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Better executive function is independently associated with full HIV suppression during combination therapy

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Objective: HIV-associated neurocognitive impairment continues to be prevalent and clinically relevant. We examined the relationship between neurocognition and full plasma HIV RNA suppression among study participants over a 15-year period at a large research program.

Design/methods: We analyzed the combined prospective studies of the HIV Neurobehavioral Research Program at the University of California at San Diego. Participants were eligible for analysis if on three drug combination antiretroviral therapy with comprehensive neuropsychological testing results. Participants who reported recent nonadherence were excluded. The primary outcome was plasma HIV RNA of 50 copies/ml or less. Generalized estimating equation was used to assess for associations with full virologic suppression taking into account longitudinal visits.

Results: There were 1943 participants at baseline, of whom 69.4% had plasma HIV RNA of 50 copies/ml or less. Participants with full suppression were slightly older, less likely to abuse cocaine, and had significantly better executive function. Multivariate analysis with incorporation of longitudinal visits (total = 5555) confirmed current cocaine abuse to be strongly associated with lack of virologic suppression (odds ratio = 0.45, 95% confidence interval = 0.31–0.63). In contrast, increasing age, increasing years of HIV infection, and increasing executive function (odds ratio = 1.18 1.18 for *T* score change of 10, 95% confidence interval = 1.07–1.30) were associated with full virologic suppression. Lack of virologic suppression at baseline was associated with a significant subsequent decline in executive function.

Conclusion: In a 15-year research cohort of almost 2000 HIV-infected individuals on combination antiretroviral therapy, better executive function was associated with full virologic suppression, possibly as a result rather than a cause.

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Keywords: AIDS, HIV, neurocognitive disorders, sustained virologic response

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Introduction

Infection with HIV has become a treatable condition in the combination antiretroviral therapy (cART) era, and virologic suppression is commonly achieved with current cART regimens [1]. The WHO has proposed a goal that at least 90% of HIV-infected (HIV+) individuals on cART attain full virologic suppression [2]. Some countries appear to have reached this goal. Sweden, for example, recently reported that 94.7% of HIV+ individuals on cART had achieved full virologic suppression [3]. Many other countries, however, have not yet reached such a high level of virologic suppression. For example, the WHO recently reported that across Latin America and the Caribbean, the median rate of virologic suppression among HIV+ individuals on cART was 66% [2]. Overall, the United States also has not yet achieved 90% virologic suppression. For example, a very large United States study published in 2017 of 339, 515 HIV+ individuals receiving care showed that 72.6% had durable virologic suppression [4]. Lack of virologic suppression predisposes infected individuals to increased rates of opportunistic infections, end organ disease, and death [5]. In addition, HIV transmission is more likely when plasma HIV RNA levels are not suppressed [6]. Therefore, the causes for and consequences of lack of full virologic suppression continue to merit study. Lack of virologic suppression during cART has been associated with multiple factors. These include younger age, differences in race, and substance abuse [7–10]. To achieve the goals of optimal health and zero transmission, a fuller understanding of the factors that may affect virologic suppression during cART is needed.

HIV-associated neurocognitive disorder (HAND) specifically and neurocognitive impairment more broadly continue to be common in the cART era, particularly if asymptomatic impairment is included. The prevalence of HAND during the cART era varies widely depending on study, but has been found to be as high as 30–40% [11,12]. HAND in the cART era is associated with decreased quality of life and increased risk of mortality [13,14]. In addition, there may be a link between worse neurocognitive performance and lack of virologic suppression. Previous studies have reported a significant association between diminished neuropsychological performance (including within individual domains such as executive function) and cART nonadherence [15–17]. In addition, individuals with decreased neuropsychological performance may believe that they are taking cART correctly, when in actuality they may not be. Alternatively, HIV+ individuals without full virologic suppression may have worse neuropsychological performance due to the detrimental effects of uncontrolled viral replication. To better understand the relationship between neuropsychological performance and virologic suppression, we undertook an analysis of a large research cohort in which all participants received comprehensive neuropsychological testing. We hypothesized that worse global neuropsychological performance would be associated with lack of full virologic suppression despite adherence by self-report. Our secondary hypothesis was that worse performance on individual neuropsychological domains such as executive function would be associated with lack of full virologic suppression despite adherence by self-report.

Methods

Data were pooled from HIV Neurobehavioral Research Program (HNRP) observational research studies at the University of California at San Diego from a 15-year period in the cART era (years 2000–2015). The analysis included data from the Central Nervous System Antiretroviral Therapy Effects Research study (which includes multiple geographic sites across the United States), the California NeuroAIDS Tissue Consortium study, and other federally and locally funded studies. For the purposes of this analysis, only participants who were prescribed three drug cART, reported recent adherence, and had full neuropsychological assessment were considered. The neuropsychological assessment by definition included at least two tests from each domain per HNRP protocol: first, Executive Function (Wisconsin Card Sorting Test-64 item, Trail Making Test Part B, or Stroop Color Word interference); second, Working Memory/Attention (WMS-III Spatial Span and Paced Auditory Serial Addition Task); third, Speed of Information Processing (WAIS III Digit Symbol, WAIS III Symbol Search, Trail Making Test Part A, or Stroop Color Naming); fourth, Learning (Hopkins Verbal Learning Test and Brief Visuospatial Memory Test); fifth, Memory (Hopkins Verbal Learning Test-delayed recall and Brief Visuospatial Memory Test-delayed recall); sixth, Verbal Fluency (Controlled Oral Word Association Test and Categories – Animals and Actions); and seventh, Fine motor skill (Grooved Pegboard Test dominant and nondominant hands). Raw scores on these tests were converted to mean T scores based on published demographic norms with mean = 50 and SD = 10 [18–22]. These were then used to compute neurocognitive domain T-scores and a global mean T-score. Commercially available HIV RNA tests were used for all of the studies. Due to the different timeframes of the studies, these tests included lower limits of detection of 40, 48, and 50 copies/ml. Therefore, for the purposes of this analysis, the primary end point was defined as plasma HIV RNA of 50 copies/ml or less. Adherence was assessed using the AIDS Clinical Trials Group (ACTG) interview form. Only participants who reported recent cART adherence were eligible for inclusion in this analysis. Therefore, participants who answered 'yes' to missing medication during any of the following intervals were excluded: 'in the last 4 days', 'within the last week',

or '1–2 weeks ago'. Instrumental activities of daily living were measured with a modified Lawton–Brody questionnaire [23]. Depression symptoms were assessed with version two of the Beck Depression Inventory [24]. Current substance abuse in the last 30 days was defined by diagnostic and statistical manual of mental disorders version four criteria [25]. Longitudinal assessments were also included when available for participants with multiple study visits. Score adjustment for practice effects was also made for longitudinal visits by using median practice effect data from previous work [26].

Statistical approach

Continuous variables were assessed for normality with the Shapiro–Wilk test. When conditions for normality were not met, the Wilcoxon rank sum test was used for differences in continuous variables. Otherwise, Student's *t* test was used for differences in continuous variables. Chi-squared test was used to examine differences in categorical variables. Cohen's *d* was reported for effect size. Risk factors for lack of full virologic suppression were then identified using logistic regression model via generalized estimating equation (GEE) to accommodate multiple visits. Observations were weighted by inverse number of visits, and covariates included demographic and medical characteristics as well as neuropsychological measures. The following covariates were screened during the modeling process: age, sex, race (white versus nonwhite), years of HIV infection, current and nadir $CD4^+$ as well as current $CD4^+/CD8^+$ ratio, months on current cART regimen, hepatitis C virus seropositivity, medical history (hypertension, stroke, and diabetes), current tobacco smoker or current abuse of alcohol, marijuana, cocaine, methamphetamine, or opiates, Beck Depression Inventory scale, and activities of daily living dependency. Individual neuropsychological domain *T* scores as well global *T* score were examined as continuous variables. In addition, an exploratory multivariate analysis of domains found to be significant as continuous variables in the primary multivariate analysis was performed by transforming those domains into impaired/not impaired (*T* score ≤ 40 versus >40) categorical variables. Covariates that were significant at the 0.05 level in univariate analysis were considered in the multivariate analysis and the final model was obtained using backward stepwise selection. Covariate values were updated for each visit analyzed, as opposed to limiting the analysis to covariate baseline values. While the primary analytic outcome was plasma HIV RNA of 50 copies/ml or less, a secondary GEE modeling analysis was performed using the outcome of plasma HIV RNA of 200 copies/ml or less, which has been recently suggested to define virologic suppression in HIV primary care guidelines [27]. For domains that were found to have a statistically significant association, we then examined change in performance over time based on virologic suppression and vice versa. This was performed with chi-squared test.

Results

The larger cohort from which the current analysis was derived encompassed 4605 individuals with a total of 20 511 study visits. Of the 4595 participants from this larger cohort with full demographic data, the mean age at the first visit was 40.8 years and 83.8% were men. In terms of race/ethnicity, 49.6% were white, 29.3% were black, and 17.3% were Hispanic. The vast majority of participant exclusions from this larger cohort resulted from: first, not taking combination antiretroviral therapy; second, comprehensive neuropsychological testing results not available; third, report of recent nonadherence; or fourth, missing data in laboratory parameters such as $CD4^+$ cell count or HIV RNA level.

The final analysis cohort of 1943 participants were older, more likely to be women, and more likely to be black compared with participants who were excluded (all $P < 0.05$). This final analysis cohort had a total of 5555 study visits between the years 2000 and 2015. Mean number of months on the current cART regimen at the baseline visit was 20.6. Demographic and disease characteristics based on baseline plasma HIV RNA status ($n = 1943$) are summarized in Table 1, while demographic and disease characteristics of the cohort with all visits combined ($n = 5555$) are summarized in Table 2. 30.6% of participants had lack of full virologic suppression (plasma HIV RNA >50 copies/ml) at baseline. These participants were slightly younger, more likely to be of non-white race, and had lower current and nadir $CD4^+$ T-cell counts (404 versus 546 cells/μl and 150 versus 175 cells/μl, respectively) compared with the group with full virologic suppression (plasma HIV RNA $\leq$50 copies/ml). Participants in the two groups had similar frequencies of hepatitis C seropositive status, diabetes, and stroke history, but participants without full suppression were on their current cART regimen for less time and were less likely to be hypertensive. Participants without full suppression were less likely to be current tobacco smokers (11.3 versus 15.9%, $P = 0.008$) but more likely to be current abusers of cocaine (12.0 versus 4.9%, $P < 0.001$). There were no differences between the two groups in terms of current abuse of other drugs. Neuropsychological testing showed that executive function was significantly lower in the group without full suppression (mean *T* score 44.6 versus 46.4, $P = 0.001$), but that verbal performance was significantly higher in this group (mean *T* score 49.2 versus 47.9, $P = 0.018$). However, the effect sizes for these differences in cognitive performance were relatively small. Specifically, Cohen's *d* effect size was 0.13 for difference in executive function and 0.18 for difference in verbal. Central nervous system penetration effectiveness score was not significantly different between the two groups (mean 7.5 in nonsuppressed group versus mean 7.6 in group with HIV RNA $\leq$ 50 copies/ml, $P = 0.8$). 83.6% of participants were on a regimen of protease inhibitor and nucleoside reverse transcriptase

Table 1. Baseline characteristics of participants by plasma HIV RNA suppression.

Variable reported as mean (SD) or number (%)	Baseline plasma HIV RNA status		*P* value
	HIV RNA > 50, *n* = 595	HIV RNA ≤ 50, *n* = 1348	
Male sex	495 (83.3%)	1090 (81.0%)	0.22
Race = white	268 (45.1%)	682 (50.7%)	**0.02**
Years of age	43.6 (8.8)	45.9 (9.7)	**<0.001**
Years since HIV diagnosis	10.7 (7.1)	11.8 (7.2)	**0.002**
Current $CD4^+$ (cells/μl)	404 (259)	546 (290)	**<0.001**
Nadir $CD4^+$ (cells/μl)	150 (143)	175 (161)	**0.005**
Current $CD4^+/CD8^+$ ratio	0.5 (0.3)	0.7 (0.4)	**<0.001**
Hepatitis C seropositive	142 (24.3%)	340 (25.7%)	0.51
Stroke history	13 (2.2%)	49 (3.7%)	0.09
Hypertension	104 (17.8%)	341 (25.8%)	**<0.001**
Diabetes	54 (9.2%)	141 (10.7%)	0.34
Global mean NP score	45.7 (7.0)	45.9 (7.4)	0.53
Verbal mean *T*	49.2 (10.5)	47.9 (10.0)	**0.018**
Executive function mean *T*	44.6 (10.0)	46.4 (10.2)	**0.001**
Information process mean *T*	48.5 (9.4)	47.9 (9.2)	0.25
Learning mean *T*	43.1 (8.6)	43.3 (9.3)	0.73
Recall mean *T*	44.5 (8.7)	44.3 (9.3)	0.72
Working memory mean *T*	45.4 (8.7)	46.1 (9.3)	0.16
Motor mean *T*	45.6 (10.2)	45.5 (11.1)	0.89
Beck depression inventory	12.4 (10.3)	12.3 (10.4)	0.64
Current smoker	66 (11.3%)	210 (15.9%)	**0.008**
Current alcohol abuse	1 (0.2%)	8 (0.6%)	0.23
Current marijuana abuse	134 (24.3%)	307 (23.3%)	0.65
Current cocaine abuse	66 (12.0%)	64 (4.9%)	**<0.001**
Current methamphetamine abuse	17 (3.1%)	30 (2.3%)	0.31
Current opiate abuse	35 (6.3%)	73 (5.5%)	0.50
IADL dependent	241 (44.6%)	574 (44.8%)	0.96
Months current regimen	14.2 (22.4)	23.3 (24.5)	**<0.001**

IADL, instrumental activities of daily living; NP, neuropsychological. *P* values <0.05 are in bold.

Table 2. Characteristics of participants by plasma HIV RNA suppression: all visits combined.

Variable reported as mean (SD) or number (%)	Plasma HIV RNA status at all visits, *n* = 5555		*P* value
	HIV RNA > 50, *n* = 1348	HIV RNA ≤ 50, *n* = 4207	
Male sex	1139 (84.6%)	3457 (82.2%)	0.77
Race = white	596 (44.3%)	2241 (53.3%)	**<0.001**
Years of age	45.4 (9.0)	48.2 (9.9)	**<0.001**
Years since HIV diagnosis	12.3 (7.0)	13.4 (7.3)	**<0.001**
Current $CD4^+$ (cells/μl)	437 (273)	581 (297)	**<0.001**
Nadir $CD4^+$ (cells/μl)	136 (133)	161 (151)	**<0.001**
Current $CD4^+/CD8^+$ ratio	0.5 (0.4)	0.7 (0.4)	**<0.001**
Hepatitis C seropositive	399 (30.7%)	1114 (28.1%)	0.99
Stroke history	40 (3.1%)	174 (4.4%)	0.1
Hypertension	324 (30.0%)	1347 (34%)	**<0.001**
Diabetes	174 (13.4%)	616 (15.5%)	0.19
Global mean NP score	46.3 (7.4)	47.0 (7.6)	0.07
Verbal mean *T*	49.0 (10.4)	48.6 (10.0)	0.08
Executive function mean *T*	45.5 (10.6)	48.0 (10.8)	**<0.001**
Information process mean *T*	48.8 (10.0)	49.1 (9.8)	0.94
Learning mean *T*	44.1 (9.2)	44.3 (9.7)	0.30
Recall mean *T*	45.3 (9.4)	44.9 (9.7)	0.67
Working memory mean *T*	46.4 (9.4)	47.5 (9.5)	**0.01**
Motor mean *T*	45.0 (10.5)	45.5 (11.0)	0.65
Beck depression inventory	11.1 (10.5)	10.7 (10.0)	0.06
Current smoker	134 (10.3%)	639 (16.1%)	**0.002**
Current alcohol abuse	4 (0.3%)	28 (0.7%)	**0.02**
Current marijuana abuse	324 (26.3%)	936 (22.9%)	0.59
Current cocaine abuse	171 (13.9%)	182 (4.4%)	**<0.001**
Current methamphetamine abuse	66 (5.4%)	134 (3.3%)	0.06
Current opiate abuse	106 (8.6%)	239 (5.8%)	0.09
IADL dependent	497 (41.9%)	1577 (41.1%)	0.97
Months current regimen	18.0 (23.2)	28.9 (27.3)	**<0.001**

IADL, instrumental activities of daily living; NP, neuropsychological. *P* values <0.05 are in bold.

Table 3. Significant variables associated with HIV RNA≤ 50 copies/ml by weighted univariate analysis using generalized estimating equation (top half); multivariate adjusted odds ratio for plasma HIV RNA≤ 50 copies/ml using generalized estimating equation (bottom half).

	Significant univariate GEE results		
Variable	Units	OR (95% CI)	*P* value
Race = white		1.50 (1.25–1.80)	<0.001
Years of age	5	1.15 (1.10–1.21)	<0.001
Years since HIV diagnosis	5	1.12 (1.06–1.19)	<0.001
$CD4^+$ nadir	50	1.07 (1.03–1.10)	<0.001
$CD4^+/CD8^+$ ratio	0.1	1.22 (1.17–1.26)	<0.001
Mean executive function	10	1.24 (1.13–1.36)	<0.001
Mean working memory	10	1.14 (1.03–1.26)	0.012
Current cocaine abuse		0.33 (0.24–0.45)	<0.001
	Significant multivariate GEE results		
Variable	Units	Adj OR (95% CI)	*P* value
Years of age	5	1.14 (1.07–1.21)	<0.001
Years since HIV diagnosis	5	1.09 (1.01–1.18)	0.037
$CD4^+/CD8^+$ ratio	0.1	1.19 (1.15–1.24)	<0.001
Mean executive function	10	1.18 (1.07–1.30)	0.001
Current cocaine abuse		0.45 (0.31–0.63)	<0.001

Adj, adjusted; CI, confidence interval; GEE, generalized estimating equation; OR, odds ratio.

inhibitor (NRTI) or a regimen of non-NRTI and NRTI at baseline. 1078 participants had multiple visits (mean number of visits = 4.4 and mean number of days between visits = 266). Table 2 shows that when all visits were taken into account ($n = 5555$) as opposed to baseline only, most differences were similar between groups based on virologic suppression.

Significant variables that were associated with HIV RNA of 50 copies/ml or less in univariate analyses by logistic regression along with GEE are shown in the top half of Table 3. The bottom half of Table 3 shows the multivariate GEE analysis. Specifically, this multivariate analysis indicated older age [odds ratio (OR) = 1.14, 95% confidence interval (95% CI)1.07–1.21 for 5 year increase], years since HIV diagnosis (OR = 1.09, 95% CI = 1.01–1.18 for 5 year increase), and executive function (OR = 1.18, 95% CI 1.07–1.30 for *T* score increase of 10) were significantly associated with full virologic suppression. $CD4^+/CD8^+$ ratio was also significantly associated with full virologic suppression (OR = 1.19, 95% CI 1.15–1.24 for every 0.1 increase). Conversely, current cocaine abuse was negatively associated with full virologic suppression (OR = 0.45, 95% CI 0.31–0.63). In the secondary analysis using of 200 copies/ml or less as the cutoff for full virologic suppression, the multivariate GEE analysis revealed similar results. Specifically, current cocaine abuse was again negatively associated with full virologic suppression (OR = 0.42, 95% CI 0.29–0.61). Similarly, executive function (OR = 1.35, 95% CI = 1.19–1.53 for *T* score increase of 10), older age (OR = 1.19, 95% CI = 1.10–1.28 for 5 year increase), and $CD4^+/CD8^+$ ratio (OR = 1.27, 95% CI = 1.19–1.35 for 0.1 increase) were again positively associated with full virologic suppression.

The exploratory multivariate analysis using executive function as a categorical predictor (impaired versus not impaired as defined by *T* score ≤ 40 versus *T* score >40) yielded a similar outcome. Specifically, executive function *T* score more than 40 was significantly associated with full virologic suppression (OR = 1.57, 95% CI = 1.25–1.97, $P < 0.001$).

To further evaluate direction of association, we then examined change in executive function based on virologic suppression (HIV RNA ≤50 copies/ml) and vice versa. Data on 908 participants who had a second study visit at least 30 days after the baseline visit were available for analysis. 71.7% had stable executive function and 8.7% had a significant increase in executive function in which the domain *T* score increased by at least 10, which is equivalent to 1 SD. A small proportion (19.6%) had a significant decrease in executive function of at least 10 at the second visit. Of those 281 participants who were not suppressed at baseline, 71 (25.3%) had a decrease in executive function *T* score of at least 10 at the second visit. Meanwhile, of those 627 who were suppressed at baseline and had a second visit, 107 (17.1%) had a decrease in executive function *T* score of at least 10, which was a significantly smaller proportion ($P = 0.004$). Among participants with plasma HIV RNA of 50 copies/ml or less at their first visit who then went on to have a second visit, 140 of 573 (24.4%) had executive impairment (defined by *T* score ≤40) at the first visit. Of this 140, 17 individuals (12.1%) had loss of virologic suppression at the second visit. Of the 433 without executive impairment, 55 (12.7%) had loss of virologic suppression at the second visit ($P = 0.86$ for difference in proportions between the two groups).

Discussion

Given that there is no vaccine available for HIV, the most effective means to prevent the spread of the virus is virologic suppression with cART. Virologic suppression through cART is also the most effective means to optimize the health of people living with HIV (PLHIV) [5]. However, certain countries have not yet reached the WHO stated goal of at least 90% virologic suppression among HIV+ on cART [2]. More research is needed to better understand why HIV-infected individuals do not achieve full virologic suppression as well as the clinical impact of incomplete virologic suppression. In this analysis of multiple prospective studies, we investigated the relationship between neuropsychological performance and full HIV suppression among a large cohort of PLHIV who reported recent adherence to their cART regimen. We found that better executive function was significantly associated with full virologic suppression in multivariate analyses. By linking neuropsychological performance with an important laboratory outcome, this extends the findings of other studies showing that better cART adherence is associated with better neuropsychological performance (particularly in the domain of executive function) [16,17]. The association between full virologic suppression and better executive function was significant for both the 50 copies/ml and 200 copies/ml suppression cutoffs. We excluded participants who reported recent nonadherence in this analysis. Despite this, a protective association between full virologic suppression and better executive function was found.

Based on our longitudinal analysis, it is more likely that worse executive function is a result of lack of virologic suppression rather than a cause of it. Specifically, we found in a subgroup analysis that lack of virologic suppression at baseline was associated with a higher frequency of significant executive performance decrease over time. Individuals with uncontrolled HIV may be more likely to develop impairment, as evidenced by the fact that HIV-associated dementia was much more common before the era of cART [11]. Therefore, the association between worse executive function and lack of virologic suppression could reflect the impact of uncontrolled viral replication on neurocognition. Conversely, there was no significant difference in loss of virologic suppression over time based on executive function. While this subgroup analysis was limited by small sample size, the finding argues against the possibility that executive dysfunction comes first. It should also be noted that the 19.6% of individuals with executive function decline at a second visit may be higher than some clinical settings, particularly in clinics with very high virologic suppression rates.

Like some other studies, we found that younger age, longer time since HIV diagnosis, and current cocaine abuse were significantly associated with lack of full virologic suppression [7–10]. Other factors such as race, while significant in univariate analyses, were not significant in multivariate analyses. We also found that increasing $CD4^+/CD8^+$ ratio was associated with full virologic suppression. Although we suspect this may be the result of full virologic suppression (as opposed to the cause of), this is not completely clear. Specifically, higher plasma HIV RNA levels and shorter duration of HIV suppression have both been associated with lower $CD4^+/CD8^+$ ratio in previous studies [28,29].

We acknowledge the limitations of our study. The integrase inhibitor class has become the standard of care for initial cART. However, few study visits (10% of total) in the analysis involved integrase inhibitor-based cART, which is reflective of the timeframe analyzed. Recent studies of the integrase inhibitors have shown that therapy with this drug class may increase the likelihood of undetectable HIV RNA [30]. With this in mind, if the study were conducted among a population of mostly integrase inhibitor treated individuals, it is possible that the overall rate of full virologic suppression would have been higher and that the association with executive function would not have been found. We also acknowledge that this study did not address functional symptoms. Studies in the cART era have shown that a large proportion of individuals with HAND have asymptomatic neurocognitive impairment [12]. It is possible that the findings of the study would have been different had we limited the study to individuals with functional symptoms. We acknowledge that certain countries have been able to achieve almost 95% virologic suppression among PLHIV on cART [3]. Our findings may not be generalizable to settings in which essentially complete virologic suppression has been achieved. We also acknowledge that because over 80% of the cohort was men, the study findings may not be generalizable to HIV-infected women.

We did not find an association between global neuropsychological performance and virologic suppression (our primary hypothesis). We did find that better executive function was associated with full virologic suppression (a secondary hypothesis), but we did not find this association with other domains. Although better working memory was associated with full virologic suppression in the univariate analysis, this association became nonsignificant in the multivariate analysis. It is somewhat surprising that none of the other domains were significant in the final analysis. However, there is evidence in the cART era that the executive function domain is more affected than other domains during HIV infection [31]. Therefore, it may be more likely to find significant associations between this domain and other outcomes. Alternatively, it is possible that adherence is more closely linked to executive function than other domains. One study has shown that while impairment in both executive

function and memory domains is associated with worse cART adherence, the effect size appears to be larger for the executive function domain [32]. Assessment of adherence in this study was performed with the ACTG adherence questionnaire. While this questionnaire has been widely used [33], self-report may not be as accurate for measuring adherence as other measures such as electronic cap measurements, pharmacy records, and therapeutic drug monitoring [34]. Going forward, further research on the clinical implications of both neurocognitive impairment and lack of virologic suppression are needed in studies of PLHIV.

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Conflicts of interest

There are no conflicts of interest.

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