive domains that correspond to function in specific IADL tasks (Vance et al., 2023), it remains less clear how to reduce cognitive IIV. Executive dysfunction may underly cognitive IIV; that is, the poorer one's executive functioning, the less cognitive resources one has to coordinate and harmonize functioning in the various cognitive domains. Thus, if one can improve executive functioning, through executive functioning training, perhaps cognitive IIV can be reduced which may improve function in particular IADLs in PWH; in fact, an NIH-funded study is currently investigating this (R21 AG076366). Another strategy would be to target those cognitive domains in which poorer cognitive performance provides more variability to the cognitive IIV coefficient and then target those cognitive domains for training, thereby reducing the cognitive IIV.

Conclusion

In prior studies in various clinical populations, cognitive IIV has been shown to be a bellwether of underlying neurological pathology, impaired everyday functioning, impending cognitive decline, and mortality (Anderson et al., 2018; Hines et al., 2016; Jones et al., 2018; Thaler et al., 2015). Based on this literature and study results, several interesting findings emerged from this study. First, this study found the cognitive IIV was slightly greater in WWH compared to HIV-uninfected women. Given the neurological sequela from HIV and factors that often accompany HIV (i.e., depression, substance use, stigma), it makes sense that those with HIV

would have a higher cognitive IIV score. Second, this study found that cognitive IIV is useful in predicting impairment in various IADLs. And third, this study is unique in comparing two different mathematical formulas of cognitive IIV and found one to be more sensitive of predicting impairment in various IADLs. This is useful in examining this relationship in other HIV populations including men and people with HAND.

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