

Does Choice of Combination Antiretroviral Therapy (cART) Alter Changes in Cerebral Function Testing after 48 Weeks in Treatment-Naive, HIV-1–Infected Individuals Commencing cART? A Randomized, Controlled Study

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(See editorial commentary by Brew, on pages 930–932.)

Background. Neurocognitive impairment remains prevalent, despite combination antiretroviral therapy (cART). Differences between changes in cerebral function and alternative cARTs have not been prospectively assessed.

Methods. Treatment-naive, HIV-1–infected individuals randomly allocated to commence cART (tenofovir-emtricitabine plus either efavirenz [arm 1], atazanavir-ritonavir [arm 2], or zidovudine-abacavir [arm 3]) were eligible. Cerebral function tests included neurocognitive testing and assessment of cerebral metabolites using proton magnetic resonance spectroscopy in several anatomical voxels, including right frontal white matter and right basal ganglia, at baseline and after 48 weeks. *N*-acetylaspartate-to-creatine (NAA/Cr) ratios were calculated. Both the differences between changes in neurocognitive function and NAA/Cr ratios over 48 weeks and the study arms (arm 1 vs arm 2; arm 1 vs arm 3) were assessed.

Results. Thirty subjects completed study procedures (9, 9, and 12 subjects in arms 1, 2, and 3, respectively). Mean CD4⁺ cell counts (\pm standard deviation) were 218 ± 87 cells/ μ L at baseline and 342 ± 145 cells/ μ L at week 48. The mean plasma HIV-1 RNA level was <50 copies/mL for 28 of the 30 subjects at week 48. Over 48 weeks, greater improvements in identification reaction time ($P = .04$) and executive function ($P = .02$) were observed in arm 3, compared with arm 1 (0.03, -0.30 , -0.50 log₁₀ ms change in identification reaction time, in arms 1, 2, and 3, respectively). Increases in the NAA/Cr ratio were observed in all voxels (maximum 38% in right basal ganglia), with greater increases observed in arm 1 than in arm 2 ($P = .03$) in frontal white matter (30%, -7% , and 0% change in the NAA/Cr ratio, in arms 1, 2, and 3, respectively).

Conclusions. To our knowledge, this is the first study to prospectively describe different changes in cerebral function testing parameters between different cARTs. Greater improvements in neuronal recovery (NAA/Cr ratio) were observed for recipients of tenofovir-emtricitabine plus efavirenz (arm 1), and greater improvements in neurocognitive function testing were observed for recipients of tenofovir-emtricitabine plus zidovudine-abacavir (arm 3).

In recent years, the development of combination antiretroviral therapy (cART) for the treatment of human immune deficiency virus type 1 (HIV-1) has been as-

sociated with extraordinary improvements in prognosis for persons living with chronic HIV-1 infection. Life expectancy has increased dramatically [1]. Despite effective therapies, challenges remain in the management of chronic HIV-1 infection. One such challenge is ongoing HIV-1–associated cerebral impairment [2, 3]. Although severe HIV-1–related cerebral impairment (also referred to as HIV-1–associated dementia) is now less frequently observed [4], less fulminant forms of neurocognitive impairment are increasingly being recognized [2, 5, 6]. Impairment in neurocognitive function among HIV-1–infected subjects in the cART era has

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been associated with poor compliance with cART [7], reduced quality of life [8], and increased mortality [9].

The reported factors associated with the development of neurocognitive function impairment in HIV-1 disease and the risks associated with the progression of such impairment include degree of immune suppression related to HIV-1 infection [10], other chronic viral infections (such as chronic hepatitis C coinfection) [11], and age [12].

Furthermore, specific antiretroviral regimens may have different effects on cerebral function. In general, neurocognitive function improves after commencing cART [13], but the effects of different antiretroviral therapies on these changes have not been prospectively assessed. The penetration of different antiretroviral agents into the central nervous system (CNS) differ [14]. Agents with better CNS penetration may offer improved HIV-1 viral suppression in the CNS compartment and may therefore be associated with greater improvements in neurocognitive function. However, cerebral toxicities may ensue, thus limiting these potential benefits [15].

The aim of this study was to assess changes in cerebral function testing in ART-naive, HIV-1-infected individuals commencing 3 different combination treatment regimens within a prospective, randomized study. Assessment of cerebral function included neurocognitive function testing and measurement of cerebral metabolite ratios using magnetic resonance spectroscopy (MRS).

METHODS

Patient selection and study procedures. Patients attending either (1) St. Mary's Hospital, London, United Kingdom; (2) Queen Elizabeth Hospital, Kowloon, Hong Kong; (3) HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre, Bangkok, Thailand; or (4) the Southern Alberta HIV Clinic, Calgary, Canada, and enrolled in the Altair Study (a randomized, open-label, 96-week study comparing the safety and efficacy of 3 different combination antiretroviral regimens as initial therapy for HIV-1 infection) [16] were eligible to enroll in this 48-week substudy.

Study subjects were randomly allocated to commence cART comprising 300 mg tenofovir and 200 mg emtricitabine once daily with either efavirenz 600 mg once daily (arm 1), 300 mg atazanavir and 100 mg ritonavir once daily (arm 2), or 250 or 300 mg zidovudine twice daily and 600 mg abacavir once daily (arm 3).

Eligible subjects tested positive for HIV-1 antibody and were naive to ART. Specific exclusion criteria for this substudy included current or recent use of antidepressant or antipsychotic therapies, current or recent history of alcohol or recreational drug dependence, recent significant head injury, established dementia, active opportunistic infections, untreated early syphilis, hepatitis C infection (ie, positive for hepatitis C antibody),

Figure 1a: Right frontal white matter and mid-frontal grey matter

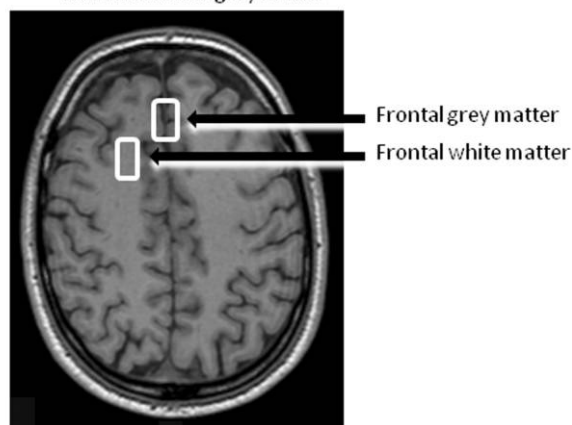


Figure 1b: Right basal ganglia

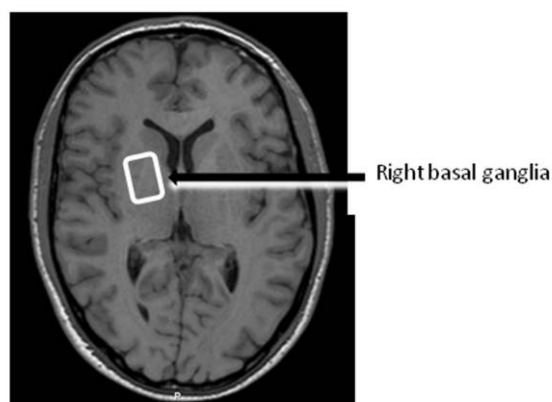


Figure 1. Volumes of interest. Plane of section. (a) Right frontal white matter and mid-frontal grey matter. (b) Right basal ganglia.

and/or evidence of established chronic liver disease, cirrhosis, or hepatic encephalopathy (in the previous 12 weeks). Furthermore, in the 48-h period prior to study investigations being performed, consumption of alcohol or caffeine was not permitted.

Specific study procedures to assess cerebral function involved patients being tested for neurocognitive function at baseline and week 48 and undergoing a cerebral MRS examination at baseline and week 48 as detailed below. Subjects were also tested after 1 month of therapy and thereafter every 3 months, for assessment of safety laboratory parameters, CD4⁺ lymphocyte count, and plasma HIV-1 RNA level (all performed by local laboratories).

Cognitive testing. A computerized cognitive test battery was undertaken (CogState) that has previously been described in detail and validated for HIV-1-infected subjects [17]. The computerized assessment was presented on a desktop computer. All tasks within the battery are adaptations of standard

Table 1. Patient Characteristics at Baseline and Follow-Up

| Characteristic | Overall (n = 30 subjects) | Arm 1 (n = 9 subjects) | Arm 2 (n = 9 subjects) | Arm 3 (n = 12 subjects) |
|---|------------------------------|---------------------------|---------------------------|----------------------------|
| At baseline | | | | |
| CD4 ⁺ cell count, cells/ μ L | 218 \pm 87 | 235 \pm 56 | 194 \pm 84 | 222 \pm 109 |
| CD4 ⁺ percentage | 13.6 \pm 4.4 | 14.3 \pm 2.7 | 13.7 \pm 6 | 13.08 \pm 4.4 |
| Nadir CD4 ⁺ cell count, cells/ μ L | 192 \pm 83 | 170 \pm 50 | 171 \pm 67 | 207 \pm 112 |
| HIV-1 RNA level, log ₁₀ copies/mL | 4.64 \pm 0.68 | 4.47 \pm 0.76 | 4.86 \pm 0.63 | 4.59 \pm 0.67 |
| Age, years | 35 \pm 10 | 35 \pm 11 | 37 \pm 10 | 33 \pm 19 |
| No. of Asian subjects | 18 | 4 | 7 | 7 |
| No. of white subjects | 11 | 4 | 2 | 5 |
| No. of Afro-Caribbean subjects | 1 | 1 | 0 | 0 |
| At week 24 | | | | |
| CD4 ⁺ cell count, cells/ μ L | 337 \pm 121 | 332 \pm 96 | 346 \pm 120 | 333 \pm 147 |
| No. of subjects with HIV-1 RNA level <50 copies/mL | 27 | 8 | 8 | 11 |
| Detectable HIV-1 RNA load, copies/mL | | 64 | 200 | 1287 |
| At week 48 | | | | |
| CD4 ⁺ cell count, cells/ μ L | 342 \pm 145 | 299 \pm 135 | 400 \pm 160 | 331 \pm 138 |
| No. of subjects with HIV-1 RNA level <50 copies/mL | 28 | 9 | 8 | 11 |
| Detectable HIV-1 RNA load, copies/mL | ... | ... | 490 | 113,988 |
| No. of subjects who had changes to randomized therapy | 1 | 0 | 0 | 1 ^a |

NOTE. Data are mean values (\pm standard deviation), unless otherwise indicated. Study subjects were randomly allocated to commence combination antiretroviral therapy comprising 300 mg tenofovir and 200 mg emtricitabine once daily with either efavirenz 600 mg once daily (arm 1), 300 mg atazanavir and 100 mg ritonavir once daily (arm 2), or 250 or 300 mg zidovudine twice daily and 600 mg abacavir once daily (arm 3).

^a Switched to boosted protease inhibitor after week 48.

neuropsychological and experimental psychological tests, which assess a range of cognitive functions. The following domains were assessed: detection, identification, learning (matching learning and associate learning), monitoring, working memory, and executive function. The computerized battery requires ~15–20 min for completion. The battery consists of tasks in the form of card games; therefore, subjects need only to have an understanding of playing cards, thereby minimizing language and cultural differences between study subjects. All study participants completed one full practice test prior to undertaking the study examination to obtain optimal performance at baseline [18].

Cerebral ¹H MRS. Proton (¹H) MRS was performed on an Achieva 1.5 Tesla scanner (at St. Mary's Hospital, London, UK), a Siemens Avanto 3.0 Tesla scanner (at Queen Elizabeth Hospital, Kowloon, Hong Kong), a 1.5 Tesla Signa General Electric scanner (at the HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand), and a 3.0 Tesla Signa Excite scanner (at the Southern Alberta HIV Clinic, Calgary, Canada). Examinations began with sagittal, coronal, and axial T₁-weighted MR images of the brain, to enable accurate positioning of the voxels, and T₂-weighted axial double-spin echo images, to exclude any visible cerebral pathology.

¹H MRS was performed at 3 voxel locations: right frontal white matter, mid-frontal grey matter, and the right basal ganglia (Figure 1). These anatomical voxels were selected on the

basis of previous imaging studies describing cerebral metabolite abnormality patterns in such voxels among HIV-1-infected individuals [19, 20]. MRS data were acquired by a single voxel examination in each of the 3 locations, using a double-spin-echo sequence in point-resolved spectroscopy with the following settings: an echo time of 36 ms, a repetition time of 3000 ms, 2048 data points, a spectral width of 2500 Hz, and 128 data acquisitions. Spectra from the MR imaging were postprocessed using the manufacturer's software for automated water signal suppression and water shimming. Each examination lasted ~35 min. A study MRS operations manual was developed to ensure that all MRS examinations at each study site were undertaken using identical operational settings.

All spectra were analyzed and quantified by a single observer (A.W.) using a Java-based version of the Magnetic Resonance User Interface package (jMRUI, version 3.0) [21] and incorporated the AMARES (Advanced Method for Accurate, Robust, and Efficient Spectral) fitting algorithm [22]. The metabolites assessed were N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myo-inositol (MI). To adjust for different MR imaging scanners across all 4 study sites, all metabolites were expressed as ratios with respect to cerebral Cr.

Statistical methods. Statistical analyses were conducted with SAS, version 9.13 (SAS), and Stata, version 10.1 (Stata-Corp). Linear regression modeling was used to estimate the effect size for absolute differences in the metabolite ratio for

Table 2. Neurocognitive Testing Parameters and Changes over 48 Weeks

| Cognitive domain | Overall | | | Arm 1 | | | Arm 2 | | | Arm 2 vs arm 1 | | | Arm 3 | | | Arm 3 vs arm 1 | | |
|---|-----------------|---------------|-----------------|---------------|-----------------|---------------|--------------------------|-----------------|------------------------------|----------------|---------------------------|-----------------|------------------------------|---------------|-----------|-----------------|------------------------------|---|
| | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD | Mean ± SD | No. of subjects | Change ^a (95% CI) | P | Mean ± SD | No. of subjects | Change ^a (95% CI) | P | Mean ± SD | No. of subjects | Change ^a (95% CI) | P |
| Detection, ^b log ₁₀ ms | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.55 ± 0.13 | 9 | 2.51 ± 0.13 | 8 | 2.56 ± 0.16 | -0.513 (-1.501 to 0.475) | .30 | 11 | 2.57 ± 0.11 | -0.717 (-1.631 to 0.197) | .12 | 12 | 2.54 ± 0.13 | | | | |
| Week 48 | 29 | 2.54 ± 0.13 | 9 | 2.55 ± 0.18 | 8 | 2.55 ± 0.10 | | | | | | | | | | | | |
| Identification, ^b log ₁₀ ms | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.74 ± 0.09 | 9 | 2.72 ± 0.12 | 8 | 2.76 ± 0.08 | -0.681 (-1.635 to 0.273) | .15 | 11 | 2.75 ± 0.07 | -0.908 (-1.791 to -0.026) | .04 | 12 | 2.70 ± 0.05 | | | | |
| Week 48 | 29 | 2.72 ± 0.09 | 9 | 2.75 ± 0.14 | 8 | 2.73 ± 0.06 | | | | | | | | | | | | |
| Monitoring, ^b log ₁₀ ms | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.61 ± 0.10 | 9 | 2.58 ± 0.10 | 8 | 2.66 ± 0.10 | -0.809 (-1.793 to 0.175) | .10 | 11 | 2.60 ± 0.10 | -0.288 (-1.198 to 0.623) | .51 | 12 | 2.58 ± 0.07 | | | | |
| Week 48 | 29 | 2.58 ± 0.09 | 9 | 2.57 ± 0.11 | 8 | 2.60 ± 0.11 | | | | | | | | | | | | |
| Learning (matched), ^b log ₁₀ ms | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.83 ± 0.06 | 9 | 2.82 ± 0.09 | 8 | 2.83 ± 0.04 | -0.290 (-1.288 to 0.708) | .56 | 11 | 2.83 ± 0.05 | -0.652 (-1.576 to 0.271) | .27 | 12 | 2.80 ± 0.06 | | | | |
| Week 48 | 29 | 2.82 ± 0.09 | 9 | 2.83 ± 0.15 | 8 | 2.83 ± 0.05 | | | | | | | | | | | | |
| One card learning, ^c arcsine | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.61 ± 0.10 | 9 | 2.58 ± 0.10 | 8 | 2.66 ± 0.10 | -0.046 (-1.060 to 0.969) | .93 | 11 | 2.60 ± 0.10 | 0.383 (-0.538 to 1.304) | .40 | 12 | 2.58 ± 0.07 | | | | |
| Week 48 | 29 | 2.58 ± 0.09 | 9 | 2.57 ± 0.11 | 8 | 2.60 ± 0.11 | | | | | | | | | | | | |
| Working memory, ^c arcsine | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 1.11 ± 0.35 | 9 | 1.08 ± 0.36 | 8 | 1.17 ± 0.21 | -0.057 (-1.094 to 0.981) | .91 | 11 | 1.09 ± 0.44 | 0.105 (-0.854 to 1.065) | .82 | 12 | 1.22 ± 0.14 | | | | |
| Week 48 | 29 | 1.22 ± 0.20 | 9 | 1.18 ± 0.30 | 8 | 1.25 ± 0.15 | | | | | | | | | | | | |
| Associate learning, ^c arcsine | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 0.88 ± 0.20 | 9 | 0.82 ± 0.26 | 8 | 0.99 ± 0.17 | 0.240 (-0.793 to 1.274) | .64 | 11 | 0.86 ± 0.16 | 0.229 (-0.727 to 1.185) | .63 | 12 | 0.89 ± 0.23 | | | | |
| Week 48 | 29 | 0.91 ± 0.22 | 9 | 0.81 ± 0.24 | 8 | 1.03 ± 0.13 | | | | | | | | | | | | |
| Executive function, ^d total no. of errors | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 49.64 ± 25.22 | 9 | 43.44 ± 27.86 | 8 | 47.38 ± 18.55 | -0.259 (-1.652 to 1.134) | .71 | 11 | 56.36 ± 27.69 | -1.539 (-2.828 to -0.251) | .02 | 11 | 39.09 ± 22.61 | | | | |
| Week 48 | 28 | 44.82 ± 20.96 | 9 | 48.44 ± 21.83 | 8 | 48.63 ± 18.28 | | | | | | | | | | | | |
| Composite speed score, log ₁₀ ms | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 2.68 ± 0.08 | 9 | 2.66 ± 0.10 | 8 | 2.70 ± 0.08 | -0.785 (-1.729 to 0.158) | .10 | 11 | 2.69 ± 0.07 | -0.939 (-1.812 to -0.066) | .04 | 12 | 2.65 ± 0.06 | | | | |
| Week 48 | 29 | 2.67 ± 0.09 | 9 | 2.68 ± 0.08 | 8 | 2.68 ± 0.07 | | | | | | | | | | | | |
| Composite accuracy score, arcsine | | | | | | | | | | | | | | | | | | |
| Baseline | 28 | 0.93 ± 0.22 | 9 | 0.88 ± 0.23 | 8 | 1.02 ± 0.15 | 0.055 (-0.974 to 1.084) | .91 | 11 | 0.91 ± 0.24 | 0.362 (-0.635 to 1.268) | .50 | 12 | 0.99 ± 0.12 | | | | |
| Week 48 | 29 | 0.99 ± 0.14 | 9 | 0.92 ± 0.18 | 8 | 1.06 ± 0.15 | | | | | | | | | | | | |

NOTE. Study subjects were randomly allocated to commence combination antiretroviral therapy comprising 300 mg tenofovir and 200 mg emtricitabine once daily with either efavirenz 600 mg once daily (arm 1), 300 mg atazanavir and 100 mg ritonavir once daily (arm 2), or 250 or 300 mg zidovudine twice daily and 600 mg abacavir once daily (arm 3). CI, confidence interval.

^a Changes assessed using the methodology recommended by CogState. In brief, changes in standardized scores were weighted by the pooled standard deviation (SD) and entered into a linear regression model with the arm as a categorical covariate. Coefficient of change represents the mean difference for each treatment group compared to arm 1, and *P* values are the pairwise comparative significance tests.

^b Used to determine speed; a lower score represents an improved response.

^c Used to determine correct responses (ie, accuracy of response); a higher score represents an improved response.

^d A lower score represents an improved response.

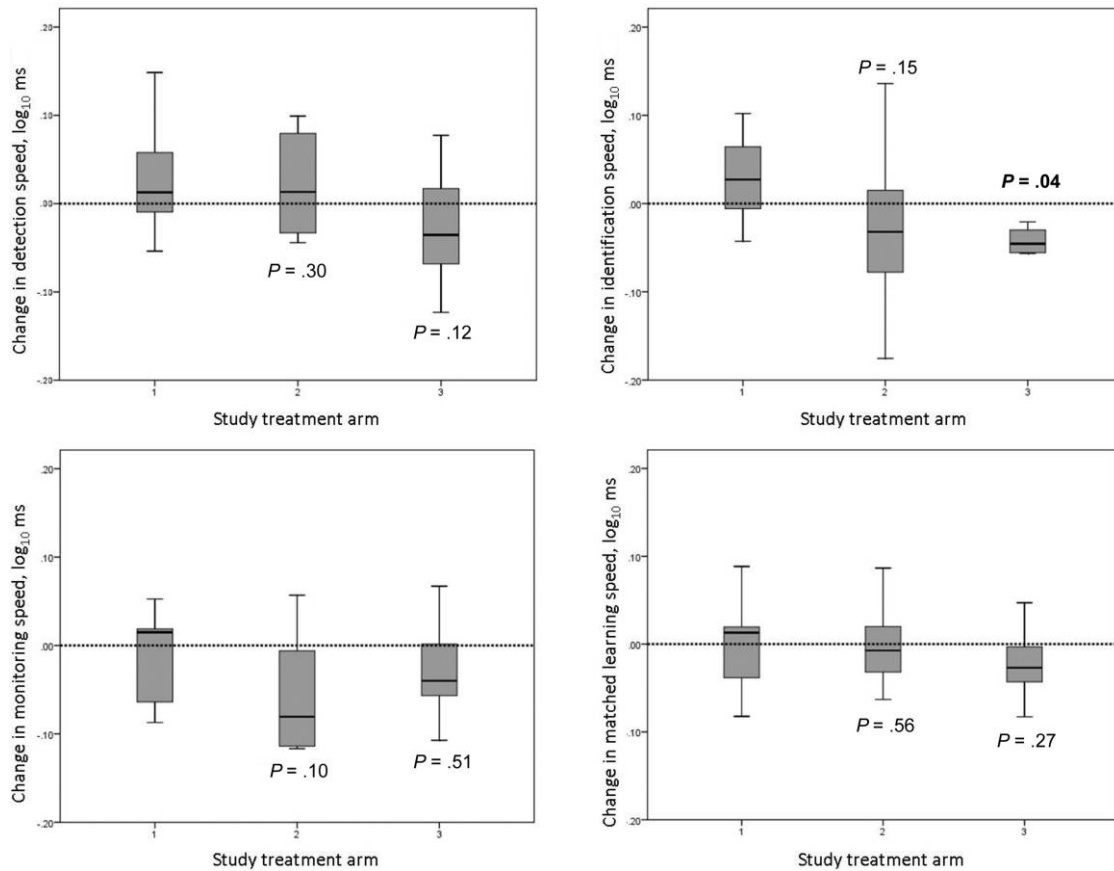


Figure 2. Box plots showing changes in neurocognitive speed domain parameters over 48 weeks. Box plot showing median absolute change (*horizontal line*), interquartile ranges (*grey boxes*), and upper and lower adjacent values (*whiskers*). The *P* values shown are mean differences in the treatment group, compared with arm 1.

individual subjects from baseline to week 48, in pairwise comparisons between arm 1 and arms 2 and 3. A Wilcoxon rank sum test was also used to confirm the *P* values derived from regression models. Other baseline covariates were also tested in univariate regression models, and those with $P \leq .15$ were entered into multivariate models. For the cognitive testing results, analysis was conducted according to CogState recommendations. Reaction times were \log_{10} transformed due to a positive skew of the distribution, and accuracy measures were transformed using arcsine-root transformation. Changes in scores were calculated for each subject, and these scores were standardized according to the within-subject standard deviation (SD). Changes in performance for arms 2 and 3, compared with arm 1, were standardized with a pooled SD, and this was used as the outcome variable in linear regression models to calculate an overall effect size for the differences between treatment groups. Composite changes from baseline scores were calculated on the average of standardized reaction time and accuracy scores.

RESULTS

Subject characteristics. Thirty subjects were enrolled, and all completed study procedures (9, 9, and 12 subjects in arms 1, 2, and 3, respectively). The mean CD4⁺ lymphocyte count (\pm SD) was 218 ± 87 cells/ μ L at baseline and 342 ± 145 cells/ μ L at week 48 (Table 1). At week 48, all subjects remained on randomized study therapy, and plasma HIV-1 RNA level was <50 copies/mL for 28 of the 30 subjects. For the remaining 2 subjects, the HIV-1 RNA level was 490 and 113,988 copies/mL, respectively. The HIV-1 RNA level of 490 copies/mL was considered a HIV-1 RNA viral blip (study arm 2; with no changes to ART undertaken for the subject and a subsequent HIV-1 RNA level below detection); the HIV-1 RNA level of 113,988 copies/mL was considered a virological failure in the treatment of the subject (arm 3), for whom ART was modified.

Cognitive testing results. Neurocognitive testing results, including changes over 48 weeks, are shown in Table 2. Overall, improvements in all neurocognitive testing parameters were observed during the study period. In domains for which speed

Table 3. Cerebral Metabolite Ratios and Changes over 48 Weeks

| Voxel | Overall | | Arm 1 | | Arm 2 | | Arm 2 vs arm 1 | | Arm 3 | | Arm 3 vs arm 1 | |
|---------------------|-----------------|---------------|-----------------|---------------|-----------------|---------------|------------------------------|------|-----------------|---------------|------------------------------|------|
| | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD | No. of subjects | Mean ± SD | Change ^a (95% CI) | P | No. of subjects | Mean ± SD | Change ^a (95% CI) | P |
| Front white matter | | | | | | | | | | | | |
| NAA/Cr ratio | | | | | | | | | | | | |
| Baseline | 28 | 1.879 ± 0.344 | 7 | 1.860 ± 0.280 | 9 | 1.834 ± 0.269 | -0.777 (-1.519 to -0.036) | .041 | 12 | 1.924 ± 0.436 | -0.686 (-1.385 to 0.014) | .054 |
| 48 weeks | 28 | 1.956 ± 0.746 | 7 | 2.481 ± 1.115 | 9 | 1.677 ± 0.174 | | | 12 | 1.859 ± 0.646 | | |
| Cho/Cr ratio | | | | | | | | | | | | |
| Baseline | 28 | 1.182 ± 0.314 | 7 | 1.107 ± 0.168 | 9 | 1.159 ± 0.283 | -0.116 (-0.450 to 0.219) | .483 | 12 | 1.243 ± 0.400 | -0.103 (-0.419 to 0.213) | .508 |
| 48 weeks | 28 | 1.162 ± 0.173 | 7 | 1.168 ± 0.183 | 9 | 1.105 ± 0.133 | | | 12 | 1.201 ± 0.195 | | |
| MI/Cr ratio | | | | | | | | | | | | |
| Baseline | 28 | 3.849 ± 1.632 | 7 | 3.854 ± 1.761 | 9 | 3.803 ± 1.092 | 1.065 (-0.842 to 2.972) | .261 | 12 | 3.881 ± 1.994 | 1.513 (-0.297 to 3.322) | .097 |
| 48 weeks | 27 | 3.711 ± 1.471 | 6 | 2.595 ± 1.581 | 9 | 3.729 ± 0.770 | | | 12 | 4.255 ± 1.596 | | |
| Frontal grey matter | | | | | | | | | | | | |
| NAA/Cr ratio | | | | | | | | | | | | |
| Baseline | 29 | 1.586 ± 0.250 | 8 | 1.561 ± 0.286 | 9 | 1.539 ± 0.166 | -0.120 (-0.758 to 0.517) | .701 | 12 | 1.637 ± 0.286 | -0.295 (-0.894 to 0.303) | .320 |
| 48 weeks | 30 | 1.815 ± 0.573 | 9 | 1.919 ± 0.357 | 9 | 1.814 ± 0.953 | | | 12 | 1.737 ± 0.312 | | |
| Cho/Cr ratio | | | | | | | | | | | | |
| Baseline | 29 | 0.687 ± 0.150 | 8 | 0.714 ± 0.146 | 9 | 0.705 ± 0.179 | 0.047 (-0.130 to 0.225) | .587 | 12 | 0.657 ± 0.137 | 0.045 (-0.121 to 0.212) | .580 |
| 48 weeks | 30 | 0.693 ± 0.155 | 9 | 0.688 ± 0.161 | 9 | 0.724 ± 0.171 | | | 12 | 0.674 ± 0.149 | | |
| MI/Cr ratio | | | | | | | | | | | | |
| Baseline | 27 | 3.041 ± 1.161 | 6 | 3.268 ± 1.804 | 9 | 3.247 ± 0.857 | -0.253 (-1.754 to 1.249) | .731 | 12 | 2.774 ± 1.017 | -0.160 (-1.606 to 1.285) | .821 |
| 48 weeks | 28 | 2.850 ± 1.439 | 8 | 2.997 ± 1.662 | 9 | 2.970 ± 1.422 | | | 11 | 2.646 ± 1.400 | | |
| Right basal ganglia | | | | | | | | | | | | |
| NAA/Cr ratio | | | | | | | | | | | | |
| Baseline | 27 | 2.022 ± 0.613 | 7 | 1.908 ± 0.431 | 8 | 2.274 ± 0.976 | -0.427 (-1.893 to 1.038) | .552 | 12 | 1.921 ± 0.340 | -0.150 (-1.467 to 1.167) | .815 |
| 48 weeks | 27 | 2.689 ± 1.096 | 8 | 2.723 ± 1.477 | 7 | 2.782 ± 0.824 | | | 12 | 2.612 ± 1.032 | | |
| Cho/Cr ratio | | | | | | | | | | | | |
| Baseline | 27 | 1.013 ± 0.618 | 7 | 0.974 ± 0.183 | 8 | 1.225 ± 1.121 | -0.347 (-1.121 to 0.427) | .363 | 12 | 0.893 ± 0.186 | 0.139 (-0.557 to 0.835) | .683 |
| 48 weeks | 27 | 0.930 ± 0.294 | 8 | 0.910 ± 0.235 | 7 | 0.875 ± 0.188 | | | 12 | 0.976 ± 0.381 | | |
| MI/Cr ratio | | | | | | | | | | | | |
| Baseline | 27 | 3.041 ± 1.161 | 6 | 3.268 ± 1.804 | 9 | 3.247 ± 0.857 | -0.016 (-1.446 to 1.414) | .982 | 12 | 2.774 ± 1.017 | 0.099 (-1.218 to 1.416) | .877 |
| 48 weeks | 25 | 2.887 ± 1.007 | 7 | 3.219 ± 1.452 | 7 | 3.001 ± 0.907 | | | 11 | 2.604 ± 0.708 | | |

NOTE. Study subjects were randomly allocated to commence combination antiretroviral therapy comprising 300 mg tenofovir and 200 mg emtricitabine once daily with either efavirenz 600 mg once daily (arm 1), 300 mg atazanavir and 100 mg ritonavir once daily (arm 2), or 250 or 300 mg zidovudine twice daily and 600 mg abacavir once daily (arm 3). Cho, choline; CI, confidence interval; Cr, creatine; MI, myo-inositol; NAA, N-acetyl/aspartate; SD, standard deviation.

^a Coefficient of change represents the difference in mean changes from week 0 to week 48 between treatment groups in a linear regression model.

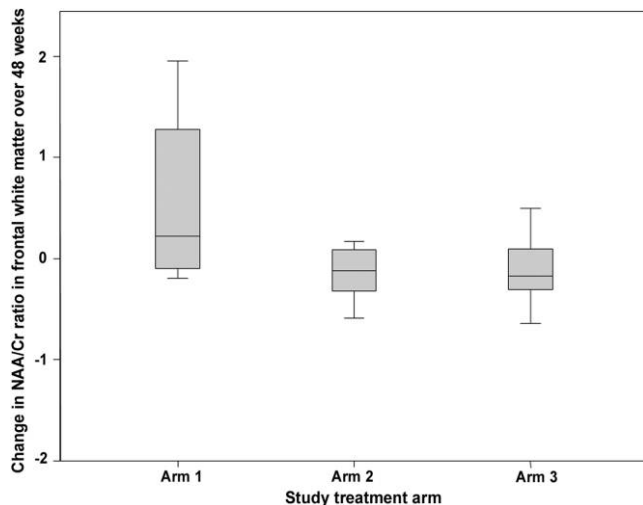


Figure 3. Box plot showing absolute changes in the *N*-acetylaspartate-to-creatine (NAA/Cr) ratio in frontal white matter over 48 weeks. Box plot showing median absolute change (*horizontal line*), interquartile ranges (*grey boxes*), and upper and lower adjacent values (*whiskers*).

of task was the primary measure (detection, identification, monitoring, and matched learning), mean speed improved (reduction in time) over the study period. For example, mean monitoring reaction time changed from 2.61 to 2.58 \log_{10} ms at baseline and week 48. In the cognitive domains for which accuracy was the primary measurement (one card learning, working memory, and associate learning), in which an increase in accuracy represents improved function, improvements were also observed over the study period. Finally, the domain of executive function was assessed via total errors made on testing, for which a reduction in score represented improvement in performance. Again, improvements were observed over the study period: the total mean number of errors on executive function tests was reduced from 49.64 errors at baseline to 44.82 errors at week 48.

Statistically significant improvements in study treatment arm 3 versus arm 1 were observed in speed of identification task ($P = .04$), in number of errors in executive function task ($P = .02$), and in overall composite speed performance ($P = .02$). A box plot showing changes in speed performance tasks between study treatment arms is shown in Figure 2. No other statistically significant differences between changes in neurocognitive testing results and study treatment arms were observed, and none of the associations described differed when excluding subjects with a detectable plasma HIV-1 RNA level at week 48 or correcting for age in a sensitivity analysis.

MRS results. Over 48 weeks, increases in NAA/Cr ratios were observed in all anatomical voxels (with mean percentage increases of 5%, 17%, and 38% in the right frontal white matter, the mid-frontal grey matter, and the right basal ganglia, respectively). Smaller changes in the Cho/Cr and MI/Cr ratios

were observed over 48 weeks (with mean percentage changes of 3%, 4%, and -12% for the Cho/Cr ratio and of 14%, 5%, and 15% for MI/Cr ratio with regard to the right frontal white matter, the mid-frontal grey matter, and the right basal ganglia, respectively).

Absolute changes in metabolite ratios between study treatment arms in a univariate model are shown in Table 3. A greater increase in the NAA/Cr ratio in right frontal white matter was observed in arm 1, compared with arm 2 (29% increase for arm 1 vs 18% increase for arm 2; $P = .041$) and compared with arm 3 (29% increase for arm 1 vs 9% increase for arm 3; $P = .054$). A box plot of absolute NAA/Cr ratio changes between study treatment arms is shown in Figure 3.

A trend toward a greater increase in the MI/Cr ratio over 48 weeks in arm 3 versus arm 1 was observed in the right frontal white matter (with a mean percentage change of 39% in arm 3 vs -24% in arm 1; $P = .097$). No other significant changes between individual metabolite ratios and study treatment arms were observed.

In a multivariate model (Table 4), absolute change in the NAA/Cr ratio over 48 weeks was statistically significantly greater in arm 1 versus arm 2 ($P = .03$). No other factors, including ethnicity, age, or detectable plasma HIV-1 RNA level, at week 48 were associated with these changes ($P > .15$ for all comparisons). Finally, no significant associations were observed between changes in cerebral metabolite ratios and neurocognitive testing results.

DISCUSSION

In this prospective, randomized study, we observed improvement in overall neurocognitive function and in cerebral metabolite ratios over the 48-week study period, with significant differences between study treatment groups. Several previous reports have described a reduction in NAA and in the NAA/Cr ratio, particularly in frontal cerebral areas, in subjects with HIV-1-associated dementia [19, 23–27], and associations between the reduction of NAA/Cr ratios and the degree of cognitive decline have been reported [28]. Improvements in MRS-measured NAA values have been described after the commencement of ART, and such improvements are associated with the degree of cognitive recovery [29, 30]. However, to our knowledge, differences in such improvements between different cART regimens have not been described before. We have observed significantly greater increases in subjects in study arm 1, compared to the other study treatment groups. A possible explanation for this finding is the greater effect on CNS HIV-1 viral replication associated with the cART regimen in study arm 1, thereby facilitating greater neuronal recovery. This treatment arm contained the nonnucleoside reverse-transcriptase inhibitor, efavirenz. In general, the nonnucleoside reverse-transcriptase inhibitors have been described to penetrate into the cerebrospinal fluid [14], and the reported CNS penetration

Table 4. Univariate and Multivariate Models Used to Assess Factors Associated with Changes to the Cerebral Metabolite Ratio over 48 Weeks

| Frontal white matter | Univariate model | | Multivariate model | |
|--|---------------------------|------|---------------------------|------|
| | Coefficient (95% CI) | P | Coefficient (95% CI) | P |
| NAA/Cr ratio change | | | | |
| Baseline CD4 ⁺ cell count, cells/ μ L | -0.002 (-0.005 to 0.002) | .36 | | |
| Ethnicity (white vs Asian) | 0.105 (-0.520 to 0.731) | .73 | | |
| Log ₁₀ HIV-1 RNA level at baseline | 0.033 (-0.428 to 0.494) | .88 | | |
| Age, years | -0.012 (-0.042 to 0.017) | .39 | | |
| Nadir CD4 ⁺ cell count, cells/ μ L | -0.003 (-0.006 to 0.001) | .15 | -0.002 (-0.006 to 0.001) | .15 |
| Detectable HIV-1 RNA level at week 48 ^a | 0.277 (-0.884 to 1.439) | .63 | | |
| Change in CD4 ⁺ cell count from baseline to week 48, cells/ μ L | 0.000 (-0.002 to 0.002) | .93 | | |
| Treatment arm | | | | |
| Arm 2 (vs arm 1) | -0.777 (-1.519 to -0.036) | .04 | -0.789 (-1.516 to -0.063) | .03 |
| Arm 3 (vs arm 1) | -0.686 (-1.385 to 0.014) | .05 | -0.610 (-1.303 to 0.084) | .08 |
| MI/Cr ratio change | | | | |
| Baseline CD4 ⁺ cell count, cells/ μ L | -0.006 (-0.014 to 0.002) | .125 | -0.003 (-0.012 to 0.005) | .443 |
| Ethnicity (white vs Asian) | -0.162 (-1.655 to 1.332) | .825 | | |
| Log ₁₀ HIV-1 RNA level at baseline | 0.612 (-0.576 to 1.799) | .299 | | |
| Age, years | 0.022 (-0.049 to 0.092) | .532 | | |
| Nadir CD4 ⁺ cell count, cells/ μ L | -0.002 (-0.010 to 0.007) | .675 | | |
| Detectable HIV-1 RNA level at week 48 ^a | 0.559 (-2.188 to 3.306) | .679 | | |
| Change in CD4 ⁺ cell count from baseline to week 48, cells/ μ L | 0.002 (-0.004 to 0.008) | .462 | | |
| Treatment arm | | | | |
| Arm 2 (vs arm 1) | 1.065 (-0.842 to 2.972) | .261 | 1.083 (-0.845 to 3.011) | .257 |
| Arm 3 (vs arm 1) | 1.513 (-0.297 to 3.322) | .097 | 1.651 (-0.214 to 3.516) | .080 |

NOTE. Study subjects were randomly allocated to commence combination antiretroviral therapy comprising 300 mg tenofovir and 200 mg emtricitabine once daily with either efavirenz 600 mg once daily (arm 1), 300 mg atazanavir and 100 mg ritonavir once daily (arm 2), or 250 or 300 mg zidovudine twice daily and 600 mg abacavir once daily (arm 3). CI, confidence interval; Cr, creatinine; MI, myo-inositol; NAA, *N*-acetylaspartate.

^a The assay detection limit was 50 copies/mL.

of efavirenz is greater than the drug concentration required to suppress HIV-1 viral replication [31]. This characteristic may have a greater effect on HIV-1 viral suppression in the cerebral compartment, thus explaining the greater increase in neuronal markers that we have observed.

Because NAA is a marker of neuronal integrity, a decreased NAA/Cr ratio is assumed to be the result of either neuronal loss or neuronal dysfunction. In this study, it is important to note that we used metabolite ratios to obviate differences in field strength and manufacturer operator-dependent differences between MR imaging scanners across all 4 study sites (which has hampered the execution of multicenter MRS studies until now).

MI is an intracellular osmolyte governing cell size regulation and is present in all brain cells, including microglia. Elevated levels of this metabolite are thought to reflect microglial activation in the context of HIV-1 disease [32]. Elevations in MI/Cr ratios [33, 34] have been identified for HIV-1-infected subjects experiencing a decrease in cognitive function. In a study by Chang et al [30], a decrease in the MI/Cr ratio was shown for HIV-1-infected subjects after they commenced ART. In our study, however, we observed a increase in the MI/Cr ratio; the MI/Cr ratio increased by 14%, 5%, and 15% in right frontal white matter, mid-frontal grey matter, and right basal ganglia,

respectively. Our study differs from previous MRS studies of HIV-1-infected individuals in that the subjects that we recruited had no prior symptoms of neurocognitive function disturbance at study enrollment, whereas other studies have focused on investigating subjects with HIV-1-associated dementia. These differences in the natural history of study populations could explain the differences in MI/Cr ratio that we have observed, compared with the published literature. Commencement of cART for neurologically asymptomatic individuals with little evidence of cerebral microglial activation may be associated with a drug-induced inflammatory response, rather than the improvements previously described.

Previous MRS studies also have suggested that some anti-retroviral agents with good CNS penetration are associated with specific CNS drug-induced toxicity. Cerebral metabolites in HIV-1-infected subjects receiving cART, containing either the nucleoside-analogue didanosine or stavudine, have been compared with those in subjects receiving zidovudine and lamivudine [35]. Because didanosine and stavudine have been associated with greater peripheral mitochondrial toxicities [36], Schweinsburg et al [35] wanted to determine whether there was evidence of CNS mitochondrial toxicity. Results from their study reported concentrations of NAA in the mid-frontal grey matter that were 11% lower, compared with healthy control

data, for subjects receiving stavudine or didanosine, whereas NAA concentrations in the zidovudine and lamivudine group were intermediate, which supports this toxicity theory. Interestingly, in our study, temporal differences in the MI/Cr ratio in right frontal white matter were observed with treatment; an increase of 39% was observed in study arm 3, and a decrease of 24% was observed in arm 1 ($P = .097$ and $P = .080$ in univariate and multivariate models, respectively). Although study arm 3 did not contain either stavudine or didanosine, it did comprise a 4 nucleoside-analogue cART regimen (tenofovir, emtricitabine, zidovudine, and abacavir). If such mitochondrial toxicities are a class effect of the nucleoside analogues, the increase in the MI/Cr ratio that we have observed may be secondary to these effects.

Despite the propensity to cause mitochondrial toxicities, the nucleoside analogues have in general been described to have beneficial CNS penetration [14] and have been associated with improvements in cerebral function. Zidovudine was the first antiretroviral agent available, and in both randomized [37] and observational [38, 39] clinical studies, improvements in neurocognitive function were observed for HIV-1-infected individuals treated with this agent. Rather disappointing results were described with the advent of abacavir with regard to improvements in neurocognitive function, but the lack of effect observed in a randomized study may have been related to HIV-1 viral resistance to this agent from HIV-1-infected subjects who have had a lot of drug therapy [40]. We have observed greater improvement in overall neurocognitive performance of subjects randomized to study arm 3. This may be related to several factors. First, a quadruple nucleoside-analogue regimen may confer optimal CNS antiretroviral drug penetration and the suppression of HIV-1 viremia in the CNS. Second, clinical toxicities secondary to other treatment arms in the study may have an effect on neurocognitive testing. For instance, efavirenz, which was a component of arm 1, is associated with several neuropsychiatric side effects [41, 42], such as abnormal dreams, lethargy, and depression. These effects may have blunted the improvement in serial neurocognitive testing in arm 1 of this study.

Other groups have reported discrepancies between antiretroviral drug penetration into the CNS and clinical neurocognitive responses. In a recently reported prospective cohort, HIV-1-infected subjects underwent serial neurocognitive function testing and had cerebrospinal fluid samples quantified for HIV-1 RNA [15]. This series included subjects on differing cART regimens. As expected, subjects receiving cART with greater CNS penetration scores [14] had a lower HIV-1 RNA level in their cerebrospinal fluid on lumbar puncture examination. However, poorer neurocognitive performance was also observed in the group with greater cART CNS penetration scores. These data suggest that some antiviral agents with good CNS penetration may have added CNS toxicities and thereby

may impair neurocognitive function. Unfortunately, the study was not powered to assess the effects of specific antiretroviral agents on neurocognitive testing results.

How do our results relate to clinical practice? We studied a small number of patients, and hence the interpretation of the findings should be made with some degree of caution. However, we have observed significant differences in cerebral effects between different antiretroviral regimens. A quadruple nucleoside-analogue regimen displayed greater benefits after 48 weeks of therapy, as measured by neurocognitive testing results. These data could be used to power future studies assessing changes in neurocognitive function as the result of using different regimens. Novel HIV-1 treatment studies are underway assessing nucleoside-analogue-sparing cART, to avoid the mitochondrial toxicities associated with this class of agents. Such studies are justified and timely, but investigators should also consider cerebral function testing as part of these programs, to ensure that neurocognitive impairment does not develop when utilizing nucleoside-analogue-sparing treatment options. Finally, we have observed the greatest improvement in neuronal cerebral metabolite recovery (NAA/Cr ratios) within the efavirenz arm (arm 1), and we have observed increased MI/Cr ratios (probably representing cerebral microglial activation) with the use of a quadruple nucleoside-analogue regimen (arm 3). These data add to the growing body of evidence suggesting that the CNS penetration of ART may have both therapeutic benefits and potential toxicities, and may assist in the design of future noninvasive imaging studies assessing the effects of different antiretroviral treatment options on the CNS.

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