# Cognitive trajectories over 4 years among HIV-infected women with optimal viral suppression

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## ABSTRACT

**Objective:** To determine whether persistent viral suppression alters cognitive trajectories among HIV-infected (HIV+) women on combination antiretroviral therapy (cART) by investigating performance longitudinally in uninfected (HIV−) and 3 groups of HIV+ women: those with consistent viral suppression after continuous cART use (VS), those without consistent virologic suppression despite continuous cART use (NVS), and those without consistent virologic suppression after intermittent cART use (Int NVS).

**Methods:** Two hundred thirty-nine VS, 220 NVS, 172 Int NVS, and 301 HIV− women from the Women's Interagency HIV Study (WIHS) completed neuropsychological testing every 2 years for 3 visits between 2009 and 2013. Mixed-effects regressions were used to examine group differences on continuous T scores and categorical measures of impairment (T score <40).

**Results:** On global function, VS women demonstrated lower scores and were more likely to score in the impaired range than HIV− women ($p = 0.01$). These differences persisted over time (group × time, $p > 0.39$). VS women demonstrated lower learning and memory scores than HIV− women ($p < 0.05$) and lower attention/working memory and fluency scores than HIV− and NVS women ($p < 0.05$). Group differences in scores persisted over time. Categorically, VS women were more likely to be impaired on attention/working memory and executive function than HIV− women ($p < 0.05$). On motor skills, VS and NVS women showed a greater decline and were more likely to be impaired than HIV− women ($p < 0.05$).

**Conclusions:** Cognitive difficulties remain among HIV+ women despite persistent viral suppression. In some instances, VS women are worse than NVS women, reinforcing the need for novel adjunctive therapies to attenuate cognitive problems. *Neurology*® 2017;89:1594–1603

## GLOSSARY

**ART** = antiretroviral therapy; **cART** = combination antiretroviral therapy; **CI** = cognitive impairment; **CPE** = CNS penetration-effectiveness; **HVLT-R** = Hopkins Verbal Learning Test-Revised; **Int NVS** = no consistent virologic suppression after intermittent combination antiretroviral therapy use; **MACS** = Multicenter AIDS Cohort Study; **NVS** = no consistent virologic suppression despite continuous combination antiretroviral therapy use; **OR** = odds ratio; **SE** = standard error; **VS** = viral suppression after continuous combination antiretroviral therapy use; **WIHS** = Women's Interagency HIV Study.

HIV penetrates the brain early in the course of infection,[1] and 30% to 60% of people with HIV will develop cognitive impairment (CI).[2] Rates of CI remain frequent among HIV-infected (HIV+) individuals with suppressed plasma HIV RNA (VS)[3,4] vs HIV-uninfected (HIV−) individuals, suggesting that CI persists despite these lifesaving treatments.[5] Less is known about the patterns of CI in the setting of VS, and few cohorts have the capacity to inform the

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Supplemental data at Neurology.org

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Data used in this study were obtained from the Women's Interagency HIV Study (WIHS) database (https://statepi.jhsph.edu/wihs/wordpress/). Investigators within the WIHS contributed to the design and implementation of WIHS and/or provided data but did not participate in analysis or writing of this report. A complete listing of WIHS investigators can be found at: https://statepi.jhsph.edu/wihs/WIHS_directory.pdf.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

longitudinal trajectories in VS individuals. Existing literature, including cross-sectional work from the cohort in the current study,[6,7] is largely informed by the examination of combined samples, including VS and unsuppressed individuals. Such heterogeneity limits the understanding of the burden of disease despite viral suppression and the identification of adjunctive therapies for VS individuals, an expanding population with the introduction of increasingly tolerable medication options.

Here, we examine longitudinal changes in CI using viral suppression and consistency of combination antiretroviral therapy (cART) use to define subgroups of HIV+ women. On the basis of prior findings,[7–9] we expected that all HIV+ women would show impairment at baseline and over time on global function, learning, attention, and executive function compared to HIV− women. HIV+ and particularly VS women were also expected to perform worse on neuropsychological measures compared to HIV− women on learning, memory, and attention. Finally, we expected VS women to perform better on neuropsychological testing and that fewer would meet criteria for impairment compared to HIV+ women not achieving persistent viral control whether consistently or intermittently on cART.

## METHODS

**Participants and data source.** Longitudinal data through September 30, 2015, were extracted from the Women's Interagency HIV Study (WIHS) in April 2016. Information about WIHS is provided at http://wihshealth.org. The first 2 waves of enrollment occurred between October 1994 and November 1995 and between October 2001 and September 2002 from Brooklyn, Bronx, Chicago, Washington, Los Angeles, and San Francisco. Barkan et al.[10] and Bacon et al.[11] provide recruitment procedures and eligibility criteria. Compared to women not completing neuropsychological testing at all visits (noncompleters, n = 607), completers (n = 932) were less likely to be Hispanic and more likely to smoke, to use marijuana and efavirenz, to be adherent to cART and on antiretroviral therapy (ART) for a longer duration, and to have a lower current CD4 count (table e-1 at Neurology.org).

WIHS was approved by the institutional review board at each site and was compliant with the Health Insurance Portability and Accountability Act. Written consent was obtained from all participants.

**Primary exposure variable.** CD4 count and plasma HIV RNA were measured concurrently with neuropsychological testing, which was implemented in 2009 and administered biennially. ART history and nadir CD4 count were obtained from chart review and self-report. With the use of Department of Health and Human Services/Kaiser Panel 2008 guidelines, HIV treatment regimens were categorized as cART, suboptimal cART, or no ART. Plasma HIV RNA was classified as below the limits of detection at <48 cp/mL. These data were used to create 4 groups: VS, HIV+ without consistent plasma viral control (≥1 visit with a detectable viral load during study period) despite continuous cART use (NVS), HIV+ without consistent plasma viral control after intermittent cART use (Int NVS), and HIV−. Individuals not falling into 1 of these groups were excluded from analysis. Plasma viral failure was defined as HIV RNA ≥10,000 cp/mL.

**Neuropsychological outcomes.** The following assessments were used: learning, Hopkins Verbal Learning Test-Revised (HVLT-R; outcome = total learning); memory, HVLT-R (outcome = delay free recall); attention/working memory, letter-number sequencing (outcomes = experimental and control conditions total correct); executive function, Trail Making Test Part B (outcome = time to completion) and Stroop Test Trial 3 (outcome = time to completion); psychomotor speed, Symbol Digit Modalities Test (outcome = total correct) and Stroop Test Trial 2 (outcome = time to completion); fluency, letter (outcome = total correct) and semantic (outcome = total correct); and motor skills, Grooved Pegboard (outcome = time to completion, dominant and nondominant hand). Timed outcomes were log transformed to normalize distributions and reverse scored, so higher equated to better performance.

Similar to other large-scale HIV cohorts[4,12,13] including WIHS,[7,14–16] demographically adjusted T scores were derived for each outcome. T scores were used to create domain scores and a global performance score for individuals with data for ≥4 domains (supplemental material). Impairment was examined with continuous (higher/lower scores) and categorical (scoring in the impaired range) outcomes. To examine impairment continuously, a composite T score was derived by averaging T scores for domains with ≥2 outcomes. If only 1 test in a domain was completed, the T score for that test was used. We computed binary outcomes (T score <40) using the Multicenter AIDS Cohort Study (MACS) procedures.[12] Continuous T scores and binary outcomes were examined to compare to previous large-scale studies.

**Statistical analysis.** We conducted mixed-effects regressions in SAS PROC MIXED (version 9.4, SAS Institute Inc, Cary, NC) to examine group differences in performance between the full sample of HIV+ and HIV−, between VS and HIV−, and between VS and the 2 other HIV+ groups defined by cART use and viral suppression status. Mixed-effects regression models were selected to handle repeated measurements nested within individuals and to handle missing data. Primary predictors included cART use and plasma viral suppression status, time (continuous), and the group by time interaction. We included the following covariates: site; enrollment wave; self-reported annual household income (≤$12,000, >$12,000, missing); depressive symptoms (Center for Epidemiological Studies Depression Scale ≥16 cutoff); heavy alcohol use (>7 drinks per week or ≥4 drinks in 1 sitting); smoking status (within the past week, former, never); marijuana use; crack, cocaine, and/or heroin use (within 6 months of the most recent visit, former, never); and hepatitis C RNA positive. Observations were trimmed (studentized residuals >|4.5|), which was the case for <1% of observations (4 for motor, 8 for speed). Secondary analyses were conducted in HIV+ women to determine whether HIV−related characteristics predicted performance on binary outcomes (nadir and current CD4 cell count, self-reported AIDS diagnosis, self-reported years on ART and efavirenz use, proportion of total WIHS visits with undetectable HIV RNA, plasma viral failure, and CNS

**Table 1** Sample characteristics by group for those women with a cognitive assessment completed at baseline

| | Group | | | | |
|---|---|---|---|---|---|
| | VS, mean (SD) (n = 239) | NVS, mean (SD) (n = 220) | Int NVS, mean (SD) (n = 172) | HIV−, mean (SD) (n = 301) | p Value |
| Age, y | 47.5 (8.5) | 47.4 (8.5) | 43.6 (9.0) | 43.2 (9.9) | <0.001 |
| Education, y | 12.5 (3.2) | 12.4 (2.8) | 12.5 (2.6) | 12.3 (3.0) | 0.86 |
| WRAT-3 reading subtest standard score | 92.9 (17.3) | 91.5 (18.1) | 92.7 (18.4) | 89.7 (18.4) | 0.13 |
| Race/ethnicity, n (%) | | | | | 0.01 |
| Black non-Hispanic | 146 (61) | 137 (62) | 126 (73) | 207 (69) | |
| White non-Hispanic | 38 (16) | 28 (13) | 14 (8) | 21 (7) | |
| Hispanic | 39 (16) | 47 (21) | 27 (16) | 60 (20) | |
| Other | 16 (7) | 8 (4) | 5 (3) | 13 (4) | |
| Annual household income <$12,000/y, n (%) | 93 (39) | 109 (49) | 83 (48) | 146 (48) | 0.16 |
| Current depressive symptoms, n (%)[a] | 62 (26) | 72 (33) | 59 (34) | 88 (29) | 0.25 |
| Hepatitis C RNA positive, n (%) | 40 (17) | 57 (26) | 37 (21) | 39 (13) | 0.001 |
| Smoking status, n (%)[b] | | | | | <0.001 |
| Current | 71 (30) | 100 (45) | 91 (53) | 149 (50) | |
| Former | 91 (38) | 74 (34) | 36 (21) | 88 (29) | |
| Never | 76 (32) | 46 (21) | 45 (26) | 64 (21) | |
| Recent heavy alcohol use, n (%)[c] | 32 (13) | 28 (13) | 37 (21) | 70 (23) | 0.002 |
| Marijuana use, n (%) | | | | | <0.001 |
| Recent | 34 (14) | 28 (13) | 32 (18) | 76 (25) | |
| Former | 131 (55) | 140 (64) | 106 (62) | 163 (54) | |
| Never | 74 (31) | 52 (24) | 34 (20) | 62 (21) | |
| Crack, cocaine, and/or heroin use, n (%) | | | | | 0.04 |
| Recent | 9 (4) | 15 (7) | 17 (10) | 31 (10) | |
| Former | 120 (50) | 125 (57) | 84 (49) | 152 (51) | |
| Never | 110 (46) | 80 (36) | 71 (41) | 118 (39) | |
| Efavirenz use at visit, n (%) | 98 (41) | 46 (21) | 6 (3) | — | <0.001 |
| Nadir CD4 count in WIHS, median (IQR) | 244 (197) | 135 (162) | 204 (221) | — | <0.001 |
| Current CD4 count, median (IQR) | 657 (359) | 456 (400) | 409 (293) | — | <0.001 |
| HIV RNA, median (IQR) | 48 (0) | 121 (649) | 2495 (21,378) | — | <0.001 |
| No. of assessments of HIV RNA ≤48 cp/mL, n (%) | | | | — | <0.001 |
| 3 | 239 (100) | — | — | | |
| 2 | — | 72 (33) | 36 (21) | | |
| 1 | — | 85 (38) | 65 (38) | | |
| 0 | — | 63 (29) | 71 (41) | | |
| HIV RNA ≥10,000 cp/mL, n (%) | — | 28 (13) | 55 (33) | — | <0.001 |
| Proportion of WIHS visits since enrollment, mean (SD) | | | | | |
| HIV RNA <500 cps/mL | 66 (25) | 49 (24) | 37 (30) | — | <0.001 |
| On HAART | 71 (25) | 69 (24) | 35 (33) | — | <0.001 |
| Adherence (≥95%) to cART, n (%) | 216 (91) | 181 (83) | 31 (45) | — | <0.001 |
| CPE score since last visit, median (IQR) | 7 (2) | 7 (2) | 0 (7) | — | <0.001 |
| CPE exposure | | | | — | <0.001 |
| Low (<8) | 136 (57) | 119 (54) | 144 (84) | | |
| Medium (8–9) | 61 (26) | 59 (27) | 11 (6) | | |
| High (>9) | 42 (17) | 42 (19) | 17 (10) | | |

*Continued*

**Table 1** Continued

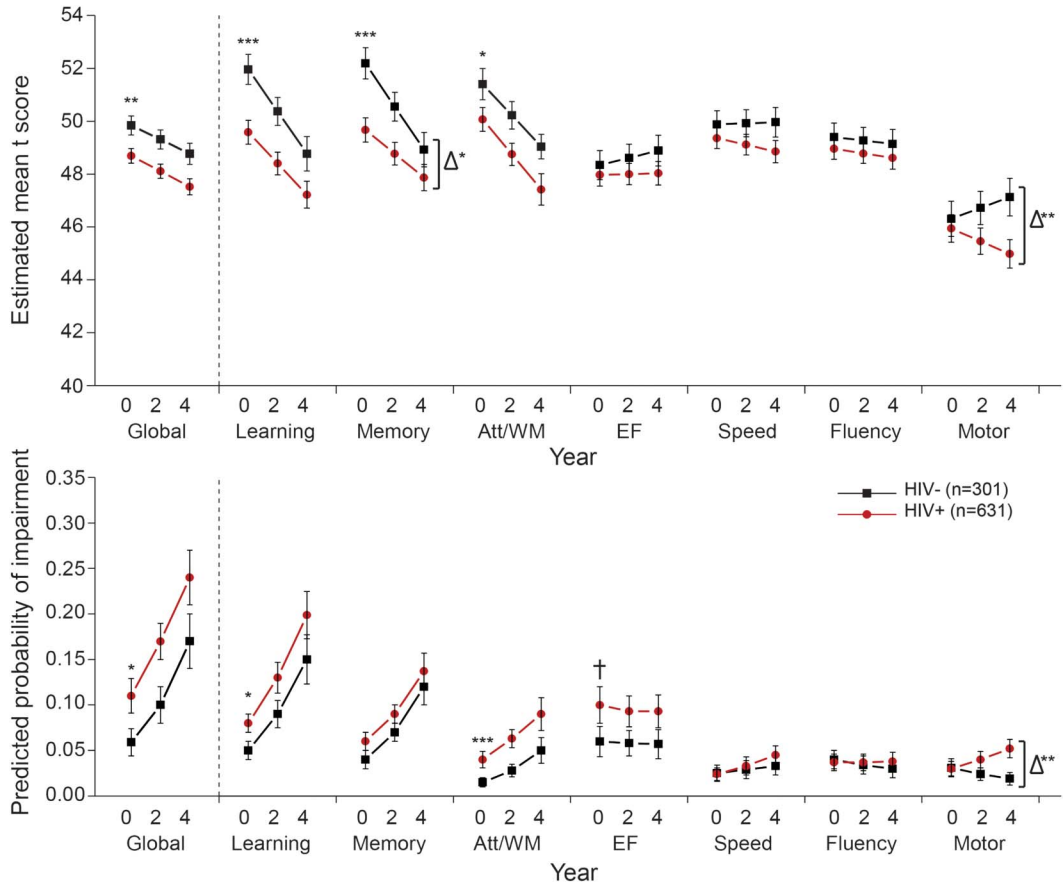
| | Group | | | | |
|---|---|---|---|---|---|
| | VS, mean (SD) (n = 239) | NVS, mean (SD) (n = 220) | Int NVS, mean (SD) (n = 172) | HIV−, mean (SD) (n = 301) | *p* Value |
| ART duration, M (SD), y | 11.7 (3.8) | 11.7 (4.1) | 8.7 (5.4) | — | <0.001 |
| HAART duration, mean (SD), y | 10.1 (3.5) | 10.2 (3.6) | 6.9 (5.0) | — | <0.001 |
| Prior AIDS diagnosis, n (%) | 96 (40) | 114 (52) | 56 (32) | — | <0.001 |

Abbreviations: ART = antiretroviral therapy; cART = combination antiretroviral therapy; CPE = CNS penetration-effectiveness; HAART = highly active antiretroviral therapy; Int NVS = intermittent cART use and inconsistent plasma viral suppression over the 4-year study duration; IQR = interquartile range; NVS = consistent use of cART but inconsistent plasma viral suppression over the 4-year study duration; VS = consistent use of cART and virally suppressed over the 4-year study duration; WIHS = Women's Interagency HIV Study; WRAT-3 = Wide Range Achievement Test.
Variables reported as number (percent) were analyzed with $\chi^2$ tests. Variables reported as mean (SD) were analyzed with 1-way analysis of variance. Variables reported as median/IQR were analyzed with the Wilcoxon-Mann-Whitney test.
[a] Center for Epidemiological Studies Depression Scale ≥16 cutoff.
[b] Current refers to within the past week; recent, refers to within 6 months of the most recent WIHS visit.
[c] Heavy alcohol use reflects >7 drinks a week or ≥4 drinks in 1 sitting.

penetration-effectiveness [CPE] score since the last WIHS visit[17] [categorized as low <8, medium 8–9, or high >9[18]]).

**RESULTS** **Sample characteristics.** Nine hundred sixty women recruited between 1994 and 2002 completed 3 neuropsychological assessments; 239 were VS, 220 were NVS, 172 were Int NVS, and 301 were HIV−. Twenty-eight were virally suppressed but not on cART and therefore excluded from analyses. The 932 women analyzed were 66% black non-Hispanic and 18% Hispanic and ranged in age from 25 to 77 years (mean = 45.3, SD = 9.2 years; table 1). Compared

**Figure 1** Longitudinal trajectories of cognitive performance (estimated mean, SE) and cognitive impairment (estimated probability, SE) for HIV+ and HIV− women



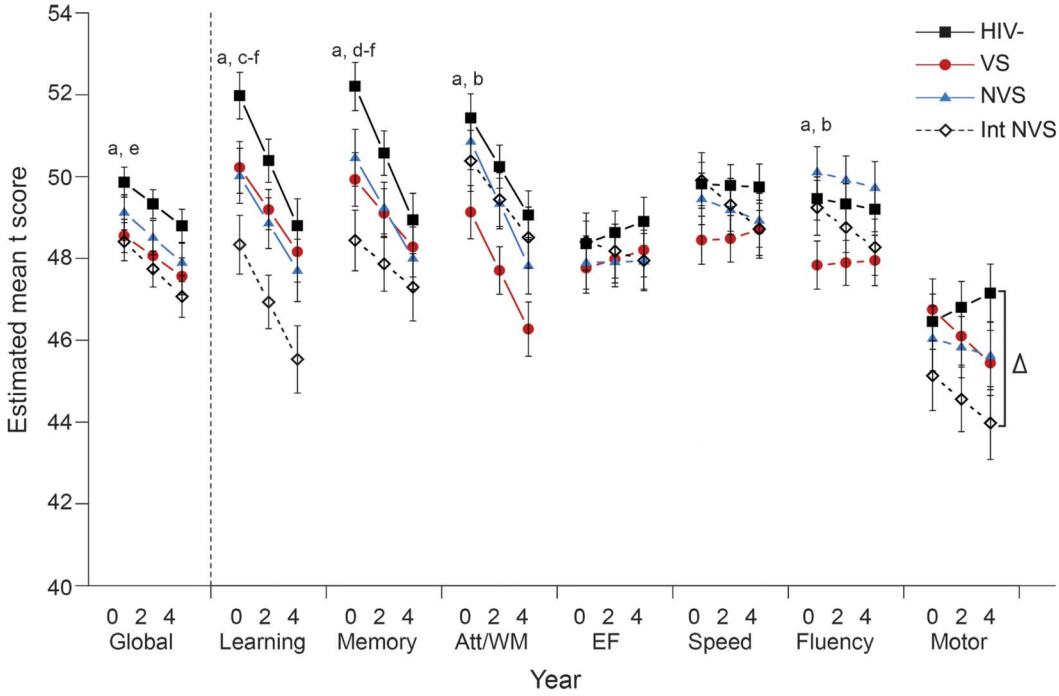

Att/WM = attention/working memory; Δ = group difference in slopes; EF = executive function; SE = standard error. ***$p$ < 0.001; **$p$ < 0.01; *$p$ < 0.05; †$p$ = 0.06.

to HIV− women, HIV+ women were slightly older (46 vs 43, $p < 0.001$), more likely to have HCV+ viremia (21% vs 13%, $p = 0.002$), and less likely to engage in heavy alcohol (15% vs 23%, $p = 0.003$) and marijuana (15% vs 25%, $p < 0.001$) use. Among those HIV+, VS women had higher proximal and nadir CD4 counts, had undetectable plasma HIV RNA levels for a greater proportion of WIHS visits, and were more likely to adhere to HIV medication than NVS and Int NVS women ($p < 0.001$). An examination of data on missed ART doses showed the following reasons: most Int NVS women reported not being prescribed (30%), CD4 count was too high or viral load was too low (20%), personal decision/feeling healthy (31%), or side effects (7%).

**Combined sample of HIV+ vs HIV− women.** ***Global function.*** At baseline, HIV+ women demonstrated lower scores ($p = 0.005$) and an increased likelihood of scoring in the impaired range ($p = 0.01$; figure 1 and table e-2) than HIV− women. Over time, the full sample showed a decline in scores and increased frequency of impaired performance ($p < 0.05$). Regardless of performance metric, there were no HIV serostatus by time interactions, noting that HIV+ and HIV− women showed consistent differences over time ($p > 0.45$). Among HIV+ women, every 10% increase in the proportion of suppressed visits was associated with being 9% less likely to score in the impaired range (odds ratio [OR] 0.91, 95% confidence interval 0.83–0.99, $p = 0.04$).

***Domains.*** At baseline, HIV+ women demonstrated lower scores on learning ($p < 0.001$), memory ($p < 0.001$), and attention/working memory ($p = 0.04$) than HIV− women (figure 1, top). HIV+ women also showed an increased likelihood of scoring in the impaired range on attention/working memory ($p < 0.001$) and learning ($p = 0.04$) but not on memory ($p = 0.16$) than HIV− women (figure 1, bottom). The full sample showed a decline in scores and an increased likelihood of impairment on learning, memory, and attention/working memory ($p < 0.05$). While there were no HIV serostatus by time interactions on attention/working memory or learning ($p > 0.27$), interactions were noted on memory when examined continuously ($p = 0.04$) and motor skills when examined continuously and categorically ($p = 0.008$). Among HIV+ women, a 10% increase in the proportion of WIHS visit being suppressed was associated with a decreased likelihood of scoring in the impaired range on learning (OR 0.89, 95% confidence interval

**Figure 2** Longitudinal trajectories of cognitive performance (estimated mean, SE) by group




Comparisons are for (a) VS vs HIV−, (b) VS vs NVS, (c) VS vs Int NVS, (d) NVS vs HIV−, (e) Int NVS vs HIV−, and (f) Int NVS vs NVS. Significant differences at baseline ($p = 0.05$). Att/WM = attention/working memory; combination antiretroviral therapy; Δ = significant group difference in slopes at $p < 0.05$; EF = executive function; Int NVS = intermittent cART use and inconsistent plasma viral suppression over the 4-year study duration; NVS = consistent use of cART but inconsistent plasma viral suppression over the 4-year study duration; SE = standard error; VS = consistent use of cART and virally suppressed over the 4-year study duration.

0.82–0.99, $p = 0.01$) and memory (OR 0.90, 95% confidence interval 0.82–0.99, $p = 0.03$).

**Subgroup differences.** ***Global function.*** At baseline, VS women demonstrated lower scores ($p < 0.05$; figure 2 and table 2) and were more likely to be impaired than HIV− women (OR 2.18, 95% confidence interval 1.14–4.18, $p = 0.02$; figure 3). Performance by Int NVS women at baseline, but not NVS women, mirrored the pattern observed in VS women (table e-3). There were no differences between VS and NVS or Int NVS women and no group × time interactions ($p > 0.59$).

***Domains.*** At baseline, VS women demonstrated lower scores on learning, memory, attention/working memory, and fluency than HIV− women ($p < 0.05$; figure 2 and, table 2). VS women demonstrated higher scores on learning than Int NVS women and lower scores on attention/working memory and fluency than NVS women ($p < 0.05$). NVS and Int NVS women demonstrated lower scores on learning and memory than HIV− women ($p < 0.05$), and Int NVS women demonstrated lower scores on memory than NVS women ($p < 0.05$). A group × time interaction was observed on motor skills ($p = 0.03$).

After HIV-related characteristics were controlled for ($p < 0.10$), all subgroup differences remained ($p < 0.05$) except in attention/working memory ($p = 0.15$), which was eliminated after accounting for nadir CD4 cell count (B = −0.6 [per 100 change], standard error [SE] = 0.2, $p = 0.01$) and CPE score (B = 1.6 [medium vs high], SE = 0.7, $p = 0.02$). Group differences remained in learning and memory after accounting for a previous AIDS diagnosis (B range = −1.4 to −1.7, SE = 0.6, $p < 0.05$), CPE score (B range = 1.4 to 1.7 [medium vs low], SE = 0.06, $p < 0.05$; also in learning B = 1.6 [medium vs high], SE = 0.7, $p = 0.03$), and ART use (B = −1.4 [per 10 years], SE = 0.7, $p < 0.06$). Differences remained in fluency even with efavirenz use (B = −1.2, SE = 0.6, $p = 0.04$), plasma viral failure (B = −1.0, SE = 0.5, $p = 0.05$), and a previous AIDS diagnosis (B = −1.2, SE = 0.6, $p = 0.06$) as significant predictors.

For binary outcomes, VS women were more likely to perform in the impaired range at baseline than HIV− women on attention/working memory (OR 2.81, 95% confidence interval 1.33–5.91, $p = 0.007$) and executive function (OR 2.28, 95% confidence interval 1.11–4.66, $p = 0.02$; figure 3). Each HIV+ subgroup was more likely to be impaired than HIV− women on attention/working memory ($p < 0.05$) but not executive function (table e-3). In learning, only Int NVS women were more likely to be impaired than HIV− women (OR 2.27, 95% confidence interval 1.21–4.27, $p = 0.01$). Interactions between HIV serostatus and time were significant for motor skills ($p < 0.05$).

In secondary sensitivity analyses, age did not alter the pattern of results. Age was not included in primary models as a covariate because age was incorporated into the T score computation.

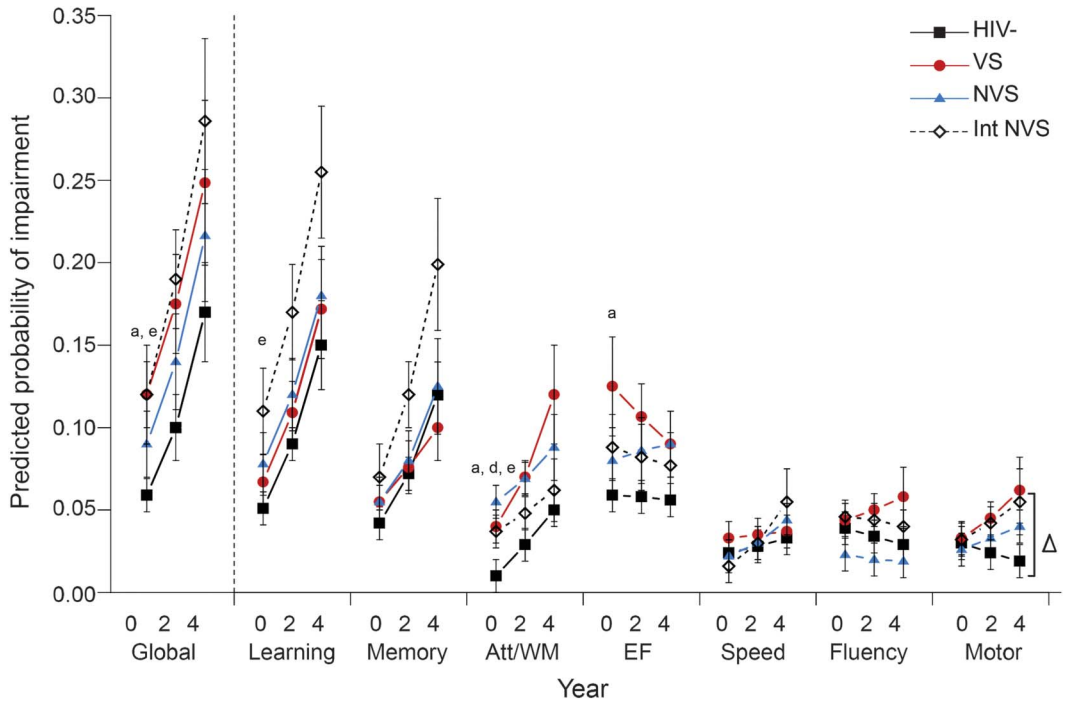
**DISCUSSION** Findings from this large-scale, longitudinal study show variation in the pattern of performance by plasma viral suppression status and in

**Table 2** Estimated group mean T score differences (standard errors) in global neuropsychological function and in each domain at baseline

| | | Group comparisons | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Primary | | | | | | Secondary | | | | | |
| | | VS (vs HIV−) | | VS (vs NVS) | | VS (vs Int NVS) | | NVS (vs HIV−) | | Int NVS (vs HIV−) | | Int NVS (vs NVS) | |
| Outcome | n | B (SE) | p Value | B (SE) | p Value | B (SE) | p Value | B (SE) | p Value | B (SE) | p Value | B (SE) | p Value |
| Global neuropsychological function | 924 | −1.3 (0.5) | 0.01 | −0.6 (0.5) | 0.30 | 0.2 (0.6) | 0.80 | −0.7 (0.5) | 0.15 | −1.4 (0.5) | 0.008 | −0.7 (0.6) | 0.22 |
| Domains | | | | | | | | | | | | | |
| Learning | 927 | −1.7 (0.8) | 0.02 | 0.2 (0.8) | 0.81 | 1.9 (0.9) | 0.03 | −2.0 (0.8) | 0.01 | −3.6 (0.8) | <0.001 | −1.7 (0.9) | 0.06 |
| Memory | 927 | −2.3 (0.8) | 0.004 | −0.5 (0.9) | 0.86 | 1.5 (0.9) | 0.10 | −1.7 (0.8) | 0.03 | −3.8 (0.9) | <0.001 | −2.2 (0.9) | 0.03 |
| Attention/WM | 818 | −2.2 (0.8) | 0.005 | −1.7 (0.9) | 0.04 | −1.2 (0.9) | 0.18 | −0.6 (0.8) | 0.50 | −1.0 (0.9) | 0.23 | −0.5 (0.9) | 0.61 |
| Executive function | 921 | −0.6 (0.8) | 0.44 | −0.1 (0.8) | 0.86 | −0.6 (0.9) | 0.46 | −0.5 (0.8) | 0.55 | 0.0 (0.8) | 0.95 | 0.5 (0.9) | 0.57 |
| Speed | 930 | −1.4 (0.7) | 0.06 | 1.0 (0.8) | 0.20 | −1.5 (0.8) | 0.08 | −0.4 (0.7) | 0.63 | 0.1 (0.8) | 0.91 | 0.4 (0.9) | 0.60 |
| Fluency | 922 | −1.6 (0.7) | 0.03 | −2.3 (0.8) | 0.004 | −1.4 (0.8) | 0.09 | 0.6 (0.7) | 0.38 | −0.2 (0.8) | 0.78 | −0.9 (0.8) | 0.30 |
| Motor | 911 | 0.3 (0.9) | 0.70 | 0.7 (1.0) | 0.49 | 1.7 (1.1) | 0.11 | −0.4 (0.9) | 0.72 | −1.3 (1.0) | 0.19 | −1.0 (1.0) | 0.37 |

Abbreviations: B = unstandardized β weight of the group difference in performance; cART = combination antiretroviral therapy; Int NVS = intermittent cART use and inconsistent plasma viral suppression over the 4-year study duration; NVS = consistent use of cART but inconsistent plasma viral suppression over the 4-year study duration; SE = standard error; VS = consistent use of cART and virally suppressed over the 4-year study duration; WM = working memory.

**Figure 3** Longitudinal trajectories of cognitive impairment (estimated probability, SE) by group




Comparisons are for (a) VS vs HIV−, (b) VS vs NVS, (c) VS vs Int NVS, (d) NVS vs HIV−, (e) Int NVS vs HIV−, and (f) Int NVS vs NVS. Significant differences at baseline ($p < 0.05$). Att/WM = attention/working memory; combination antiretroviral therapy; Δ = significant group difference in slopes at $p < 0.05$; EF = executive function; Int NVS = intermittent cART use and inconsistent plasma viral suppression over the 4-year study duration; NVS = consistent use of cART but inconsistent plasma viral suppression over the 4-year study duration; SE = standard error; VS = consistent use of cART and virally suppressed over the 4-year study duration.

examining impairment continuously and categorically. This study expanded our cross-sectional work[7] and allows direct comparison to previously published large-scale HIV+ cohorts.

Within our cohort, the full sample of HIV+ women demonstrated initial and continued impairment compared to HIV− women on global function. Findings confirm persistent deficits in global function among HIV+ women despite continual plasma viral suppression. In addition, our findings demonstrate the persistence and slow evolution of CI in long-term–treated cART cohorts and in global cohorts despite demographic differences. This persistent impairment also suggests that early intervention for HIV+ women may improve neuropsychological function. While HIV serostatus differences were observed in other domains, the pattern of benefits and decrements varied across metrics. This is not surprising because the use of continuous variables that assess the full spectrum of behavior provides greater statistical power than the comparison of proportions below a chosen cut point with a dichotomous outcome.[19,20]

Despite optimal treatment, VS women demonstrated an initial and continued likelihood of impairment in global function, attention/working memory, and executive function but not learning compared to HIV− women. VS women also showed an increased likelihood of impairment in motor skills compared to HIV− women. From the pre-cART to post-cART era, studies in largely male cohorts that used categorical measures report primary deficits in global function, learning,[8,9] attention,[8] and executive function[9] and show decreased likelihood of impairment in motor skills.[8] These reports, in part, align with our cross-sectional findings[7] and longitudinal analysis in MACS showing no effect on psychomotor speed,[19] but they also demonstrate the need for longitudinal data and subgroup analyses to detect differences in fluency and susceptibility over time on motor skills. Consistent with the finding for motor skills, studies demonstrate subcortical brain atrophy in HIV+ men with predominantly well-controlled immune status and viral loads vs controls.[20] Inconsistencies across studies could be due to differences in sociodemographic characteristics, neuropsychological battery, and outcomes incorporated into domains and/or the degree of cohort viral suppression.

Unexpectedly, VS women had worse scores in attention and fluency when performance was measured continuously compared to NVS women. HIV-related clinical factors eliminated group

differences in attention but not in fluency. Although the underlying factors driving this pattern of results are unclear, it is possible that cART itself contributes to brain injury, perhaps through mitochondrial injury.[21,22] In addition to nucleoside reverse transcriptase inhibitors, non–nucleoside reverse transcriptase inhibitors (e.g., efavirenz) are associated with CNS symptoms possibly through mitochondrial perturbations[23–25] or diminished blood-brain barrier integrity.[26] Consistent with these findings, current efavirenz use was associated with poorer fluency, a domain in which VS women performed worse than NVS women. Additional work is needed to disentangle specific cART effects that might provide insights into the pattern of vulnerabilities among VS women. Furthermore, findings underscore the importance of examining HIV+ patients by suppression status. Overlooking this heterogeneity may lead to conclusions less pertinent to treated HIV and yield a less relevant framework for studying mechanisms and adjunctive treatments for HIV+ individuals.

Analyses indicated that the Int NVS group performed worse than other HIV+ subgroups on learning and memory, suggesting that the fluctuation in both treatment and plasma viral suppression is more damaging than simply fluctuation in suppression with persistent cART use. However, it is important to note that at any given time, Int NVS women may have stopped taking cART because they felt healthy or the intermittent use could have been linked to fluctuation in other potentially confounding health-related factors. Sixty-two percent of Int NVS women stated they did not take cART because it was not prescribed, their CD4 count was too high or viral load too low, or they felt healthy. These responses could be taken as an indication of health, although in some cases, not being prescribed ART could be due to detrimental factors such as nonadherence.

The strongest HIV-related predictor of neuropsychological performance was the proportion of time with undetectable viral load. Specifically, we found that an increasing proportion of time with undetectable viral load was associated with improved performance in some domains, an encouraging finding. Potent ARTs with less neurotoxicity may support the protective effects of viral suppression on cognition.

In analyses determining whether HIV+ subgroup differences remained in the domains of learning, memory, attention/working memory, and fluency treated continuously, we found that the most consistent predictor across outcomes was a lifetime AIDS diagnosis. Many studies have shown that a past AIDS diagnosis is one of the greatest vulnerabilities among HIV+ individuals,[27,28] a finding that may represent decreased cognitive reserve from irreparable brain injury before cART initiation. Consistent with some studies,[29,30] we also found nadir CD4 count, years of ART use, plasma viral failure, and efavirenz use to negatively influence performance. Conversely, when CPE scores were averaged, performance was optimized compared to lower or higher CPE score. These findings are consistent with others showing that higher CPE scores are associated with a lower frequency of CI[31,32] but somewhat inconsistent with reports that more penetrant cART regimens are associated with worse neuropsychological function.[18,33]

The present study has limitations. First, more time points would improve the understanding of cognitive trajectories associated with variations in viral suppression and cART use and determine those showing improvement, persistent decline, and fluctuations over time in global and domain-specific neuropsychological functioning. Nevertheless, with 3 time points over 4 years, we demonstrated specific vulnerabilities among HIV+ women despite consistent viral suppression. Second, we used at-risk HIV− women as our normative-based sample, which may bias our results to yield an underestimation of the magnitude of group differences. We selected our control group as the comparison because they are similar to our HIV+ participants in ethnic composition, socioeconomic status, and substance use. What highlights the comparability between these 2 groups is that even the HIV− women demonstrated a decline in scores and an increased risk of CI similar to the HIV+ women in learning, memory, and attention/working memory. If healthier, the HIV− women would have been expected to demonstrate either improvement (demonstrating practice) or a stable performance over time. HIV− WIHS women, on average, demonstrate CI compared to demographically adjusted normative standards.[34,35] HIV− WIHS participants performed on average 2 SDs below HVLT manual age-adjusted norms of individuals 40 to 49 years of age on learning and memory. Normative standards adjusted for age, education, and race indicate that our HIV− participants performed 1 SD below published norms[34] on HVLT outcomes. The differences observed between serostatus groups suggest an added cognitive injury and persistent vulnerability despite viral suppression. Future studies comparing WIHS women to all or predominantly male HIV+ cohorts will enable us to assess the magnitude and pattern of impairment in WIHS women vs others and to directly assess sex differences because HIV+ women may be more vulnerable than HIV+ men.[36,37]

Overall, global function, learning, memory, attention/working memory, and fluency continue to be vulnerabilities among HIV+ women, particularly among those who are virally suppressed. Future longer-term studies are needed to confirm these observed patterns and to investigate the neurobiological mechanisms underlying these findings.

## AUTHOR CONTRIBUTIONS

L.H.R., V.G.V.: conception and design of the study. L.H.R., G.S., C.A., L.B.: acquisition and analysis of data. L.H.R., V.G.V., L.B., G.S., E.M.M., P.M.M.: drafting a significant portion of the manuscript or figures. All authors provided a critical review of manuscript for important intellectual content and contributed to and approved the final manuscript.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## DISCLOSURE

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