Class-Based Antiretroviral Exposure and Cognition Among Women Living with HIV

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Abstract

Neurologic complications of the human immunodeficiency virus (HIV) are common in treated individuals, and toxicity of certain antiretroviral therapies (ART) may contribute to cognitive impairment. We investigated exposures to specific ART and cognition among women living with HIV (WLWH). Virologically suppressed (viral load <200 copies/mL during at least two semi-annual visits) WLWH and age/race matched HIV-seronegative controls enrolled in the Women's Interagency HIV Study who completed at least two biennial cognitive assessments were included. Analysis of WLWH was restricted to those with exposure to the drug class of interest and a nucleoside reverse transcriptase inhibitor (NRTI) backbone. Generalized estimating equations were used to evaluate repeated measures of cognition over time in association with ART class exposure. Among 1,242 eligible WLWH, 20% ($n = 247$) had isolated drug exposure to non-nucleoside reverse transcriptase inhibitors (NNRTI), 18% ($n = 219$) to protease inhibitors (PIs), and 6% ($n = 79$) to integrase inhibitors with a NRTI backbone. Cognitive assessments were performed at a median of 3 biennial visits {IQR 2–4 visits}. At the index assessment, 21% of WLWH demonstrated global cognitive impairment versus 29% at their last cognitive assessment. In multivariable analyses adjusted for hypertension, depression, diabetes mellitus, history of AIDS-defining illness, alcohol use, number of medications, and time on ART, WLWH exposed to NNRTIs demonstrated verbal learning improvements (mean T-score change 1.3, $p = .020$) compared to other treated women. Compared to HIV-seronegative women, WLWH exposed to PIs had worse verbal learning (mean T-score difference −2.62, $p = .002$) and verbal memory performance (mean T-score difference −1.74, $p = .032$) at baseline. Compared to HIV-seronegative women, WLWH exposed to PIs had improvements in verbal learning (mean T-score slope difference 0.36, $p = .025$) and verbal memory (mean T-score slope difference 0.32, $p = .042$). The index T-score and slope of change in the T-score were similar among other treated groups and the HIV-seronegative group. We noted emerging trends in cognition in WLWH exposed to specific drug classes. Ongoing study of this relatively young group is important to characterize long-term cognitive outcomes and effect of antiretrovirals as treatment guidelines evolve.

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Background

With the advent of effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) has become a chronic illness with expected long-term survival.[1] In 2018, over one half of persons living with HIV (PLWH) were greater than age 50 years.[2] In this aging population of PLWH, the recognition and management of comorbid conditions, including those associated with aging such as cognitive disorders, is a priority.[3,4] Over one half of PLWH demonstrate cognitive impairment with changes dependent on HIV treatment status, demographics, and medical comorbidities.[5,6] There are also sex differences in cognitive impairment among PLWH with women being more cognitively vulnerable compared to men living with HIV.

However, the factors contributing the greatest risk of cognitive impairment in women are not completely understood.[7] It is important to understand specific factors contributing to cognitive impairment and change, especially the contribution of ART in women and diverse populations of PLWH as patients are expected to continue therapy with long-term ART.

Although the use of effective ART decreased the incidence of severe cognitive impairment, cognitive complications remain common even among PLWH on ART.[8–11] Further, cognitive impairment, especially milder forms of impairment, has been noted even among those with treated HIV and viral suppression.[11]

Direct neurotoxicity of ART may contribute to cognitive impairment in PLWH.[9,12–14] There is clinical evidence of worse cognitive performance in some domains with exposure to specific ART.[15] Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), is known to cause neurologic side effects in as many as 50% of PLWH and is associated with cognitive impairment.[16,17] Typically these effects are transient and occur shortly after initiation. However, there are reports of severe ataxia and encephalopathy associated with high drug concentrations, which are conditions associated with cognitive impairment.[18]

The immediate and long-term cognitive and other central nervous system effects of other classes of ART are not well characterized. Among the protease inhibitors (PIs), ritonavir (RTV) is known to cause dizziness, nausea, and paresthesias; however, this was in the context of higher dosing and not the currently used lower dose intended to boost levels of concurrently administered PIs.[19,20] Both *in vivo* and *in vitro* models demonstrate that PIs induced neuronal damage and the production of β-amyloid, a protein implicated in the pathogenesis of Alzheimer's disease.[21] Further, PI use is associated with incident diabetes among women living with HIV (WLWH), and there is some evidence that integrase inhibitor (INSTI) use may contribute to the development of metabolic syndrome.[22–24] Diabetes is associated with risk of cognitive disorders.[25–27] Thus, use of these classes of medication may contribute to risk of cognitive impairment.

There are reports of adverse neurologic effects with the use of INSTIs but there are limited data on their long-term cognitive effects.[28–30] In addition, there are no large studies examining cognitive effects of the PI or INSTI classes of medication. Understanding the effects of INSTIs on cognitive outcomes is especially relevant as they are currently recommended as first-line agents in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in treatment naive PLWH.[31]

Understanding the cognitive consequences of different therapeutic approaches is important to develop treatment and management strategies for persons living and aging with HIV. Our aims were to determine associations between exposure to specific ART classes, specifically evaluating the class effect of PIs and INSTIs, on cognitive performance over time.

Methods

Study population

The Women's Interagency HIV Study (WIHS) is a multicenter, prospective observational cohort study of both treated and untreated HIV. The study methodology has been previously described, but the study participants include HIV-seronegative controls in addition to PLWH. Initial study sites included Bronx and Brooklyn, NY; Washington, DC; Los Angeles and San Francisco, CA; and Chicago, IL, with three enrollment waves in 1994–1995, 2000–2001, and 2012–2013.[32,33] In 2013, the Los Angeles site was closed and new sites were added in Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham, AL; and Jackson, MI.[34] The study was approved by the Institutional Review Board at all participating sites, and all enrolled women provided written informed consent to participate in the study.

Participants provided self-reported data on sociodemographic status, health care utilization, and medical comorbidities at semiannual visits. Study participants also underwent targeted physical examinations, provided biological specimens, and underwent certified laboratory testing, including $CD4^+$ T lymphocyte and quantitative HIV RNA.

To evaluate our primary objective, we restricted our analysis to WLWH who were virologically suppressed (HIV RNA <200 copies/mL) and on ART for at least two biennial cognitive follow-up visits, and had isolated exposure to the class of interest with a NRTI backbone (i.e., women in the INSTI group were not exposed to NNRTIs or PIs). An age and race matched group of HIV-seronegative women from enrolled participants was used for comparison.

Cognitive function

A standardized cognitive assessment measuring seven domains was initiated in 2009 and subsequently administered biennially to WIHS participants in either English or Spanish. Staff are trained in its administration.

Domains assessed include fine motor skills (Grooved Pegboard), psychomotor speed (Symbol Digit Modalities Test), attention [Stroop Test Trials 1 and 2, Trail Making Test Parts A and B, Letter- Number Sequencing (LNS) Test, control/attention condition], executive function [working/verbal memory, behavioral inhibition, and mental flexibility (Stroop Test Trial 3 of color-word interference condition, Trail Making Test Parts B, LNS test, working memory condition)], verbal learning [Hopkins Verbal

Learning Test-Revised (HVLT-R)—single trial and total words recalled across the three trials], verbal memory (HVLT-R delayed recall and percent retention), and verbal fluency (letter fluency task and category fluency task).[35]

Demographically adjusted T-scores (adjusted for baseline and repeated administration of assessment, age, education, race, and literacy based on the reading recognition subtest of the Wide Range Achievement Test[36]) were determined and T-scores were used to create domain scores and a global cognitive performance score for individuals with data for ≥4 domains.[35,37–39] T-scores for each cognitive domain were converted into clinical rating scores of 1–9 (ranging from above average to severe impairment) as described previously in the WIHS.[40,41] The domain-specific clinical rating scores were further categorized into the following: 1–4 no cognitive impairment, 5–6 mild-moderate cognitive impairment, and 7–9 moderate to severe cognitive impairment. Global cognitive impairment was defined as a global clinical rating score of ≥5.

Variables

Potential covariates were selected based on prior knowledge of factors associated with cognitive function and data availability in the WIHS. Thus, they included ART exposure, any illicit drug use, any marijuana, alcohol use (dichotomized as 0–7 or >7 drinks per week), and WIHS clinical research site. Laboratory variables included $CD4^+$ T Lymphocyte count at index cognitive assessment, $CD4^+$ T Lymphocyte nadir since study enrollment, and HIV RNA levels across visits.

Clinical factors included presence of clinically relevant depressive symptoms [Center for Epidemiologic Studies Depression Scale (CES-D) ≥16][42] and comorbidities, including hypertension, diabetes mellitus, menopausal status, alcohol use (>7 drinks per week), and hepatitis C virus (HCV) coinfection. Comorbidities were determined by self-report, medication use for treatment of disease (i.e., antihypertensives for hypertension), and laboratory testing (i.e., positive HCV RNA).

Statistical analysis

The index visit was defined as the first visit at which WIHS participants completed the cognitive battery. As noted previously, cognitive assessments began in 2009, and cognitive data were used thereafter. For sites that were added in 2013, data were included from 2013 onward. Summary statistics were stratified by ART class among WLWH and HIV-serostatus and compared using chi-square, ANOVA, or Wilcoxon rank sum test. Index and last available cognitive assessments were compared between virologically suppressed WLWH and a matched HIV-seronegative control group based on age and race. In analyzing relationships between longitudinal t-scores for each domain and drug exposure categories, we used a generalized linear model with generalized estimating equation to account for correlation from repeated measures in our cohort.

Covariates significant at $p < .05$ based on univariate analyses and/or prior knowledge of effect on cognition were included in the multivariate regression models. The CES-D score for depressive symptoms was a time varying covariate in our analysis. Analyses were conducted using SAS v9.4 for Windows version 10.

Results

Participant demographics

Among the 1,242 WLWH who met defined criteria for viral suppression, 20% ($n = 247$) had isolated drug exposure to NNRTIs, 18% ($n = 219$) PIs, and 6% ($n = 79$) to INSTIs with a NRTI backbone. Full demographic information is outlined in Table 1. Women prescribed INSTIs for treatment were older with a mean age of 50 (1.2) years of age versus 47 (2.6) years for women on NNRTIs and 46 (2.5) years for women on PIs, $p < .0001$. Women receiving INSTIs had fewer mean years of drug exposure at 3.5 (3) years compared to 6.7 (4.4) years for NNRTIs and 8.7 (4.9) years PIs, $p < .0001$. The mean $CD4^+$ T lymphocyte nadir was lower for participants taking PIs at 284 cells/μL versus 305 cells/μL for NNRTIs, and 429 cells/μL for INSTIs, $p < .0001$.

Index and follow-up clinical rating scores

Table 2 includes initial and follow-up categorical cognitive performance using clinical rating scores for virologically suppressed treated women (INSTI, PI, NNRTI exposed), and HIV-seronegative controls. At the index visit, 22% of WLWH demonstrated impairment in global cognitive function, and at the end of follow-up, impairment was 29%. At the index assessment, cognitive impairment was noted across all domains, including 18% in executive function, 14% psychomotor speed, and 14% verbal fluency among virologically suppressed WLWH in the WIHS cohort treated with ART.

Compared to the index visit, more treated WLWH showed cognitive impairment at the end of follow-up with respect to the following domains: verbal learning 23%, $p < .0001$; verbal memory 21%, $p < .001$; and attention 18%, $p = .001$. Supplementary Table S1 describes categorical index and follow-up cognitive testing among class-specific-treated individuals.

Among the HIV-seronegative women, 20% demonstrated impairment in global cognitive function at the index visit, and at the end of follow-up, impairment was 26%. At the index assessment cognitive impairment was noted across all domains for the HIV-seronegative women including. Compared to the index visit, more HIV-seronegative women showed cognitive impairment at the end of follow-up with respect to the following domains: attention 12%, $p = .0104$; verbal learning 22%, $p < .001$; and verbal memory 11%, $p = .0123$.

Index and longitudinal T-scores

During the follow-up period, cognitive assessments were administered biennially for WLWH and were performed at a median of 3 visits {IQR 2–4} for HIV-seronegative women. Table 3 outlines the estimated difference in mean T-scores by domain and isolated drug class exposure compared to other WLWH on ART as well as HIV-seronegative individuals.

Among women who were exposed to PIs or INSTIs compared to other treated individuals, there were no differences in cognitive function as measured by T-score based on drug class exposure after adjustment for hypertension, depression, diabetes mellitus, history of AIDS-defining illness, time on ART, alcohol use, and total number of medications. Women exposed to NNRTIs demonstrated improvement in verbal learning (estimated mean T-score change 1.3, $p = .020$) compared to other treated WLWH. There was a trend for verbal memory to decline among women with

Table 1. Demographic Characteristics of Virologically Suppressed Women[a] in the Women's Interagency HIV Study with Isolated Drug Exposures of Interest

		HIV-seropositive			
	HIV-seronegative, % (n = 868)	*NNRTI % (n = 247)*	*PI % (n = 219)*	*INSTI % (n = 79)*	p
Mean age, years (SD)	47 (2.7)	47 (2.6)	46 (2.5)	50 (1.2)	<.001
Mean years of antiretroviral exposure (SD)	NA	6.7 (4.4)	8.7 (4.9)	3.5 (3.0)	<.001
Mean years since HIV diagnosis (SD)	NA	21 (2.6)	21.3 (2.2)	20.8 (2.0)	.3261
Mean number of medications taken (SD)	3.9 (3.3)	7.6 (3.5)	8.0 (3.1)	7.5 (3.1)	<.0001
Mean years of education (SD)	12.6 (3.0)	12.5 (3.0)	12.1 (2.7)	13.3 (3.3)	.0243
Race/ethnicity					
Black, non-Hispanic	68 (593)	79 (193)	66 (146)	82 (65)	.3939
White, non-Hispanic	9 (76)	10 (27)	12 (25)	13 (10)	
Hispanic	18 (159)	7 (17)	15 (35)	4 (3)	
Other	4 (38)	4 (10)	6 (13)	1 (1)	
Baseline CD^+ T lymphocyte count, cells/μL					
<200	0.3 (1)	3 (7)	8 (16)	5 (4)	<.0001
200–500	2 (6)	27 (64)	27 (52)	26 (20)	
>500	97.7 (289)	74 (174)	76 (148)	71 (55)	
Mean $CD4^+$ T lymphocyte count nadir, cells/μL	NA	305 (208)	284 (194)	429 (273)	<.001
History of AIDS defining illness	NA	23 (53)	32 (63)	8 (6)	<.0001
Comorbidities					
Diabetes	20 (176)	17 (40)	20 (38)	17 (13)	.1080
Hypertension[b]	63 (544)	64 (150)	70 (136)	65 (51)	.8431
Depression (CES-D = >16)	31 (265)	27 (68)	28 (62)	32 (25)	.6616
HCV coinfection[c]	0.5 (4)	23 (54)	27 (52)	19 (15)	<.0001
Menopausal status	24 (189)	28 (66)	30 (59)	28 (22)	.0116
Alcohol use (>7 drinks/week)	19 (167)	12 (27)	10 (20)	13 (10)	.0004
Illicit drug use	10 (89)	9 (21)	5 (10)	4 (3)	.0326
Other drugs[d]	33 (284)	28 (65)	28 (55)	23 (18)	.0074
Marijuana use	23 (200)	22 (51)	19 (37)	21 (16)	.2293
Tobacco use					
Current	25 (239)	44 (102)	44 (60)	41 (32)	.0067
Former	47 (409)	26 (62)	31 (85)	23 (18)	
Never	27 (218)	35 (83)	38 (74)	37 (29)	

[a]Viral load <200 copies/mL during at least two time points in the follow-up period.
[b]Defined as self-report of hypertension, use of antihypertensive medication, or systolic blood pressure ≥140, or diastolic blood pressure ≥90.
[c]Self-report of history of HCV or positive HCV RNA.
[d]Other drugs include methadone, methamphetamines, amphetamines, narcotics, hallucinogens, tranquilizer, and suboxone.
CES-D, Center for Epidemiologic Studies Depression Scale; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

INSTI exposure (estimated mean T-score change −1.80, $p = .072$) compared to other treated WLWH. Women exposed to INSTIs also showed a trend toward improvement in fine motor function (estimated mean T-score change 1.78, $p = .072$) compared to other treated WLWH.

Compared to matched HIV-seronegative women, the index cognitive assessments were similar among WLWH exposed to INSTIs or NNRTIs after adjustment for hypertension, enrollment site, depression, alcohol use, total number of medications, and follow-up time as an interaction term (Table 4). At the index testing visit, WLWH exposed to PIs performed worse on verbal learning (mean T-score difference −2.62, $p = .002$) and verbal memory (mean T-score difference −1.74, $p = .032$) at baseline compared to HIV-seronegative women. Among other ART classes and cognitive testing domains, the index T-score was similar compared to HIV-seronegative controls.

The slope of T-score change was similar across ART women treated with INSTIs or NNRTIs compared to HIV-seronegative controls. However, women treated with PIs demonstrated improvements in verbal learning (mean T-score slope difference 0.36, $p = .025$) and verbal memory (mean T-score slope difference 0.32, $p = .042$) compared to the HIV-seronegative women.

As a subanalysis, we assessed time-dependent changes in domain-specific cognitive function among women exposed to NNRTIs. Compared to women with <3 years of exposure to NNRTIs, women with ≥3 years of exposure had a trend toward worse attention, $p = .0548$. We did not note significant time-dependent cognitive change among women exposed to NRRTIs related to other cognitive domains. An additional subanalysis was performed on women exposed to the INSTIs. Compared to women with <3 years of exposure to INSTIs, more years of INSTI exposure was associated with a trend toward worse psychomotor processing speed, $p = .0524$. We did not note significant time-dependent cognitive change among women exposed to INSTIs related to other cognitive domains.

Table 2. Categorical Comparisons of Baseline and Last Visit of Women with Antiretroviral Therapy Exposure (Integrase Inhibitor, Protease Inhibitor, or Non-Nucleoside Reverse Transcriptase Inhibitor) and HIV Seronegative-Matched Controls

	*HIV treated % (*n*)*			*HIV-seronegative % (*n*)*		
	Baseline visit	*Last visit*	p	*Baseline visit*	*Last visit*	p
Global,[a] *n*	1,241	1,237	<.0001	534	533	.00022
No impairment	79 (975)	71 (879)		80 (429)	73 (391)	
Mild-moderate impairment	16 (195)	20 (247)		16 (83)	18 (100)	
Moderate-severe impairment	6 (71)	9 (111)		4 (22)	8 (42)	
Executive, *n*	1,239	1,238	.4691	532	531	.6254
No impairment	82 (1,011)	83 (1,032)		84 (448)	86 (459)	
Mild-moderate impairment	14 (172)	11 (142)		12 (63)	9 (47)	
Moderate-severe impairment	5 (56)	5 (64)		4 (21)	5 (25)	
Attention, *n*	1,241	1,240	.0002	533	534	.0104
No impairment	87 (1,081)	82 (1,011)		91.5 (488)	87 (463)	
Mild-moderate impairment	11 (135)	15 (187)		7.5 (40)	11 (61)	
Moderate-severe impairment	2 (25)	3 (42)		1 (5)	2 (10)	
Psychomotor speed, *n*	1,237	1,233	.4745	533	530	.0279
No impairment	86 (1,067)	85 (1,043)		88 (469)	85 (451)	
Mild-moderate impairment	10 (121)	12 (148)		10 (55)	10 (53)	
Moderate-severe impairment	4 (49)	3 (42)		2 (9)	5 (26)	
Verbal learning, *n*	1,240	1,239	<.0001	534	533	<.0001
No impairment	88 (1,097)	77 (959)		88 (469)	78 (417)	
Mild-moderate impairment	10 (128)	19 (230)		11 (57)	18 (96)	
Moderate-severe impairment	1 (15)	4 (50)		1 (8)	4 (20)	
Verbal memory, *n*	1,238	1,235	<.0001	533	534	.0123
No impairment	87 (1,081)	79 (977)		87 (462)	80 (432)	
Mild-moderate impairment	11 (131)	17 (204)		11 (57)	15 (80)	
Moderate-severe impairment	2 (27)	4 (54)		3 (14)	4 (22)	
Fine motor, *n*	1,229	1,214	.5318	526	520	.7899
No impairment	89 (1,094)	88 (1,069)		88 (464)	87 (453)	
Mild-moderate impairment	7 (88)	8 (100)		8 (41)	9 (48)	
Moderate-severe impairment	4 (47)	4 (45)		4 (21)	4 (19)	
Verbal fluency, *n*	1,242	1,240	.0678	534	534	.8729
No impairment	86 (1,073)	84 (1,044)		88 (472)	89 (476)	
Mild-moderate impairment	11 (140)	12 (149)		10 (54)	9 (48)	
Moderate-severe impairment	2 (29)	4 (47)		1 (8)	2 (10)	

[a]Clinical rating scores were defined as follows: 1 = above average, 2 = average, 3 = low average, 4 = borderline, 5 = definite impaired, 6 = mild to moderate impairment, 7 = moderate impairment, 8 = moderate to severe impairment, 9 = severe impairment. Categorical scores were trisected into three categories based on clinical rating scores: 1: no cognitive impairment (1–4), 2: mild to moderate cognitive impairment (5–6), 3: moderate to severe cognitive impairment (7–9).

Table 3. Comparison of Longitudinal Neurocognitive Change in Virologically Suppressed Women in the Women's Interagency HIV Study with Different Drug Class Exposures Overtime

	INSTI vs. other treated		*PI vs. other treated*		*NNRTI vs. other treated*	
Domain	*Estimated change based on drug exposure (95% CI)*	p	*Estimated change based on drug exposure (95% CI)*	p	*Estimated change based on drug exposure (95% CI)*	p
Executive function	−1.06 (−2.89 to 0.77)	.255	0.68 (−0.78 to 2.14)	.362	0.08 (−1.13 to 1.42)	.905
Attention	−0.31 (−2.12 to 1.51)	.741	0.60 (−0.79 to 2,00)	.396	−0.69 (−1.32 to 1.87)	.914
Psychomotor speed	−0.29 (−1.85 to 1.28)	.720	0.54 (−0.76 to 1.85)	.413	0.37 (−0.92 to 1.66)	.574
Verbal learning	−1.01 (−2.88 to 0.86)	.289	−0.15 (−1.47 to 1.16)	.818	1.30 (0.20 to 2.40)	.020
Verbal memory	−1.80 (−3.75 to 0.16)	.072	0.28 (−1.00 to 1.57)	.663	0.72 (−0.42 to 1.87)	.226
Fine motor	1.78 (−0.16 to 3.73)	.072	0.036 (−1.32 to 1.39)	.959	0.48 (−0.76 to 1.72)	.444
Verbal fluency	0.46 (−1.49 to 2.42)	.6147	−0.14 (−1.57 to 1.28)	.843	0.32 (−0.89 to 1.54)	.600

Adjusted for HTN, depression, DM, AIDS defining illness, alcohol use, total number of medications.
CI, confidence interval; DM, diabetes mellitus; HTN, hypertension.

Table 4. Comparison of Baseline and Change in Cognition Among HIV Seronegative Women and Virologically Suppressed Women in the Women's Interagency HIV Study with Different Drug Class Exposures

Domain	*Mean baseline T-score*	p	*T-score slope*	p
Executive function				
PI	51.62	.301	0.24	.099
INSTI	50.49	.103	0.25	.342
NNRTI	51.48	.216	0.02	.939
HIV-seronegative (Ref.)	52.51	—	0.01	(.949)[a]
Attention				
PI	48.68	.360	–0.29	.584
INSTI	49.68	.892	–0.37	.632
NNRTI	48.08	.520	–0.27	.520
HIV negative (Ref.)	48.52	—	–0.20	(.015)[a]
Psychomotor speed				
PI	51.00	.448	0.32	.092
INSTI	50.42	.227	0.09	.358
NNRTI	51.10	.503	0.38	.608
HIV negative (Ref.)	51.64	—	–0.12	(.216)[a]
Verbal learning				
PI	51.77	.002	0.20	.025
INSTI	53.71	.569	–0.17	.622
NNRTI	53.72	.375	–0.20	.334
HIV negative (Ref.)	54.39	—	–0.33	(.0004)[a]
Verbal memory				
PI	52.00	.032	0.06	.042
INSTI	53.54	.874	–0.02	.403
NNRTI	53.72	.979	–0.25	.903
HIV negative (Ref.)	53.74	—	–0.27	(.004)
Fine motor				
PI	53.56	.484	0.15	.252
INSTI	53.83	.478	0.45	.128
NNRTI	54.42	.060	–0.004	.853
HIV negative (Ref.)	52.90	—	–0.17	(.868)[a]
Verbal fluency				
PI	49.48	.347	–0.01	.645
INSTI	49.87	.707	0.05	.989
NNRTI	49.76	.468	0.0057	.621
HIV negative (Ref.)	50.23	—	0.06	(.496)[a]

Adjusted for hypertension, enrollment site, depressive symptoms, and follow-up time as an interaction term.
[a]*p*-Value of slope in reference group.

Discussion

As in previous studies from the WIHS and other studies of men and WLWH, we found evidence of cognitive impairment despite virologic control with more than a quarter of women with cognitive impairment.[43,44] However, our estimates were not as high as have been reported in other cohorts.[5,45] Further, a significant portion of the age and race matched HIV-seronegative controls had cognitive dysfunction with 20% having global impairment at baseline, which increased to 26% at the last follow-up. This cognitive dysfunction in both the WLWH and HIV-seronegative controls was noted despite the relatively young age of the cohort.

By design, the HIV-seronegative control group in the WIHS was recruited based on risk of HIV acquisition and both groups are socioeconomically vulnerable, have high rates of intimate partner violence, and stress.[33,46,47] These are all known risk factors for impaired cognition and may be reflected in the high rates of cognitive impairment across both groups.[48–50]

Other studies in HIV-seronegative women suggest that cognitive decline occurs in middle-aged women, particularly in processing speed.[51] However, the scientific literature has yet to fully describe the age of onset, rate of decline, and/or contribution of ART to cognitive function among WLWH. This is especially important as we are beginning to see the long-term effects of ART on cognition. Our findings also demonstrate variability in domain-specific cognitive function. This demonstrates the importance of comprehensive serial cognitive testing to determine longitudinal changes in cognition among women exposed to ART as they age.

We did not note statistically significant evidence of cognitive decline in women exposed to PIs as we had originally hypothesized, and even noted improvement in verbal learning and memory compared to HIV-seronegative women in the context of lower baseline performance. Most reports of neurotoxicity related to PIs use are related to RTV exposure with clinical manifestations of dizziness, nausea, paresthesia, and taste alterations, but not cognitive change. These effects

were noted in the context of higher treatment doses.[19,20,52] In the modern era of ART, RTV is used at lower doses as a pharmacologic boosting agent for other PIs.[52]

Other PIs such as indinavir, RTV, aquinavir, and nelfinavir have been implicated in alterations of taste, and PI use has been cited as a risk factor for peripheral neuropathy.[53,54] This suggests that PIs may impact fine motor skills, but this was not demonstrated in our analysis.

In an evaluation of PLWH treated with boosted PI monotherapy or boosted PIs plus two NRTIs, no differences in cognitive performance were found between groups. This study, however, was limited in that the authors compared those with the similar PI exposure.[55] Large studies have not demonstrated significant neurologic effects with other newer members of the PI class of medication.

It is unknown if our findings of improvement with respect to verbal learning and memory is a return to baseline, reflection of the comparator group, and/or related to specific drugs and individual level factors. Future studies may focus on specific drugs within the PI class and/or examination of individualized factors that affect drug levels, including adherence, drug metabolism, central nervous system penetrance, genomics, and comorbidities, which may lead to polypharmacy and drug–drug interactions.

In addition, our findings of cognitive improvements in verbal learning were not expected with the NNRTI class of medication as prior studies have reported cognitive side effects with EFV and nevirapine, two NNRTIs.[16,17,56,57] The newer NNRTIs may have less central nervous system side effects than EFV and other older NNRTIs. When studied, switching patients from EFV to rilpivirine (RPV), a newer NNRTI, led to improved sleep quality and self-perceived cognition, but had no impact on objective cognitive performance.[58] Furthermore, other studies showed that RPV was associated with fewer neurological and psychiatric adverse events compared to EFV.[59] It is unclear if our findings are driven by a shift away from first generation NNRTIs, mediated by long-term viral suppression, and/or by time on therapy.

Further study of the cognitive outcomes of persons using the older NNRTIs as well as newer NNRTIs, including doravirine, are needed. Current guidelines from the Department of Health and Human Services and International Antiviral Society have moved away from the NNRTIs as first-line therapy toward INSTIs, citing greater drug toxicity with the NNRTIs, drug tolerability issues, high barrier to resistance, and less drug–drug interactions with the INSTIs.[31,60] If long-term outcome data show tolerability of newer NNRTIs, these agents may be favored in certain clinical situations.

Our study population had significant differences in the duration of drug exposure. Women in the INSTI group had a significantly shorter duration of ART exposure versus those in the PI or NNRTI groups. Even with the short duration of follow-up, nonstatistically significant trends in improved fine motor performance and verbal memory decline were demonstrated differences among those exposed to INSTIs versus other medications.

Other studies have linked INSTIs to changes in learning, and psychiatric effects such as depression and anxiety have been reported with this class of medication.[15,61,62] Although the long-term psychiatric and cognitive effects of this class of medication are not yet fully understood, we expect that with a longer duration of observation, and cognitive changes will be more apparent. Thus, we completed a subset analysis and noted time-dependent changes in cognition by drug class exposure. The duration of NNRTI drug exposure significantly impacted the measured attention function and the duration of INSTI exposure impacted psychomotor processing speed. We postulate that drug class effects on cognition may become more apparent with more years of exposure, especially among the INSTI group where our median duration of drug exposure was only 3.4 years.

This study was conducted in a cohort of virologically suppressed WLWH and age/race matched HIV-seronegative controls participating in a longitudinal observational cohort study and findings may be different among men living with the virus as prior reports indicate that WLWH have greater cognitive impairment than men.[7] Thus, our findings may not be generalizable among other community-based groups of WLWH not enrolled in research studies or other PLWH. In addition, our study was limited by the duration of follow-up for the women exposed to the INSTI class of medication compared to the follow-up time for women exposed to the NNRTI and PI classes of medication.

We did note a trend with worsening memory with INSTIs, but suspect that a longer duration of follow-up is needed to fully see the cognitive effects of this class of medication as our analysis indicated time-dependent changes with use of INSTIs and NNRTIs. As previous studies have suggested, there is considerable variability in clinical response to ART as well as drug-related toxicities.[63] There is also variable directional change in cognition and fluctuating cognitive status over time on an individual level among PLWH exposed to specific ART.[64,65] Our analysis focused on group- and class-based outcomes and cannot fully describe individual level responses to therapy or effects of individual within class drugs, but examined group trends and outcomes. Thus, changes in cognition may be underappreciated by this methodology.

Conclusions

Our study demonstrated that a significant portion of virologically suppressed WLWH had evidence of cognitive dysfunction in the context of long-standing HIV infection. We noted emerging trends in both cognitive decline and improvements in women exposed to ART. We suspect that age, ART, and HIV-related cognitive changes are emerging in this cohort of WLWH. Detailed longitudinal characterization of WLWH as they age will help define long-term cognitive outcomes, including the effects of ART, HIV, social determinants of health, and aging.

Authors' Contributions

All authors contributed to this work. A.B.S. and S.K., conceived and designed the project. A.B.S. interpreted the results and wrote/edited the article. S.K., L.R. and R.S.T. contributed scientific and clinical guidance to the study design and critically revised the article. C.L. analyzed the data and critically revised the article. B.A., D.E.V., H.B., C.D.L. A.A.A, K.W., D.G., and O.S. critically revised the article. All authors approved the final version of the article.

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Supplementary Material

Supplementary Table S1

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