

Enhancing Antiretroviral Therapy for Human Immunodeficiency Virus Cognitive Disorders

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The benefits of combination antiretroviral therapy (ART) for HIV cognitive disorders vary substantially between individuals. This study evaluated whether cerebrospinal fluid (CSF) drug penetration and CSF virological suppression influence the extent of neuropsychological (NP) improvement during ART. Overall performance on a battery of NP tests administered at baseline and follow-up (median 15 weeks) was computed by using the global deficit score (GDS) methods in 31 cognitively impaired, HIV-infected individuals who began new ART regimens. Virological suppression (attaining undetectable viral load by RT-PCR at follow-up) was assessed separately for plasma and CSF. Subjects on regimens containing greater numbers of CSF-penetrating drugs showed significantly greater reduction in CSF viral load. Subjects attaining CSF virological suppression demonstrated greater GDS improvement than those who did not (median GDS change, 0.62 vs 0.23; $p = 0.01$). A similar trend for plasma did not reach statistical significance ($p = 0.053$). NP improvement was greater in ART-naïve versus treatment-experienced subjects. In a multivariate model (overall $p = 0.0008$), significant, independent predictors of GDS reduction were CSF HIV RNA suppression, baseline antiretroviral history, and their interaction. Including CSF-penetrating drugs in the ART regimen and monitoring CSF viral load may be indicated for individuals with HIV-associated cognitive impairment.

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Antiretroviral (ARV) therapy (ART) markedly improves morbidity and mortality in HIV by reducing plasma viral load to undetectable levels and restoring immune function. Despite this improvement in overall health, many HIV-positive individuals remain neurocognitively impaired. Neurocognitive impairment is associated with poor medication adherence,^{1,2} social and occupational disability,^{2,3} and accelerated mortality.⁴

The central nervous system (CNS) often harbors viral populations distinct from those present in plasma and lymphoid tissues.⁵ Furthermore, because the blood–brain barrier limits exposure to ARVs, HIV replication may persist in the brain even during effective antiretroviral therapy. Although brain viral replication cannot be assessed directly, viral RNA levels in cerebrospinal fluid (CSF) represent a better surrogate than those in blood plasma.

We previously demonstrated that elevated viral loads in CSF, but not plasma, predicted subsequent neuro-

cognitive worsening among patients who did not initiate optimal ART.⁶ Other studies have demonstrated that initiation of ART lowers both plasma and CSF HIV RNA viral loads, and that virological suppression in plasma during ART is associated with improved cognitive performance among individuals with little or no initial impairment.^{7,8} However, no previous study has evaluated whether targeting ART to reduce CSF viral load might enhance cognition in subjects who are already neurocognitively impaired. Because CSF is not routinely obtained in clinical practice, evidence of an independent benefit of CSF suppression would warrant a change in the standard of care.

We performed a prospective, observational study of virological and neurocognitive outcomes after ART initiation in 31 cognitively impaired individuals with HIV infection. The objectives of the study were (1) to determine if reduction in CSF HIV RNA is enhanced by regimens containing CSF-penetrating ARVs; and

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(2) to determine if CSF viral load suppression was associated with improved neurocognitive outcomes above and beyond benefits related to plasma viral load suppression.

Subjects and Methods

Subjects

Written informed consent was obtained from all participants according to a protocol approved by the institutional human subjects review panel. The protocol included steps to ensure that the neurocognitively impaired subjects were capable of understanding the study's procedures and purpose before giving consent. Subjects were 4 women and 27 men studied between November 1996 and June 2003 at the University of California, San Diego's HIV Neurobehavioral Research Center. All had documented HIV-1 infection and neurocognitive impairment and were about to begin a new ART regimen. Exclusion criteria included undetectable plasma HIV RNA viral load, evidence of central nervous system opportunistic disease, active psychosis or other disorder deemed likely to interfere with study participation, and disinclination to begin or change ART.

Treatment

Subjects either began ($n = 24$) or changed ($n = 7$) individualized ARV regimens prescribed by their primary medical care providers. Subjects who failed to maintain adequate adherence to ART, as revealed in biweekly interviews with the study nurse, were excluded. During the follow-up interval, treating physicians chose to modify the drug regimens of 5 of the 31 subjects (16%). Excluding these five cases from the analysis did not alter the pattern of findings; thus, they are included in analyses reported here.

Neuropsychological Testing

All participants completed one of two comprehensive neuropsychological (NP) testing batteries that assessed seven ability domains that can be affected by HIV infection (information processing speed, executive functions, working memory, verbal fluency, learning, recall, and motor coordination). Tests

comprising both batteries are listed in Table 1. NP inclusion criteria included global neurocognitive impairment as indicated by clinical ratings (ie, global clinical rating ≥ 5) of test results, performed by a neuropsychologist.^{9,10}

Participants who received the older ($n = 15$) and newer batteries ($n = 16$) did not differ in terms of baseline NP impairment, age, education, CD4 cell count, or HIV RNA viral loads (all p values >0.10). Accordingly, these two groups were combined for all subsequent analyses. A Global Deficit Score (GDS)^{11,12} summarized participants' overall performance on the NP test batteries. Raw test scores were converted to T-scores ($M = 50$; standard deviation [SD] = 10) using published demographically corrected normative references cited in Table 1. The T-scores then were transformed into deficit scores using the following conversions: 40T or higher = 0; 39T to 35T = 1; 34T to 30T = 2; 29T to 25T = 3; 24T to 20T = 4; and 19T or less = 5. The deficit scores from each test then were averaged to derive a GDS for each participant (range, 0–5), such that higher scores indicate greater levels of impairment.^{11,12}

Clinical and Laboratory Measures

Each subject underwent a comprehensive neuromedical evaluation performed using structured clinical data forms that assessed medical and neurological history, general physical and neurological examinations, and antiretroviral medication use history. Laboratory studies included CD4⁺ T-lymphocyte (CD4) counts and tests of hematologic, renal, and hepatic function. Severity of HIV disease was assessed according to the 1993 Centers for Disease Control classification system.¹³ To ensure the absence of CNS opportunistic disease, neuroimaging was performed (computed tomography or magnetic resonance imaging) on all participants whose screening CD4 count was below 200/ μ L.

A board certified neurologist (R.J.E.) evaluated available clinical data at baseline and assigned neurocognitive diagnoses [HIV associated dementia [HAD] and minor cognitive motor disorder [MCMD]] according to criteria of the American Academy of Neurology Task Force (AAN, 1991). In addition, a Memorial Sloan-Kettering dementia scale rating was assigned.

Table 1. Neuropsychological Tests Grouped by Domain

Information Processing Speed

Symbol Digit Modalities Test^{40a}
 Figural Visual Scanning^{41a}
 Trail Making Test, Part A^{42,43a,b}
 WAIS-III Symbol Search and Digit Symbol tests^{44,45b}

Motor Coordination and Praxis

Grooved Pegboard Test^{43,50a,b}
 WAIS-R Block Design^{54a}

Attention and Working Memory

Paced Auditory Serial Addition Test^{53,54a,b}
 WAIS-III Letter-Number Sequencing^b
 WMS-R Visual Span^{49a}
 WAIS-R Digit Span^{55a}

Learning and Recall

Rey Auditory Verbal Learning Test^{46a}
 Hopkins Verbal Learning Test-Revised^{47b}
 Brief Visuospatial Memory Test-Revised^{48b}
 WMS-R Visual Reproductions^{49a}

Verbal Fluency

Semantic verbal fluency^{51b}
 Controlled Oral Word Association Test^{51,52a,b}

Executive Function

Trail Making Test, Part B^{42,43a,b}
 Stroop Color-Word Test^{56b}
 Wisconsin Card Sorting Test-64^{57b}
 Halstead Category Test^{43,58a,b}

WAIS-III = Wechsler Adult Intelligence Scale, 3rd edition; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised;

^aTest comprised first NP battery.

^bTest comprised second neuropsychological battery.

Five to 15ml of CSF was collected by lumbar puncture. HIV RNA levels in plasma and CSF were measured by reverse transcriptase polymerase chain reaction (RT-PCR) using the Amplicor HIV-1 Monitor Test (Roche Molecular Diagnostics, Pleasanton, CA). For CSF, an ultrasensitive version of the assay, with detection limit of 50 copies per milliliter (c/ml) was used; whereas for plasma the standard assay (detection limit 400c/ml) was used. Blood CD4 counts were quantified by flow cytometry.

CSF-penetrating ARVs were defined as those with CSF concentrations (as determined by the median concentration from human studies) that exceeded the level needed to inhibit replication of HIV (as determined by the median 50% inhibitory concentration in the ViroLogic PhenoSense assay¹⁴). Specifically, these were stavudine (D4T), zidovudine (ZDV), abacavir (ABV), efavirenz (EFV), nevirapine (NVP), and indinavir (IDV).^{15–31} The number of CSF-penetrating ARVs in each subject's regimen was counted for use in analyses. Among the five subjects who modified their drug regimens during the follow-up interval, four changes occurred at least 1 month before follow-up assessment. Therefore, the designation of the number of CSF-penetrating ARVs was based on the regimen that the subjects were on at follow-up assessment. The remaining subject reported a regimen change that did not affect the number of CSF-penetrating ARVs in his regimen.

Statistical Analyses

Plasma and CSF HIV RNA values were log₁₀-transformed before analysis. The assay detection limits for each fluid were used when values decreased below these limits. Changes in HIV RNA levels and the GDS were determined by subtracting each subject's follow-up value from baseline. Change in CD4 count was calculated by subtracting each subject's baseline CD4 count from the follow-up value. Significance of change was determined by performing Wilcoxon signed rank tests for paired samples. Associations between change in GDS and change in clinical characteristics (HIV RNA viral loads and CD4 counts) were determined using Spearman's P correlations. Jonckheere–Terpstra tests for ordered alternatives were performed to test for significant associations between change in viral loads and the number of CSF-penetrating ARVs per regimen. A multivariate standard least squares model was used to determine the significance of ARV history at baseline, CSF RNA viral load suppression at follow-up, and their interaction as predictors of change in GDS scores. Analyses were performed using JMP and SPSS statistical packages.^{32,33}

Results

Demographic and Select Clinical Characteristics of the Cohort

Table 2 describes the predominantly male, white, and severely immunosuppressed participants in the study. Twenty-one (68%) of the subjects met criteria for the diagnosis of HAD or MCMD; the remaining 10 subjects met criteria for neuropsychological impairment but did not report sufficient functional decline to meet diagnostic criteria for MCMD or HAD.

Changes in Neurocognitive Performance, Immune Suppression, and Human Immunodeficiency Virus RNA Levels

HIV-related clinical variables at baseline and their changes during the follow-up interval are shown in Table 3. Cognitive impairment (GDS) improved markedly (median decrease, 0.44) from baseline to follow-up visits. At follow-up, HIV RNA levels in plasma (median = 2.05 log c/ml), and CSF (median = 1.74 log c/ml) were significantly reduced by the new ART regimens. CD4 count improved between the two time points (median increase, 52 cells/μl).

Baseline Predictors of

Neuropsychological Improvement

Subjects who were ARV naive at baseline had greater improvement in GDS from baseline to follow-up (median, 0.59; interquartile range [IQR], 0.44–1.6) than did ARV-experienced subjects (median, 0.36; IQR, 0.04–0.63; $\chi^2 = 4.36$; $p = 0.04$). Results are represented in Figure 1. ARV-naive subjects demonstrated a higher median baseline CSF HIV RNA levels (naive, 4.5 log c/ml; experienced, 3.6 log c/ml; $\chi^2 = 4.01$; $p = 0.05$) but did not differ from ARV-experienced subjects in baseline plasma HIV RNA ($p = 0.93$), CD4 count ($p = 0.41$), baseline GDS ($p = 0.36$), or percentage with dementia diagnoses by AAN guidelines or Memorial Sloan-Kettering score ($p = 0.93$). Previous ARV experience was not significantly related to reduction in plasma ($p = 0.28$), or CSF ($p = 0.18$), or increase in CD4 count ($p = 0.76$). There was no significant difference in neurocognitive improvement between subjects who started or switched ART regimens ($p = 0.64$).

NP improvement was associated with baseline NP performance; participants who were more impaired at

Table 2. Demographic and Clinical Characteristics of Study Participants

Baseline characteristics	No. (interquartile range) ^a
Age at baseline (yr)	39 (35–45)
Percentage male	87
Percentage white Caucasian	74
Years of education	13 (12–16)
Years of known infection ^b	5.16 (3.4–9.9)
Nadir CD4 ⁺ T-lymphocyte count cells/μl	30 (20–145)
CDC classification of AIDS (%)	81
ART naïve at baseline (%)	29
Off ART at baseline (%)	77

^aContinuous values express medians (interquartile range)

^bYears from self-reported first HIV-1-positive test to baseline visit, n = 27, data not available for four subjects.

AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy.

Table 3. Change in Clinical Parameters from Baseline to Follow-up, Median (interquartile range)

	Baseline	Follow-up	Z	p
Global Deficit Score	1.00 (0.63–1.63)	0.60 (0.38–1.25)	−3.93	<0.001
Plasma HIV RNA (log copies/ml)	5.3 (4.7–5.7)	2.6 (2.6–4.6)	−4.70	<0.001
CSF HIV RNA (log copies/ml)	4.1 (2.9–4.5)	1.7 (1.7–2.4)	−4.80	<0.001
CD4 ⁺ T-lymphocyte count (cells/ μ l)	117 (29–344)	209 (53–401)	−3.40	0.001

HIV = human immunodeficiency syndrome; CSF = cerebrospinal fluid.

baseline showed greater improvement ($r_s = +0.47$; $p = 0.008$). Persons with higher CSF RNA levels at baseline showed greater improvement in GDS scores ($r_s = +0.37$; $p = 0.04$). Neurocognitive improvement was not associated with ethnicity, years of education, age, CDC classification of AIDS, baseline plasma HIV RNA, baseline CD4 count, reported duration of HIV infection, or subject-reported nadir CD4 count (all p values >0.20).

Neurocognitive Improvement and Suppression of Human Immunodeficiency Virus RNA Viral Load

Suppression of CSF HIV RNA viral load at follow-up was significantly related to reduction in GDS (Fig 2). Participants who achieved suppression of CSF HIV RNA levels ($n = 17$) had a median reduction in GDS of 0.62 (IQR, 0.36–0.72), compared with only 0.23 (IQR, −0.05 to 0.48) in those with measurable HIV RNA (>50 c/ml) in CSF ($\chi^2 = 6.25$; $p = 0.01$). Subjects who suppressed CSF viral load at follow-up demonstrated a greater reduction in CSF viral load (not suppressed = 1.11 log c/ml; suppressed = 2.49 log c/ml;

$\chi^2 = 6.45$; $p = 0.01$) and a greater reduction in plasma viral load (not suppressed, 0.68 log c/ml; suppressed, 2.29 log c/ml; $\chi^2 = 5.12$; $p = 0.02$) than subjects who did not suppress at follow-up, but the groups did not differ in CD4 increase ($p = 0.15$). Subjects who suppressed CSF HIV RNA at follow-up did not differ from subjects who failed to suppress for baseline CSF HIV RNA, plasma HIV RNA, CD4 count, GDS, or percentage with dementia diagnoses (all p values >0.20).

Participants who achieved complete suppression of HIV RNA levels in plasma ($n = 16$) had median reduction in GDS that was only marginally better than those who were not suppressed (0.55 vs 0.43; $p = 0.08$). Subjects who attained complete suppression of plasma viral load exhibited a median decrease in plasma HIV RNA of 2.56 log c/ml compared with 0.32 log c/ml in those who did not.

Because the plasma samples, in contrast with the CSF samples, were run using a standard assay with a detection limit of 400 copies/ml, plasma samples falling below 400 copies/ml at follow-up were reassayed using an ultrasensitive version with a detection limit of

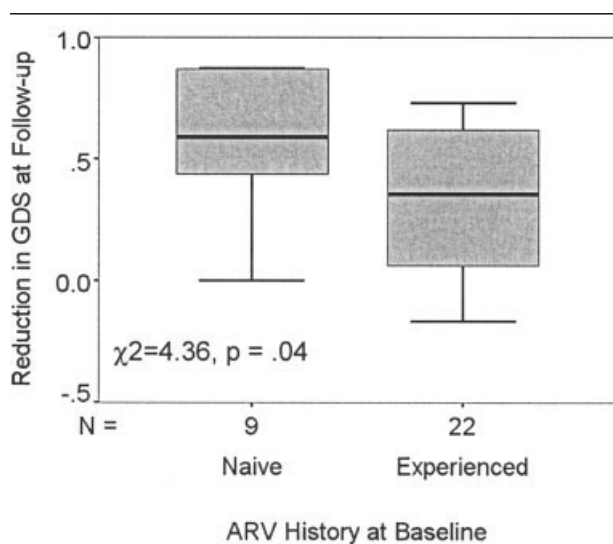


Fig 1. Reduction (improvement) in global deficit score from baseline to follow-up among antiretroviral-naïve and experienced subjects. Box-and-whisker plots show the median (center line), interquartile range (box), and 5th and 95th percentiles (whiskers). GDS = global deficit score; ARV = antiretroviral.

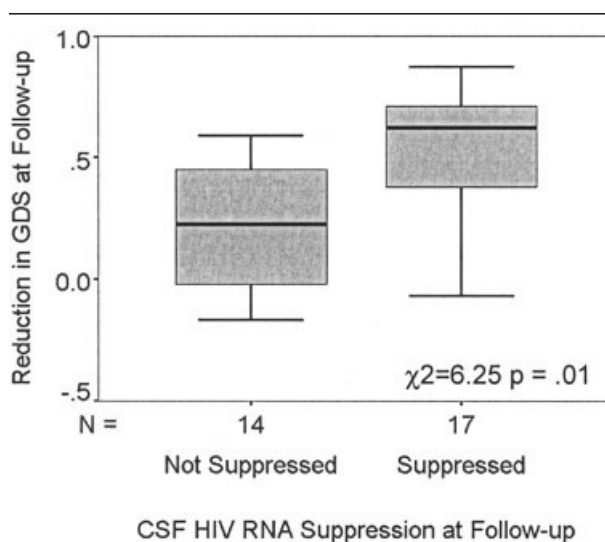


Fig 2. Reduction (improvement) in GDS among subjects with and without suppressed CSF HIV RNA viral load at follow-up. Box-and-whisker plots show the median (center line), interquartile range (box), and 5th and 95th percentiles (whiskers). GDS = global deficit score; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus.

50 copies/ml. Remaining sample was not available for two subjects. Using a modified definition of plasma suppression (≤ 50 copies/ml), we repeated the analysis comparing GDS change for suppressed and nonsuppressed subjects. The pattern of results was identical to that obtained with the original detection limit; suppression of viral load in plasma failed to reach statistical significance as a predictor of GDS change ($p = 0.053$).

Cerebrospinal Fluid–Penetrating Antiretrovirals and Suppression of Cerebrospinal Fluid Human Immunodeficiency Virus RNA Viral Load

To evaluate whether subjects taking more CSF-penetrating ARVs attained better virological suppression, we determined the relationship between the number of CSF-penetrating ARVs in a regimen (median, 2; IQR, 1–2) and the magnitude of CSF viral load reduction using a Jonckheere–Terpstra test. A higher number of CSF-penetrating ARVs was associated with greater decrease in CSF viral load (J^* statistic = 1.77; $p = 0.04$). This result was not simply attributable to a greater number of ARVs per regimen, because the total number of ARVs in the regimen was not significantly related to CSF viral load reduction (J^* statistic = 0.65; $p = 0.50$). In addition, this result was not attributable to the potency of antiretroviral drugs in a regimen, because reduction in plasma viral load was not related to the number of CSF-penetrating ARVs per regimen (J^* statistic = 0.13; $p = 0.45$).

Seven of the 31 subjects (23%) were taking least one CSF-penetrating ARV before study entry. The number of CSF-penetrating ARVs before study entry was not significantly related to CSF viral load change during study ($p = 0.38$). Nor were the number of CSF-penetrating ARVs per regimen correlated with the number of CSF-penetrating ARVs in the study regimen ($p = 0.18$).

Cerebrospinal Fluid Human Immunodeficiency Virus RNA Suppression and Antiretroviral History

Prior ARV experience at baseline and suppression of CSF HIV RNA at follow-up were both significant predictors of GDS improvement. These variables and their interaction were entered into a standard least squares model to determine the contribution of each to improvement in NP performance. The model itself was significant ($r^2 = 0.46$; $F = 7.60$; $p = 0.0008$). Both baseline ARV experience ($F = 11.65$; $p = 0.002$) and CSF suppression at follow-up ($F = 13.01$; $p = 0.001$) were significant predictors of reduction in GDS, as was their interaction ($F = 5.29$; $p = 0.03$). Subjects who were ARV-experienced at baseline and did not achieve CSF HIV RNA suppression at follow-up exhibited the least reduction in GDS ($n = 9$; mean GDS reduction = 0.15). Subjects who were ARV naive at baseline

and attained CSF HIV RNA suppression at follow-up displayed the greatest reduction in GDS ($n = 4$; mean, 1.75). Experienced subjects who suppressed in CSF ($n = 13$) demonstrated a reduction in GDS (mean, 0.45) similar to that of ARV-naive subjects without follow-up CSF suppression ($n = 5$; mean, 0.41). These four groups did not differ significantly for baseline CSF HIV RNA levels ($p = 0.12$) or baseline GDS ($p = 0.24$).

Discussion

This study's findings support the systematic evaluation of targeted strategies to optimize neurocognitive benefit in HIV-infected patients receiving antiretroviral therapy. We found that subjects with HIV-associated neurocognitive disorders initiating a new ART regimen experienced significant clinical benefits, manifested as reductions in plasma and CSF viral loads, increases in CD4 counts, and improvements in NP performance at follow-up. NP improvement was significantly greater among those who achieved virological suppression in CSF. Treatment with CSF-penetrating antiretroviral drugs was associated with greater reduction in CSF HIV RNA viral load.

Improvements in NP performance were greater among subjects attaining complete suppression of CSF viral load than among those in whom CSF virus remained detectable despite highly active antiretroviral therapy. This effect of CSF suppression was not attributable to factors such as initial viral loads, plasma viral suppression, or severity of initial impairment. Some subjects achieved CSF viral suppression despite persistence of detectable plasma virus, and these individuals experienced similar neurocognitive benefit to those who achieved suppression in both plasma and CSF. These findings suggest that inhibiting HIV replication in the CNS reduces viral neuropathogenicity, allowing neuronal repair and restoration of cognitive function. This evidence supports the hypothesis that CNS damage is more directly related to replication of HIV in CNS tissues than systemically.

Previous research has demonstrated that plasma viral load suppression during ART is associated with improvements in performance on tasks assessing psychomotor speed.³⁴ Another prior study⁷ found that improvements in motor and cognitive performance among subjects who initially were normal or mildly impaired were correlated with CSF viral load decline. Our study assessed several additional cognitive domains frequently affected in HIV, specifically, learning, retrieval, executive functions, and working memory. In our study, all subjects were initially impaired, and NP improvement was better correlated with CSF suppression than with plasma suppression.

The greatest improvements in NP performance were seen among subjects who were ARV naive and attained

CSF viral suppression at follow-up. Previous studies have reported similar findings.³⁵ Lesser degrees of improvement among ARV-experienced subjects might result from the accumulation of antiretroviral drug resistance mutations. Resistant HIV strains may be especially hard to treat in the CNS, where drug penetration is limited. The superior benefit obtained in subjects achieving complete CSF suppression is consistent with the hypothesis that autonomous viral replication in the CNS is a major cause of impairment. Subjects with higher initial CSF viral loads and more severe initial impairment also may be more likely to have HIV as the primary cause of impairment. Among less severely impaired patients, neurocognitive impairment from causes other than HIV may contribute, rendering deficits less reversible with ARV treatment.

We considered the possibility that improvements in neurocognitive performance were principally caused by “practice effects”; in other words, performance benefited from repeated experience with the tests rather than being caused by any systematic change related to treatment. Because this study had no comparison group of subjects remaining on stable or no ART, the effects of practice are difficult to evaluate. Nevertheless, neurocognitive change was systematically related to CSF virological responses, which varied substantially between individuals. Thus, subjects achieving good virological responses showed greater neurocognitive improvement than those achieving poor responses; moreover, NP improvement was not related to baseline age, education, ethnicity, disease stage, duration of infection, and level of immunosuppression. Because practice effects should be unrelated to HIV suppression in CSF, the strong correlation of improvement with CSF suppression makes the improvement we observed unlikely to result from practice.

Successful treatment of HIV neurocognitive disorders may require suppression of viral replication in the CNS reservoir. We found that subjects taking higher numbers of CSF-penetrating antiretroviral drugs showed greater CSF viral load reduction than those taking fewer such drugs. This was not attributable to a higher total number of drugs in the regimen or greater potency of the regimen. Similar findings were reported in a previous study,³⁵ but no measurements of neurocognitive performance were obtained. Although our findings suggest that it may be possible to enhance CSF virological and neurocognitive outcomes by prospectively selecting component drugs in an antiretroviral regimen to maximize expected CNS penetration, this strategy has yet to be tested in a randomized clinical trial.

These findings are consistent with other evidence that the CNS represents a unique virological compartment. During ART, HIV RNA reductions in CSF may be delayed or discordant compared with those in plas-

ma.^{15,36} HIV in the brain and CSF can replicate autonomously and evolve separately from HIV in the plasma and lymphatic tissue compartments.^{37–39} Thus, even in the absence of therapy, selection pressures in the CNS are sufficiently different that HIV cloned at autopsy from brain and CSF are genetically distinct from those in spleen.³⁹

Our findings support the view that antiretroviral therapy that suppresses viral replication is beneficial for cognitive impairment in HIV and argue for the potential utility of monitoring CSF HIV responses in patients with cognitive impairment. Furthermore, our results delineate several clinically relevant hypotheses that may be tested in future research. These involve devising ways to target and monitor antiretroviral therapy to maximize neurocognitive benefit for particular subgroups of HIV-infected individuals. For example, cognitively impaired patients with detectable CSF viral loads, despite plasma suppression, should undergo modifications to their treatment regimens designed to maximize CSF suppression. Although this circumstance is infrequent, a more common situation arises in which virological failure occurs in plasma even after multiple therapeutic modifications, whereas CSF suppression is maintained. Our findings suggest that such individuals may continue to benefit, at least neurocognitively, if CSF suppression can be achieved. Furthermore, ART regimens containing agents with a high likelihood of CNS penetration are advisable for such patients.

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Appendix

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