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Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy

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ABSTRACT

Objective: To rigorously evaluate the time course of cognitive change in a cohort of individuals with HIV-associated neurocognitive disorders (HAND) initiating combination antiretroviral therapy (CART), and to investigate which demographic, laboratory, and treatment factors are associated with neuropsychological (NP) outcome (or "any NP improvement").

Methods: Study participants included 37 HIV+ individuals with mild to moderate NP impairment who initiated CART and underwent NP testing at 12, 24, 36, and 48 weeks thereafter. NP change was assessed using a regression-based change score that was normed on a separate NP-stable group thereby controlling for regression toward the mean and practice effect. Mixed-effect regression models adjusting for loss to follow-up were used to evaluate the time course of cognitive change and its association with baseline and time-varying predictors.

Results: In persons with HAND initiating CART, cognitive improvement happens soon after initiation (13% at week 12), but more often 24, 36, and up to 48 weeks after initiation (up to 41%), with fewer than 5% demonstrating significant worsening. In multivariate analyses, unique predictors of NP improvement included more severe baseline NP impairment and higher CART CNS penetration index. Greater viral load decrease was associated with NP improvement only in univariate analyses.

Conclusion: Clinically meaningful neuropsychological improvement seemed to peak around 24–36 weeks after combination antiretroviral therapy initiation and was prolonged over the 1-year study period. This study also provides new evidence that benefit may be maximized by choosing antiretroviral medications that reach therapeutic concentrations in the CNS. ***Neurology***® ●●●

GLOSSARY

ANI = asymptomatic neurocognitive impairment; **CART** = combination antiretroviral therapy; **CI** = confidence interval; **CIT** = Cognitive Intervention Trial; **CPE** = CNS penetration effectiveness; **GDS** = Global Deficit Score; **IQR** = interquartile range; **HAD** = HIV-associated dementia; **HAND** = HIV-associated neurocognitive disorders; **MND** = mild neurocognitive disorder; **MS-Reg-CS** = mean scaled score regression-based change score; **NP** = neuropsychological.

The temporal profile and magnitude of neuropsychological (NP) change after combination antiretroviral therapy (CART) initiation and the biologic, clinical, and treatment factors associated with this change have not been well studied.

Previous studies have showed that CART is beneficial to cognitive functions within a few months and more likely to improve in virally suppressed individuals in the plasma[1] and in the CSF[2,4] as well as in ART-naïve persons[2,4] and in persons on highly CNS-penetrating CART regimens.[4,5]

However, these studies have important limitations. First, only group statistics were used with no untreated comparison group. No study standardized NP change against a comparison group in

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Table 1 Demographic, clinical, laboratory, and treatment characteristics at baseline

	Mean/median/%	SD	Range
HAD; MND; ANI	13.5%; 51.3%; 35.2%	—	—
Age, y	39.7	7.3	19–55
Education, y	13.6	3.2	6–20
Sex	86.5% men	—	—
Ethnicity	73% Caucasian; 24% Hispanic; 3% African American	—	—
Nadir CD4	106.9	102.4	0–360
CD4 at baseline	195.6	161.9	0–668
Plasma HIV RNA (log 10)	4.9	—	IQR: 4.01–5.6
Detectable plasma HIV RNA	95%		
CSF HIV RNA (log 10)	3.6	—	IQR: 2.9–4.3
Detectable CSF HIV RNA	85%		
% AIDS	77%		
ARV experienced at baseline	62%	—	—
No. of ARVs at initiation	3.5	0.7	2–5
At least three ARV (CART)	97%	—	—
CPE	1.4	0.5	0–2.5
High penetration (≥2)	27%	—	—
Medium penetration (1.5)	30%	—	—
Low penetration (<1.5)	43%	—	—

HAD = HIV-associated dementia; MND = mild neurocognitive disorder; ANI = asymptomatic neurocognitive impairment; IQR = interquartile range; CPE = CNS penetration effectiveness.

order to control for practice effect and regression toward the mean, potentially providing erroneous estimates of NP improvement.[6] Some included participants who were not NP impaired at baseline.[2,3,5] Others did not assess the time association of HIV biomarkers and NP change.[2,3]

The current study has two aims: 1) to estimate the rate and nature of NP improvement in persons initiating CART; 2) to determine which demographic, clinical, laboratory, and treatment factors are associated with NP improvement. We hypothesized that many but not all individuals would positively benefit from CART initiation. We hypothesized that individuals with worse baseline performance, individuals who were ART naïve, and individuals who were on better penetrating CNS treatment would benefit the most. Finally, we hypothesized that both plasma and CSF viral load reduction would be associated with NP improvement.

METHODS

Subjects. A previous report of the Cognitive Intervention Trial (CIT) was published using a subset of the current sample (n = 31) who were assessed after 15 weeks of CART.[4] The current study examines cognitive performance from four assessments over 48 weeks following CART initiation.

Thirty-seven HIV+ participants were enrolled into the CIT study at the HIV Neurobehavioral Research Center (see appendix), San Diego, between 1996 and 2006 (table 1). All eligible participants were either untreated or failing therapy (defined as plasma HIV RNA greater than 5,000 copies/mL) at baseline and planned initiation of a new CART regimen. They also had to be NP-impaired at baseline as defined by the Global Deficit Score (GDS) method.[7,8] Participants were excluded if they reported a lifetime history of neurologic disease unrelated to HIV infection, or psychiatric disorder on the psychotic axis (e.g., schizophrenia), or met criteria for drug dependence or abuse within the last 6 months, or ever experienced traumatic brain injury with loss of consciousness greater than 1 hour. This research was approved by the Human Research Protections Program of the University of California, San Diego. All participants provided written informed consent.

Procedure. All participants received a battery of standardized NP tests composed of six measures that have been shown to be sensitive to HIV-associated neurocognitive disorders (HAND).[9] The six NP measures were Grooved Pegboard (dominant and nondominant hand), Paced Auditory Serial Addition Test (50 items), Trail Making Test A & B, and Letter fluency (F, A, S). These six NP measures were selected because they comprised the common tests that the CIT cohort received between 1996 and 2006 (see reference 4 for more details). The prorated GDS based on these six measures was highly correlated with the original full battery GDS ($r = 0.79$; $p < 0.001$). The average full-battery GDS for the CIT sample was 1.45 ± 0.98 and the average prorated GDS was 1.44 ± 0.93. All 37 participants were NP impaired on both GDSs (GDS ≥0.5).

Data analysis. The six NP test measures had previously been transformed into normalized scaled scores (with a mean of 10 and SD of 3) and these scores were averaged to develop a summary mean scaled score. Also using normative longitudinal data from a separate sample of NP stable individuals, a mean scaled score regression-based change score (MS-Reg-CS) was computed from baseline to each follow-up session for each participant (appendix e-1 on the *Neurology*® Web site at www.neurology.org).[10-17] The MS-Reg-CS can be used as a continuous or as a discrete variable with cutoffs for improvement or decline representing clinically meaningful NP change. These computations were conducted using JMP 6.1 software. All 37 subjects completed week 12, 28 completed week 24, 22 completed week 36, and 18 completed week 48, the final time point of the study.

To explore the overall time pattern and magnitude of NP change, a mixed effects model was fitted for the longitudinal MS-Reg-CS (weeks 12, 24, 36, and 48), with a linear time effect and random, subject-specific intercepts and slopes (appendix e-1). Note that since the MS-Reg-CS scores reflect changes from baseline, the week 0 responses are not used in the model. The statistical analysis was conducted in two phases. First, we identified the appropriate temporal model, without including covariates. Then, additional analyses included potential covariates in the model one by one. For each covariate, we tested for an overall covariate effect via the likelihood ratio test. If significant, we further tested for an interaction effect and for a main effect (with the interaction term removed) via the Wald test (table 2; appendix e-1). These analyses were conducted for baseline and time-varying demographic, HIV-biomarkers, and treatment variables. The covariates included factors that had been shown to affect

Table 2 Significant baseline factors and time varying factors of neuropsychological improvement

	p Value overall effect	*p* Value time interaction effect	*p* Value main effect	Coefficient
Baseline log GDS	0.021	0.17	0.095	
Current log 10 plasma HIV RNA	0.05	0.038	—	−0.0105 per 12-week period; 95% CI = −0.0204, −0.0006
Current plasma HIV RNA detectable vs undetectable	0.05	0.030	—	−0.0289 per 12-week period; 95% CI = −0.0549, −0.0029
ARV penetration index (≥2)	0.005	0.57	0.002	2.46 per 12-week period; 95% CI = 1.02, 3.91

The main effect means that the week 12 MS-Reg-CS change depends on the covariate. A significant time interaction effect means that the slope of change in the MS-Reg-CS depends on the covariate. The main effect *p* value is reported when the interaction term is not significant. The overall covariate effect was tested using the likelihood ratio test. The interaction effect was tested using the Wald test (see also model 5 in appendix e-1). One unit on the MS-Reg-CS scale corresponds to a standard deviation of the neuropsychological response in the normative sample, such that 95% of the subjects would have a response between −2 and 2.
GDS = Global Deficit Score; CI = confidence interval; MS-Reg-CS = mean scaled score regression-based change score.

long-term NP performance in HIV+ individuals in previous studies[4,18] (table 2). Furthermore, multivariate analyses were conducted as follows: the covariates significant at the 0.10 level in the univariate analysis were included in the multivariate analyses, with both a main term and a time interaction. These analyses were done in the statistical package R. The comparison between models used the χ^2 approximations to the likelihood ratio test. Variables were log transformed when appropriate to normalize the distribution (viral load measures and GDS).

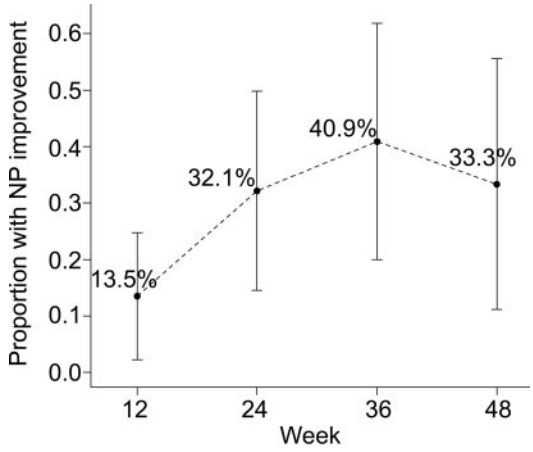
The analyses of the longitudinal CD4 and plasma and CSF viral loads were conducted in a similar manner, using models[4] (figures e-1 and e-2). Of note, for these models the analysis of variance–like time-profile model was appropriate, rather than the linear time trend model. For the plasma and CSF viral load analysis an adjustment was made for censoring below the limit of detection of each viral load assay.[19-21]

RESULTS Frequency and pattern of NP change from baseline. As illustrated in figure 1 and using the categorical cutoffs for a 90% CI in classifying clinically meaningful NP change, we found that between 13.5% and 40.9% of participants improved from baseline across the study time.

Results from the mixed-effect regression model showed that the average NP performance change (continuous MS-Reg-CS; figure 2) dramatically improved at week 12 when compared to normative expectations ($p < 0.001$). Then, when compared to week 12, improvement at week 24 was not different ($p = 0.11$). However, improvements were found on the subsequent visits at weeks 36 ($p = 0.02$) and 48 ($p = 0.003$) as compared to week 12.

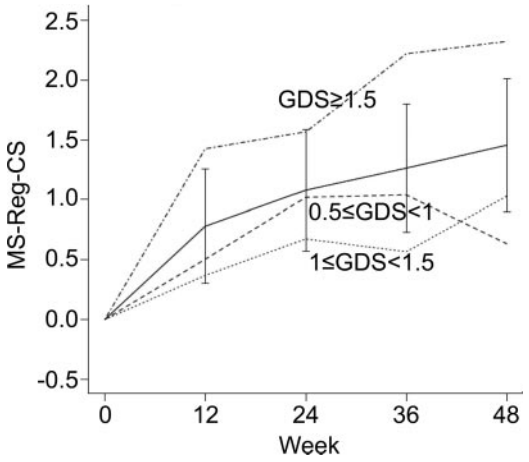
Change in HIV-related biomarkers. The CD4 cell count improved sharply at week 12 ($p < 0.0001$), and more gradually at the subsequent time points (week 36, $p = 0.037$; week 48, $p = 0.015$) compared to week 12 (figure e-1). The kinetics of the viral load in the plasma and the CSF sharply improved at week 12 ($p < 0.0001$), without significant change thereafter (figure e-2). When considering detection level (<50 c/mL) in the plasma, we found that among the 36 patients who had available viral load at baseline, 95% were detectable. At week 12, 50% (18/36) became undetectable. Then at week 24, 59% (16/27) were undetectable, 58% (11/19) at week 36, and 53% (8/15) at week 48. In the CSF, among the 34 patients had who had available viral load at baseline, 85% were detectable. At week 12, 80% (29/34) became undetectable. Then at week 24, 81% (17/21)

Figure 1 Proportion of HIV+ individuals with neuropsychological improvement from baseline



Proportion of participants with neuropsychological (NP) improvement at each session was derived from the categorical mean scaled score regression change score (MS-Reg-CS). The MS-Reg-CS provides a standard score that can be used as a continuous score or a categorical score (i.e., significant NP improvement as MS-Reg-CS ≥1.645 and NP decline as MS-Reg-CS ≤−1.645, based on a two-tailed 90% confidence interval; individuals within these ranges were classified as NP stable). Only one individual declined at week 36 (4.5%). In this figure, 95% confidence intervals are provided around the observed proportions of NP change at each visit. At each study time point, proportion of improving cases is different from zero.

Figure 2 Average change in neuropsychological performance across study time



MS-Reg-CS = mean scaled score regression change score. A negative MS-Reg-CS indicates decline, while a positive MS-Reg-CS indicates improvement. Significant decline was defined as a MS-Reg-CS ≥−1.645 and improvement was defined as a MS-Reg-CS ≥+1.645, which is equivalent to a 90% confidence interval. Observed standard deviation for MS-Reg-CS: week 12 = 1.19; week 24 = 1.37; week 36 = 2.00; week 48 = 1.83. Mixed effect regression model (4*) showed that change in the MS-Reg-CS was significant at visit 12 ($p = 0.002$) as compared to baseline. Subsequent MS-Reg-CS at week 36 ($p = 0.019$) and week 48 ($p = 0.003$) visits were significantly different compared to week 12 visit, but not at week 24 visit ($p = 0.11$). *Wald test of random intercept model. A higher GDS represents lower performance. We illustrated three profiles of improvement depending on three different levels of baseline impairment (mild impairment: 0.5 ≤ GDS < 1; moderate impairment: 1 ≤ GDS <1.5; and severe impairment: GDS ≥1.5). Only the 37 patients' average MS-Reg-CS was tested. In other words, the impairment subgroups were not statistically compared due to sample sizes and resulting power issues. To explore the advantage of using the MS-Reg-CS as the outcome variable, we conducted the same statistical analyses simply using the uncorrected mean scaled scores. We found NP improvement to be highly significant at all time points ($p < 0.0001$), which differs substantially from the above p values, reflecting an inflated improvement probably corresponding to uncorrected regression toward the mean and practice effect. Note that since the response measures change from baseline, the week 0 responses are not used in the model.

were undetectable, 69% (11/16) at week 36, and 65% (9/14) at week 48.

Predictors of NP change. ***Univariate analyses.*** Among baseline factors, only initial NP performance (continuous $\log_{10}$ GDS) was predictive of NP change ($p = 0.021$). But the main effect for baseline NP performance and the time interaction effect between baseline NP performance and NP change (here in the absence of the interaction term) were not significant (table 2). Indeed, inspection of individual change scores and baseline performances revealed that the most marked improvements throughout the study tended to occur in individuals with lowest baseline performance (figure 2).

Among serially assessed covariates of NP improvement (time-varying covariates), we found that $\log_{10}$ plasma HIV RNA change trended toward an overall effect ($p = 0.056$) with a time-interaction effect ($p = 0.038$; coefficient = −0.0105 $\log_{10}$ per week, 95% CI = −0.0204, −0.0006). These results can be interpreted as follows: one $\log_{10}$ decrease in viral load is equivalent to an increase of 0.126 points in the MS-Reg-CS (NP improvement) over a 12-week period. In other words, greater reductions in plasma viral load were associated with greater NP improvements and this association increased in time by −0.0105 $\log_{10}$ per 12-week period.

Likewise, if change in plasma HIV RNA is defined categorically (i.e., detectable vs undetectable), we found an overall effect ($p = 0.050$) with a time interaction ($p = 0.030$; coefficient = −0.023, 95% CI = −0.055, −0.0029 per 12-week period). This means that an MS-Reg-CS change at week 12 is 0.35 more (95% CI 0.035 to 0.66) for patients with undetectable vs detectable viral loads.

Higher CNS penetration of the CART regimen (defined as an index ≥2 using the method of reference 22) had an overall effect ($p = 0.005$) on NP change and showed a main effect on NP change ($p = 0.002$), but a nonsignificant time interaction effect. Specifically, CART CNS penetration ≥2 yielded a NP improvement of 2.46 (95% CI 1.02, 3.91) units on the MS-Reg-CS per 12-week period. No other time-varying covariates were significantly associated with the MS-Reg-CS (table 3).

Multivariate analyses. Factors that were found to be significant predictors of NP change in the univariate model were entered as covariates in the multivariate model. Both the CNS penetration effectiveness (CPE) score ($p = 0.002$) and baseline NP performance (continuous $\log_{10}$ GDS; $p = 0.024$) remained predictive covariates. The model had an R^2 value of 0.59, of which 0.56 was explained by the follow-up time (including the random slope, i.e., the time components on model 4; appendix e-1), and 0.03 by the CPE score and baseline NP performance.

DISCUSSION Findings from this study show that for some persons with HAND initiating CART, cognitive improvement happens soon after initiation (13% at week 12), but more often 24, 36, and 48 weeks after initiation (up to 41%). In addition, whether the initial NP improvement happens sooner or later, the magnitude of improvement was greater in individuals who had the lowest baseline performance, although improvement of lesser magnitude was observable in less impaired participants at base-

Table 3 Nonsignificant baseline factors and time-varying factors of neuropsychological improvement

	p Value overall effect
Baseline predictors	
Age	0.44
Education	0.17
Sex	0.67
Ethnicity	0.53
Nadir CD4	0.59
Treatment history (naïve/experienced)	0.22
Current CD4 at baseline	0.98
Plasma HIV RNA/detectable vs undetectable	0.86/0.68
CSF HIV RNA/detectable vs undetectable	0.75/0.74
Hemoglobin	0.97
MCP1	0.21
Time-varying covariates	
Current CD4	0.77
Log 10 CSF viral load	0.27
CSF HIV RNA detectable/ undetectable	0.56
Hemoglobin	0.66
CSF MCP-1*	0.48

Because most participants reported being highly adherent (more than 95% of the time) to their combination antiretroviral therapy regimen across the study (87% at week 12, 90% at week 24, 100% at week 36, and 83% at week 48), variance among patients was small and we could not meaningfully test adherence association with NP change over time.
*MCP1 was only available at week 12.

line (figure 2). This does not appear to be an artifact of regression to the mean because the latter should be controlled by the MS-Reg-CS methodology. Indeed, the regression change scores were derived from a normative sample from which no NP change was expected beyond practice effect or statistical artifact such as regression toward the mean. In other words, the "normed" definition of NP change in the CIT sample was exclusive of these confounds. Moreover, the pattern of NP change in the impairment subgroups (figure 2) cannot be explained on the basis of regression to the mean because the least impaired subgroup does not show the lowest amount of improvement.

NP improvement was associated with decreasing plasma HIV viral load (but not CSF, potentially due to a lack of data variability by week 12 as detailed below), whether HIV viral load was treated as a continuous or dichotomous variable, and the effect was strongest at 24 and 48 weeks after CART initiation. This result is in accordance with previous studies.[1,4] However, in the multivariate model that also includes baseline NP impairment, plasma viral load does not remain a unique contributor. Several mechanisms to explain NP improvement have been proposed in the literature. First, CART reduces HIV replication in the brain (as well as the blood).[4] As a result, circulating activated monocytes are reduced, leading to a reduction of their migration into the brain and a resulting further reduction of HIV in the CNS.[23] With a reduction of HIV and activated monocytes, neuroinflammation and production of neurotoxins is also reduced.[24]

The CPE score (greater than 2), for the participants' CART regimens, was the other predictor of NP improvement in our multivariate analyses. The beneficial effect of CSF penetrating drugs has been observed in one other longitudinal study but only in univariate analyses.[25] It was observed also over one time point in the subanalysis of this sample.[4] Not only is this finding the first robust extension of the long-term beneficial effect of CART with better CNS penetration, our change score method and mixed effect modeling also yielded a specific magnitude of NP improvement of 2.46 units on average per 12-week period. This represents a large improvement arguably supporting a non-negligible effect of this factor and provides valuable information for future clinical trials. Better CART CNS penetration likely leads to more neurocognitive improvement because it better suppresses CNS viral replication.[26] However, we were not able to show the latter. Potential reasons are that CSF viral load may only imperfectly reflect the state of HIV replication in the brain, that currently available viral load assays are not sufficiently sensitive for CSF, and that secondary effects of CART, such as reduction in mediators of neuroinflammation, may be important in neurocognitive recovery. Perhaps the most likely explanation is related to the data variance, as we found that 80% of subjects suppressed CSF viral load at week 12. This leaves only 20% detectable, a very small subgroup. Thus the categorical analysis of CSF viral suppression was probably not powered to demonstrate the expected effect. By comparison, proportions remaining detectable and undetectable at week 12 for plasma were better balanced, providing more power.

The therapeutic implications of our study are twofold: 1) HAND should be proactively monitored; and 2) to minimize impact of HAND on productivity and life quality, drug regimens with the estimated CNS penetration (CPE scores greater than 2; see reference 22 for details) should be selected when possible based on treatment and toxicity histories and drug resistance testing. Adherence to CART presumably also is critical to improving cognitive functions,

and may improve with better cognition.[27] Since reported levels of treatment adherence were high in this study as compared to those observed in clinical practice, extra measures to promote good adherence, especially initially, may be needed for impaired patients to achieve results similar to ours.

Our study detected continuing improvement up to 1 year after a change in therapy. This supports findings of long-term observational cohorts demonstrating benefit of CART up to 3 years[18,28] and even in patients with immune reconstitution syndrome up to 5 years.[29] This suggests that the window for recovery of HIV-related brain injury may be relatively long.

Two findings from this study differed from those which were reported in our prior analysis of the CIT data.[4] First, we did not find that CSF viral load was significantly associated with NP improvement. Secondly, we did not confirm that ART naive (38%) participants were more likely to improve. We believe that these differing findings result from different analytic approaches, and the inclusion of all study timepoints. Also, the initial study measured cognitive changes with the GDS, a measure that ignores changes within the normal range. For the current analysis, we used scaled scores which encompass the full range of performance, capturing not only return to normal, but also return to best levels of functioning. Moreover, the prior study found that higher CNS penetration was associated with better CSF viral load suppression, but not with better neurocognitive performance. This may have resulted from the use of updated estimates of CNS penetration based on data published after 2004 in the present study, as well as better estimate of NP change.

We believe that our current approach provides a more sensitive and yet stricter estimate of cognitive improvement when compared to the published literature. Indeed, the standardized change scores for expected NP change which were derived from a demographically comparable group of HIV− and clinically stable HIV+ participants correct for practice effects, regression toward the mean, and normal test-retest variation. These measures are more likely to reflect the "true" NP improvement without these sources of error (see figure 2 legend).

Several limitations to our study should be recognized. First, our small sample size may have limited detection of less robust contributions to improvement by some of our predictors. Larger longitudinal studies with strategies to reduce attrition are needed. Secondly, the battery of tests ideally would have been larger. However, we found that our limited battery was highly correlated to the original GDS derived from more comprehensive NP evaluations.[4] Still, when using this prorated battery, a number of important cognitive functions known to be affected by HIV infection and effective CART were not represented (e.g., learning, memory, executive functions). Finally, we used two sets of regression equations to compute the MS-Reg-CS for four time periods (baseline–12 weeks, 12–24 weeks, 24–36 weeks, 36–48 weeks). These equations may not account for some of the practice effects in our study at week 36 and 48. However, several studies indicate that practice effect most substantially applies to the second assessment and is greatly diminished with subsequent tests.[17] The ideal design would have been to have a reference sample of comparable individuals tested at the exact same times as our participants. This highlights the need for normative data for NP change at various intervals relevant to clinical trials. Finally, we did not explore how cognitive improvement translated into potential everyday functioning. Future studies should aim at defining to what extent everyday functioning measures covary with NP change.

AUTHOR CONTRIBUTIONS

The statistical analyses were conducted by L.A.C. and F.V.

DISCLOSURE

Dr. Letendre has received investigator-initiated research grants from GlaxoSmithKline, Merck, Schering-Plough, and Tibotec, and honoraria from GlaxoSmithKline and Abbott Laboratories. Dr. Letendre has served on the advisory board of Abbott Laboratories. S. Gibson was an employee of the HIV Neurobehavioral Research Center. Dr. McCutchan has received grants from Abbott and honoraria from Merck and GlaxoSmithKline. Dr. Ellis has received an honorarium from Glaxo SmithKline.

APPENDIX

The San Diego HIV Neurobehavioral Research Center (HNRC) group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes the following: Director: Igor Grant, MD; Co-Directors: J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, and J. Allen McCutchan, MD; Center Manager: Thomas D. Marcotte, PhD; Naval Hospital San Diego: Braden R. Hale, MD, M.P.H. (PI); Neuromedical Component: Ronald J. Ellis, MD, PhD (PI), J. Allen McCutchan, MD, Scott Letendre, MD, Edmund Capparelli, PharmD, Rachel Schrier, PhD; Neurobehavioral Component: Robert K. Heaton, PhD (PI), Mariana Cherner, PhD, Steven Paul Woods, PsyD; Neuroimaging Component: Terry Jernigan, PhD (PI), Christine Fennema-Notestine, PhD, Sarah L., Archibald, MA, John Hesselink, MD, Jacopo Annese, PhD, Michael J. Taylor, PhD; Neurobiology Component: Eliezer Masliah, MD (PI), Ian Everall, FRCPsych, FRCPath, PhD, Cristian Achim, MD, PhD; Neurovirology Component: Douglas Richman, MD (PI), David M. Smith, MD; International Component: J. Allen McCutchan, MD (PI); Developmental Component: Ian Everall, FRCPsych, FRCPath, PhD (PI), Stuart Lipton, MD, PhD; Clinical Trials Component: J. Allen McCutchan, MD, J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, Scott Letendre, MD; Participant Accrual and Retention Unit: J. Hampton Atkinson, MD (PI), Rodney von Jaeger, MPH; Data Management Unit: Anthony C. Gamst, PhD (PI), Clint Cushman, BA (Data Systems Manager), Daniel R. Masys, MD (Senior Consultant); Statistics Unit: Ian Abramson, PhD (PI), Christopher Ake, PhD, Florin Vaida, PhD.

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