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Randomized Trial of Central Nervous System–Targeted Antiretrovirals for HIV-Associated Neurocognitive Disorder

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Background. Antiretroviral (ARV) medications differentially penetrate across the blood-brain barrier into central nervous system (CNS) tissues, potentially influencing their effectiveness in treating brain infection.

Methods. This randomized controlled clinical trial (RCT) called for 120 participants at 5 study sites to be randomized 1:1 to CNS-targeted (CNS-T) or non–CNS-T ART. Entry clinical factors such as ARV experience were balanced across arms using an adaptive randomization approach. The primary outcome, change in neurocognitive performance, was measured as the difference in global deficit score (GDS) from baseline to week 16.

Results. The study was terminated early on the recommendation of its data safety monitoring board on the basis of slow accrual and a low likelihood of detecting a difference in the primary outcome. No safety concerns were identified. Of 326 participants screened, 59 met entry criteria and were randomized. The primary intent-to-treat analysis included 49 participants who completed week 16. These comprised 39 men and 10 women with a mean age of 44 years (SD, 10 years), and median nadir and current CD4$^+$ T-cell counts of 175 cells/µL and 242 cells/µL, respectively. The proportional improvement in GDS from baseline was nonsignificantly larger (7%; 95% confidence interval [CI], −31% to 62%) in the CNS-T arm than in the non-CNS-T arm, representing a treatment effect size of 0.09 (95% CI, −.48 to .65). Prespecified secondary analysis showed a trend interaction (*P* = .087), indicating that participants who had baseline plasma virologic suppression may have benefited from CNS-T.

Conclusions. This study found no evidence of neurocognitive benefit for a CNS-T strategy in HIV-associated neurocognitive disorders. A benefit for a subgroup or small overall benefits could not be excluded.

Clinical Trials Registration. NCT00624195.

Keywords. HIV; AIDS; cognitive disorders/dementia; antiretroviral therapy.

Antiretroviral therapy (ART) benefits cognition in most people living with human immunodeficiency virus (HIV) [1], but not all benefit equally, and impairment persists in up to 50% [2]. Cognitively impaired individuals are less likely to achieve virologic suppression [3]. In 2007, these and other changes prompted revisions in diagnostic criteria for HIV-associated neurocognitive disorder (HAND [4]), which includes HIV-associated dementia, mild neurocognitive disorder, and asymptomatic neurocognitive impairment.

The present study hypothesized that achieving better distribution of antiretrovirals (ARVs) into the central nervous system (CNS) would reduce viral replication, normalize downstream mediators of neuronal

dysfunction, and maximize neurocognitive improvement. The CNS penetration effectiveness (CPE) method [5] produces rank estimates of the likelihood that different regimens will reduce CNS HIV. Observational studies have yielded mixed results, some suggesting greater benefits with higher CPE, others not [6]. In a recent review [7], more rigorously designed studies with greater power were more likely to demonstrate benefits, a view supported by expert opinion [8]. However, inconsistent reports and competing toxicity considerations lead to clinical equipoise, mandating a randomized trial.

We therefore designed a randomized comparison to evaluate the effectiveness for treating HAND of a CPE-based, CNS-targeted (CNS-T) strategy [5] vs non–CNS-T ART. We hypothesized that CNS-T would yield superior neurocognitive improvement. A secondary objective was to compare the 2 strategies on cerebrospinal fluid (CSF) HIV suppression.

METHODS

Design

This multisite, randomized, controlled trial was designed to provide evidence for the neurocognitive benefit of a CNS-T ART strategy vs a non–CNS-T comparison strategy for individuals with HAND initiating or changing ART. Decisions to change treatment were made by treating clinicians and were consistent with current consensus guidelines [9]. Participants were randomized 1:1 to the study arms according to an adaptive approach designed to balance important factors across the study arms (Supplementary Methods). The primary outcome was change in neuropsychological (NP) performance from entry to week 16. Secondary outcomes were the proportions of participants achieving virologic suppression in plasma and CSF. Details of the study design were described previously [10].

Standard Protocol Approvals, Registrations, and Patient Consents

Study procedures were approved by the human subjects protection committees of each institution. Written informed consent was obtained from all study participants. The protocol was registered at http://www.clinicaltrials.gov (identifier NCT00624195).

Eligibility

Individuals eligible for screening were HIV seropositive (HIV+), on stable or no ARVs for at least 8 weeks, and under consideration by their treating clinicians to initiate or change ART regimens. At screening, a study coordinator completed a detailed history including prior ARV exposure and intolerances, nadir CD4+ T-cell count, prior AIDS-defining illnesses, and comorbidities including hepatitis C virus (HCV) coinfection. Viral load, current CD4 cell count, and plasma resistance were measured. At screening, a brief NP battery that demonstrated good predictive power relative to a larger battery [11] was administered (Supplementary Methods). Participants with demographically corrected T-scores <40 on 2 screening tests, or <35 on 1 test, were considered impaired and then completed the comprehensive battery. This battery, repeated at the 16-week visit, provided the following outcomes of interest: (1) performance scores on individual NP test measures, presence or absence and level of global NP impairment; (2) measures of NP change from visit to visit; (3) self-assessments of cognitive difficulties in everyday life, employment, and degree of dependence to complete activities of daily living; and (4) in conjunction with neuromedical information, a diagnosis according to Frascati diagnostic criteria for HAND [4] (Supplementary Methods).

Exclusion criteria were active opportunistic disease, NP impairment due to neurological disorders other than HIV, meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for substance dependence within the prior 12 months and active, severe psychiatric disorders (eg, major depression, schizophrenia). Participants were not evaluated if their urine drug screen identified substances of abuse other than cannabis at any NP visit.

Data for eligible subjects were reviewed by an ARV planning committee (described below), and ARV regimen lists were created. The participant's primary care provider eliminated unacceptable regimen options prior to randomization. Lumbar punctures were done under aseptic conditions by an experienced physician or nurse at baseline, week 6, and week 16. After 2 weeks, pharmacokinetic testing was performed (Supplementary Methods).

Viral Load Assays

Plasma and cerebrospinal fluid HIV RNA levels were quantified using the Roche Amplicor Ultrasensitive assay with a detection and quantitation range of 50–100 000 copies/mL. Readouts above the upper limit were retested using an assay with a higher quantitation limit.

Safety, Tolerability, and Adverse Events

For patients who failed to show an adequate virologic response to ART at week 4 (>1 $\log_{10}$/mL drop in HIV RNA levels), the ARV planning committee reviewed adherence, concomitant medications, and resistance assays. Recommendations were made for a change in regimen (intensification or substitution with new ARVs) to preserve the patient's original assignment. If participants were virologically unresponsive to ART despite complete adherence but had no additional therapeutic options, or if treatment-limiting side effects or intercurrent illnesses/hospitalizations interfered with the schedule of evaluations, the committee recommended that the subject be removed from the study and outcome data collected as soon as possible. Study monitoring is described in Supplementary Methods.

Statistical Analyses

Primary Analyses

Comparisons of demographic and clinical characteristics between the 2 arms were done separately for baseline and week 16 using Wilcoxon rank-sum and Fisher exact tests. The primary outcome analysis compared the 2 arms on (log-transformed) GDS change from baseline to week 16. The differences in GDS change were tested using analysis of covariance (ANCOVA) model adjusting for baseline GDS. Prior to ANCOVA, assumptions regarding normality and homogeneity of variances were confirmed. An intent-to-treat (ITT) analysis included all participants who provided GDS outcome data at week 16. Normative adjustments for practice effects due to repeated NP test exposures became available after the study began [12] and were used in secondary analyses. An as-treated analysis was performed on all participants who remained on the regimen to which they had been randomized through week 16. For each model, the effect size, analogous to Cohen d, was estimated as the coefficient of treatment term divided by the residual standard deviation. Positive effect size values indicate greater NP improvement in the CNS-T arm.

Prespecified Secondary Analyses

Secondary analyses were performed on the ITT subset to determine how treatment affected change in GDS under different conditions. In a series of linear regressions, outcome differences between treatment arms were analyzed after controlling for covariates, which included virologic suppression at baseline, ethnicity, and site. Interactions between treatment and covariates were investigated and retained only if significant at .10.

Generalized estimating equations logistic models were used to test the effect of treatment on plasma and CSF viral loads (dichotomized as detectable vs undetectable) over time. Time was measured in weeks of study and treated as continuous predictor. The interaction between time and treatment was evaluated. The models predicted the log odds of being undetectable in plasma and CSF viral load.

Efficacy and Futility Analysis

Planned interim analyses reviewed by the data safety monitoring board (DSMB) included efficacy and futility analyses. Proposed stopping guidelines [13] consisted of the following: (1) A significant difference would be declared at the interim analysis and the trial would be stopped for efficacy if the 2-sided P value corresponding to the effect of treatment on GDS change score was ≤.00305 (beneficial or hazardous effect); (2) the trial would be stopped for futility if the conditional power crossed the 40% futility boundary, selected prior to the analysis. The conditional power is defined as the probability that the final analysis will show a significant difference between 2 arms given the observed data at the time of the interim analysis and the originally designed effect size (Cohen d = 0.5).

RESULTS

Accrual to the study began at 3 sites in 2007. During 2008 and 2009, accrual was not on a trajectory to meet the planned goals, and 2 new sites were added in 2010. The subsequent accrual rate increased, but when the DSMB met in December 2011 to review the planned interim analysis, the trajectory predicted another 3–4 years to complete enrollment, and funding was nearly depleted. Although the conditional power was low (48%), it did not cross the prespecified 40% futility threshold. Despite this, the DSMB recommended that the study be terminated as completing accrual and achieving the study goals in a reasonable timeframe were judged to be improbable. No safety concerns were identified.

As shown in the CONSORT diagram (Figure 1), 326 individuals were screened. Of these, 59 (18%) met inclusion/exclusion criteria and were randomized: 29 to CNS-T and 30 to comparison. At week 16, 49 participants (83%) remained on study and contributed data to the primary ITT analysis. The dropout rate did not differ by treatment arm (P = .30). The 10 participants with missing week 16 primary outcome data differed from those in the ITT analysis only on ARV experience at entry (100% vs 69%; P = .052). They were otherwise similar on demographics, baseline GDS, baseline virologic suppression, and nadir and current CD4$^+$ count (all P > .10).

Table 1 provides entry characteristics of the 49 participants contributing to the primary ITT analysis. The arms were well-balanced with respect to demographic and disease variables (Table 1), with the exception that nadir CD4$^+$ count was more likely to be <200 cells/μL for CNS-T vs comparison (P = .08). The CNS-T arm also had a numerically larger proportion of participants coinfected with HCV (35% vs 13%; P = .10).

Table 2 summarizes the drugs used in each of the treatment arms according to their frequency. Excluding ritonavir, the 2 most frequently used drugs were emtricitabine and zidovudine in the CNS-T arm and tenofovir and lamivudine in the comparison arm. Average adherence across all visits, defined as >95% of pills reported taken in the previous 4 days, did not differ significantly between the CNS-T and non–CNS-T arms (88% vs 86%, P = .72).

Intent-to-Treat Analysis

For the 49 participants with primary outcome data, the proportional improvement in GDS at week 16, adjusted for baseline, was not different between the arms (Figure 2). Nonsignificantly larger improvement was observed for the CNS-T vs non–CNS-T arm (difference 7%; 95% CI −31% to 62%). The treatment effect size, measured as the standardized mean difference, was 0.09 (95% CI, −.48 to .65). Applying a practice-effect adjustment yielded a nonsignificant difference (32% [95% CI, −64% to 479%]) with an effect size of 0.25 (95% CI, −.32 to .81; P = .39). Figure 3 shows changes in GDS, adjusted for practice effect, by
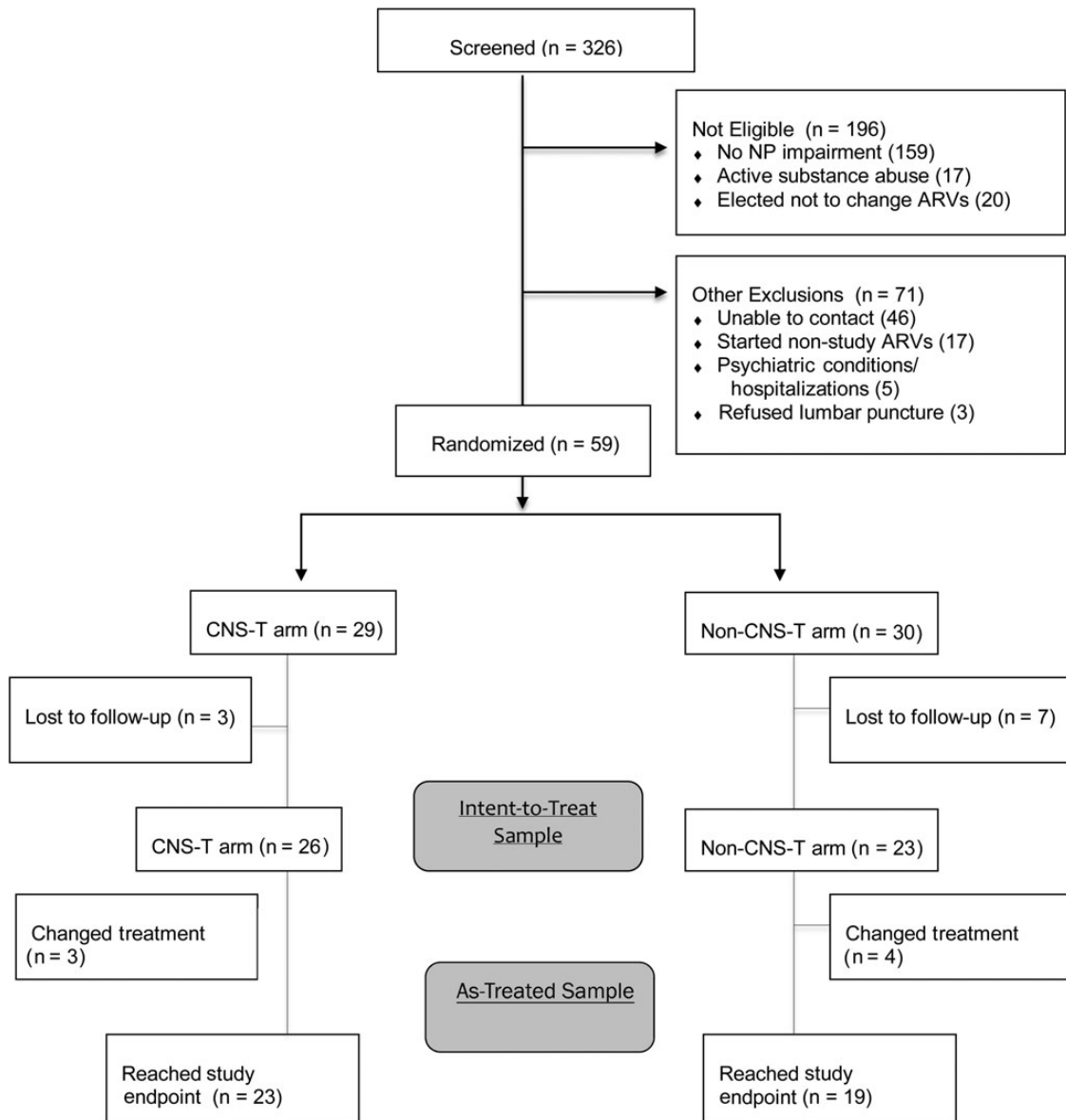
Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Abbreviations: ARV, antiretroviral; CNS-T, central nervous system targeted; NP, neuropsychological.

treatment arm and by participant. As-treated and sensitivity analyses are described in Supplementary Results.

The median regimen CPE scores were 2.5 (range, 2–3.5) for CNS-T and 1 (range, 0.5–1.5) for non–CNS-T. The mean relative phenotypic susceptibility scores (Supplementary Results) did not differ between the arms (1 vs 0.95, $P = .19$). The median number of ARVs per regimen, not including ritonavir used at boosting doses, was higher in the CNS-T than in the non–CNS-T arm (4 vs 3, Wilcoxon $P = .060$). GDS change was not related to the number of drugs in the regimen (Spearman rank $r = 0.11$, $P = .44$).

Figure 3 shows that virologic suppression rates (plasma viral load <50 copies/mL (%) improved over the 16-week trial for both

plasma ($P = .006$) and CSF ($P = .006$). There was no significant interaction between time and treatment arm for plasma ($P = .23$) or CSF ($P = .37$). Although suppression rates across all visits were similar for the 2 arms in plasma ($P = .80$) and CSF ($P = .78$), the proportion of participants reaching suppression at week 16 was numerically smaller for CNS-T (54% vs 82%; $P = .07$).

Prespecified Secondary Analyses

Regardless of treatment assignment, study participants who were ARV-naive (n = 15) demonstrated greater adjusted GDS improvement (mean, −0.30; 95% CI, −.61 to .02) than those who were ARV experienced (n = 34; mean = −0.02; 95% CI,

Table 1. Baseline Demographic and Clinical Characteristics of 49 Participants in Primary Intent-to-Treat Analysis

Characteristic	CNS Targeted	Comparison	P Value[a]
No.	26	23	
Age, y, mean (SD)	44.9 (8.7)	43.6 (11.6)	.79
Sex, male	22 (85%)	17 (74%)	.48
Race/ethnicity			.18
White, non-Hispanic	10 (38%)	9 (39%)	
Black	12 (46%)	13 (57%)	
Hispanic	4 (15%)	0 (0%)	
Other	0 (0%)	1 (4%)	
Education, y, mean (SD)	12.1 (2.6)	12.4 (1.6)	.68
Current CD4 count, cells/μL, median (range)	214 (5–964)	306 (3–1224)	.27
Prior nadir CD4 count <200 cells/μL	16 (67%)	8 (38%)	.08
Plasma HIV RNA[b], median (range)	4.2 (1.7–5.9)	3.5 (1.7–6.2)	.71
Plasma HIV RNA undetectable	7 (27%)	6 (26%)	>.99
CSF HIV RNA[b], median (range)	3.1 (1.7–4.6)	3.1 (1.7–5)	.52
CSF HIV RNA undetectable	7 (27%)	7 (30%)	>.99
Prior AIDS-defining illness	11 (46%)	7 (32%)	.75
Prior ARV treatment	17 (65%)	17 (74%)	.55
HCV coinfection	9 (35%)	3 (13%)	.10
Baseline GDS, mean (SD)	0.88 (0.6)	0.92 (0.6)	.84

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ARV, antiretroviral; CNS, central nervous system; CSF, cerebrospinal fluid; GDS, global deficit score; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

[a] Fisher exact test for categorical variables; Wilcoxon rank-sum test for continuous variables.

[b] Viral load in $\log_{10}$ copies/mL.

Table 2. Antiretrovirals Used in the 2 Arms

Antiretroviral Drug	CNS-T, No. (%)	Comparison, No. (%)
Ritonavir	21 (81)	20 (87)
Tenofovir	11 (42)	**18 (78)**
Lamivudine	5 (19)	**18 (78)**
Emtricitabine	**21 (81)**	1 (4)
Zidovudine	**18 (69)**	0 (0)
Darunavir	2 (8)	**10 (43)**
Raltegravir	5 (19)	7 (30)
Lopinavir	**16 (62)**	0 (0)
Etravirine	0 (0)	**8 (35)**
Abacavir	**6 (23)**	1 (4)
Atazanavir	1 (4)	5 (22)
Saquinavir	0 (0)	**4 (17)**
Nevirapine	**5 (19)**	0 (0)
Fosamprenavir	2 (8)	2 (9)
Efavirenz	1 (4)	0 (0)
Tipranavir	0 (0)	1 (4)
Maraviroc	1 (4)	0 (0)

Bold text indicates the 5 drugs for each treatment arm that differed most in frequency between the 2 arms. Abbreviation: CNS-T, central nervous system targeted.

Compared to participants entering the trial with detectable viral loads, the subgroup with virologic suppression was older (50.2 years [7.3] vs 42.2 years [10.2]; $P = .007$), more likely to be of white race/ethnicity (69% vs 28%; $P = .005$), and had higher current CD4^{+} counts (median, 532 cells/μL [interquartile range {IQR}, 69–1224] vs 183 cells/μL [IQR, 3–928]. The subgroups did not differ by sex, prior nadir CD4^{+} count, HCV confection, or initial GDS. After adjusting for age and race/ethnicity, the P value for the interaction was >.10. Additional secondary analyses are provided in the Supplementary Results.

Safety

One grade 3–4 adverse event was reported—hospitalization for morbid depression at week 6 in a patient with a prior history of psychiatric hospitalization. The event was deemed unrelated to study treatment. No differences were seen in rates of grade 1 or 2 laboratory abnormalities in the 2 study arms.

DISCUSSION

This randomized strategy trial did not show a neurocognitive benefit of CNS-T ART compared to non–CNS-T. However, confidence in accepting the null hypothesis of no difference between the arms was weakened by 3 considerations. First, study accrual was incomplete. Second, at entry the study arms were unbalanced on factors hypothesized or known to influence neurocognitive status and likelihood of neurocognitive improvement with
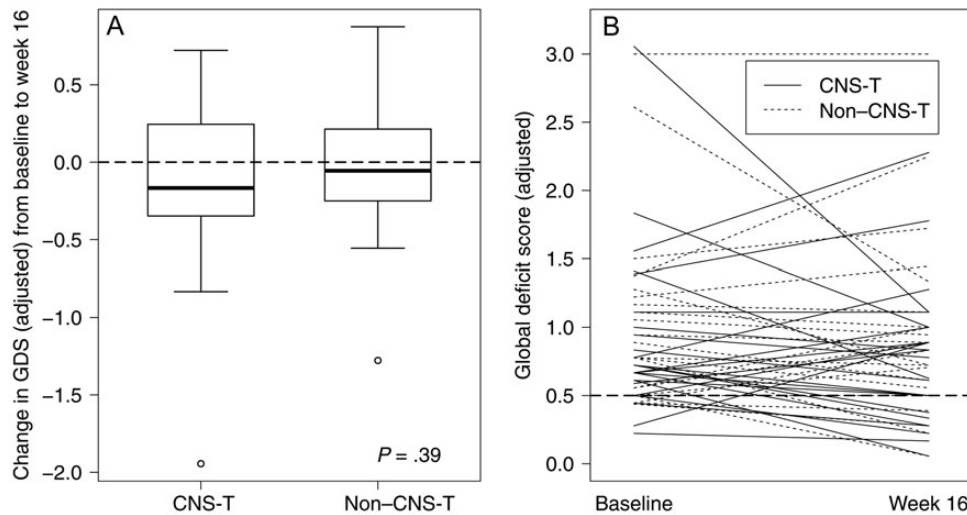
−.17 to .13), corresponding to a medium effect size (0.68; 95% CI, .06 to 1.30; $P = .032$). The interaction between treatment arm and ARV experience was not significant ($P = .80$).

Participants were stratified based on virologic suppression in plasma at baseline (≤50 copies vs >50 copies/mL). The interaction between treatment arm and virologic suppression for the outcome of adjusted GDS trended toward significance ($P = .087$). Specifically, among the 13 individuals who were virologically suppressed at baseline, the difference in GDS change between the treatment arms was 0.48 (95% CI, .0–.95; $P = .057$), compared with −0.02 among the 36 participants with detectable plasma viral load at baseline (95% CI, −.31 to .27; $P = .88$). Within the virologically suppressed subset, those randomized to CNS-T (n = 7) had a mean GDS improvement (−0.27 [95% CI, −.56 to .02]), whereas those randomized to non–CNS-T (n = 6) worsened (0.16 [95% CI, −.24 to .57]). The standardized difference (effect size) between arms was 1.09 (95% CI, −.11 to 2.25).

Figure 2. Intent-to-treat Analysis. Adjusted change in GDS from baseline to Week 16, by treatment arm (panel A) and by participant (panel B). Lower values indicate improving performance. Abbreviations: CNS-T, central nervous system targeted; GDS, global deficit score.

ART: the CNS-T arm had numerically lower mean CD4 nadir and higher rates of hepatitis C coinfection. Third, the CNS-T arm showed a trend for poorer plasma virologic suppression.

Overall, virally suppressive CART over 16 weeks in this trial was associated with modest overall improvements in cognition. A previous study showed that neurocognitive improvement in a mixed sample of ART-naive and experienced individuals reached an asymptote between 24 and 48 study weeks [14]. Thus, the short duration of the current study may have limited the effect size that could be observed. The choice of 16 weeks for the primary outcome assessment reflected a trade-off between considerations

of effect size and previously observed lower retention rates beyond 16 weeks in neurocognitively impaired individuals.

The trial's DSMB recommended study termination after reaching about half of the planned enrollment total due to slow accrual and because post hoc power was lower than a priori power. Because the predicted (based on prior experience and published literature) and observed screening-to-eligibility ratio were equal at 5:1, overly strict entry criteria did not explain the slow accrual. Instead this was due to fewer than expected referrals, possibly reflecting reluctance on the part of patients or their providers to accept treatment randomization, despite
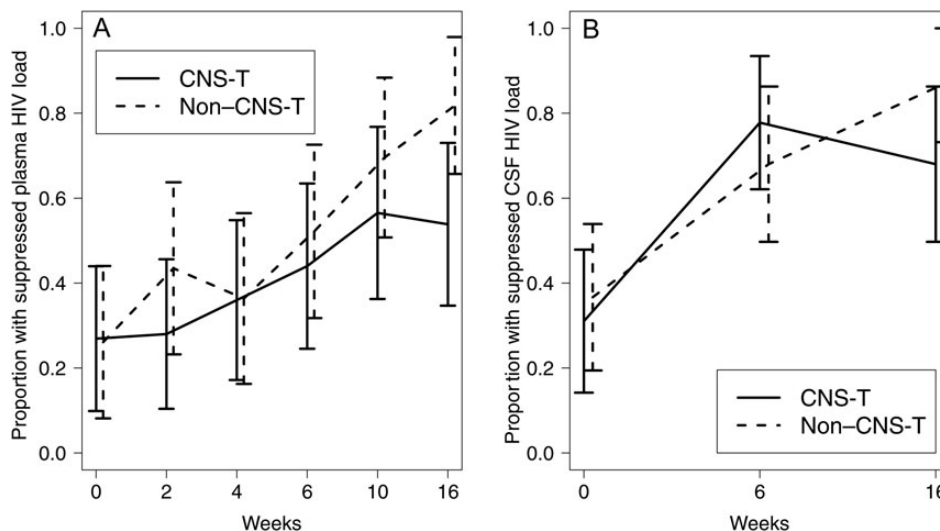

Figure 3. Proportions of participants with suppressed HIV viral loads and 95% confidence intervals in plasma (panel A) and in CSF (panel B) by study week. Abbreviations: CNS-T, central nervous system targeted; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

therapeutic equipoise with regard to the efficacy of ARV CNS penetration in HAND. Indeed, adding an additional constraint—cognitive impairment—to the already complex considerations involved in constructing an individualized ART regimen (prior ART, drug resistance, comorbidities, concomitant medications) may have seemed overly burdensome. Low rates of HAND in the population screened did not explain the incomplete accrual, as sufficient numbers of impaired individuals were in fact identified. Instead, many NP-eligible individuals chose not to enroll, perhaps because of perceived urgency to begin ART. Further, many NP-impaired participants were deemed otherwise ineligible because of confounding comorbidities, psychiatric conditions, and substance abuse. Refusal of lumbar puncture was rarely a reason for failure to enroll.

Baseline HIV Disease and Treatment Characteristics

The trial design attempted to limit potentially influential differences between the arms by using adaptive randomization. While this balanced several of the most influential factors such as HAND severity and ART history (naive vs experienced), the arms differed in 2 characteristics known or suspected to be associated with more frequent neurocognitive impairment and a lower likelihood of neurocognitive improvement. Participants randomized to the CNS-T arm had lower nadir CD4$^+$ T-cell counts and more frequent HCV coinfection. Although individually these differences did not reach statistical significance, their combined effect may have limited the benefit of CNS-T, if one exists.

Approximately one-third of the neurocognitively impaired participants in this trial were ARV-naive. Of the remaining ARV-experienced participants, one-quarter entered with virologic suppression in plasma, and the remainder had virologic failure on ART. These entry characteristics were balanced between the study arms. A prespecified secondary analysis demonstrated an interaction between plasma virologic suppression and treatment arm. Among participants virologically suppressed at study entry, CNS-T was associated with superior neurocognitive improvement. However, the robustness of this finding was limited by small numbers and was confounded by age, as virologically suppressed participants tended to be older. For virologically suppressed individuals, the difference between treatment arms was no longer significant when age was statistically covaried.

Characteristics of ARV Regimens and Treatment Responses

Study treatments in both arms typically comprised 2 nucleoside reverse transcriptase inhibitors plus either a ritonavir-boosted HIV protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. As in prior reports [15], the number of agents was higher for CNS-T. However, the relative phenotypic susceptibility scores did not differ significantly between the arms. The most common differences in agents between the arms were the use of more zidovudine, abacavir, and ritonavir-boosted lopinavir in the

CNS-T arm and more tenofovir, darunavir, and raltegravir in the non-CNS-T arm. Overall, 70% of participants in this study achieved virologic suppression in plasma (<50 copies/mL) by week 16, and 85% in CSF. Virologic suppression rates in this trial were less than in most clinical trials, but similar to those in community practice (eg, [16]). There are several potential explanations for this. First, more than two-thirds of subjects were ART experienced, with many having been exposed to multiple previous failed ART regimens. Such individuals may harbor resistance mutations that reduce the likelihood of success with future regimens. Second, this trial accrued neurocognitively impaired individuals, demonstrated previously to show poor ARV adherence. Although suppression rates did not differ statistically between the treatment arms, they were numerically poorer for CNS-T, a finding that differs from previous observational reports [15, 17]. Lower CD4 nadir and higher rates of HCV coinfection in the CNS-T arm may have contributed to this result. Additionally, drug potency may have played a role, as there is evidence that darunavir, used more frequently in the non–CNS-T arm, is more potent than lopinavir, and that etravirine is more potent than nevirapine. Occasional reports of CSF viral escape, as indicated by detectable CSF viral load despite plasma virologic suppression, have emerged [18]. We did not observe this phenomenon in our trial participants.

The balance of competing benefits and risks of increased ART CNS penetration is not well understood. Benefits of CNS-T might be counterbalanced by increased CNS toxicities. Two recent studies demonstrated in vitro neurotoxic effects of efavirenz [19, 20], and such effects might translate to neurocognitive impairment in humans. Efavirenz was infrequently used in the current study and did not differ between the treatment arms. However, neurotoxicities of other ARVs might have masked or otherwise confounded the expected treatment effects. Indeed, some ARVs used more frequently in this study's CNS-T regimens (eg, zidovudine, abacavir) might have greater CNS toxicity than those used in non–CNS-T regimens (eg, tenofovir, raltegravir). Also, as CNS-T regimens tended to include more drugs (4 vs 3), there may be more opportunity for toxicities. Loss to follow-up was not different between the study arms, arguing against major differences in tolerability.

This study was designed to detect at least a moderate effect size; thus, a possible small effect size cannot be excluded. Potential benefits for specific subgroups, such as aging individuals or those with successful virologic suppression, also cannot be excluded. ARV-naive participants showed more neurocognitive improvement than those who were ARV experienced, regardless of treatment assignment. This is consistent with prior reports [21], and argues for prompt initiation of ART in neurocognitively impaired, ARV-naive individuals.

Future studies should consider longer follow-up to detect beneficial effects of CNS-T. Imaging outcomes such as functional magnetic resonance imaging might provide a more sensitive tool

to evaluate short-term changes. Measures to mitigate low screening referral rates are important. Also, future trials may elect to focus on CNS-T's possible subgroup benefits for virologically suppressed or older participants. When neurocognitive impairment persists despite durable suppression on ART, switching to a CNS-T strategy remains a reasonable therapeutic option. Other potential explanations for the incomplete success of ART in treating HAND should be explored, including persistent CNS immune activation and CNS toxicities of ART.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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