Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort

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ABSTRACT

Objective: Prior studies have shown improved neurocognition with initiation of antiretroviral treatment (ART) in HIV. We hypothesized that stopping ART would be associated with poorer neurocognitive function.

Methods: Neurocognitive function was assessed as part of ACTG 5170, a multicenter, prospective observational study of HIV-infected subjects who elected to discontinue ART. Eligible subjects had CD4 count >350 cells/mm^3, had HIV RNA viral load <55,000 cp/mL, and were on ART (≥2 drugs) for ≥6 months. Subjects stopped ART at study entry and were followed for 96 weeks with a neurocognitive examination.

Results: A total of 167 subjects enrolled with a median nadir CD4 of 436 cells/mm^3 and 4.5 median years on ART. Significant improvements in mean neuropsychological scores of 0.22, 0.39, 0.53, and 0.74 were found at weeks 24, 48, 72, and 96 (all $p < 0.001$). In the 46 subjects who restarted ART prior to week 96, no significant changes in neurocognitive function were observed.

Conclusion: Subjects with preserved immune function found that neurocognition improved significantly following antiretroviral treatment (ART) discontinuation. The balance between the neurocognitive cost of untreated HIV viremia and the possible toxicities of ART require consideration.

Classification of evidence: This study provides Class III evidence that discontinuing ART is associated with an improvement in 2 neuropsychological tests (Trail-Making Test A & B and the Wechsler Adult Intelligence Scale–Revised Digit Symbol subtest) for up to 96 weeks. Resuming ART was not associated with a decline in these scores for up to 45 weeks. ***Neurology*® 2010;74: 1260–1266**

GLOSSARY

ACTG = AIDS Clinical Trials Group; **ART** = antiretroviral treatment; **EFV** = efavirenz; **HAART** = highly active antiretroviral therapy; **HAD** = HIV-associated dementia; **NP** = neuropsychological summary score; **TI** = treatment interruption; **VL** = viral load.

HIV enters the CNS within days of infection, and can result in nervous system disease including HIV-associated dementia (HAD) and the less severe dysfunction mild neurocognitive disorder. Antiretroviral therapy (ART) has led to prolonged survival in patients with HIV,[1-3] and a dramatic decrease in the incidence of HAD.[4]

In the past, many HIV-positive patients with preserved immune function were prescribed ART, consistent with treatment guidelines at the time.[5-7] After the recognition that ART led to significant toxicities and did not eradicate latent HIV infection, updated guidelines recommended delayed treatment initiation.[8,9] There are conflicting results as to whether these patients can safely discontinue ART.[10-12]

Studies have shown that cognitive deficits are associated with ongoing viral replication in the CNS and that neurocognitive functioning improves in patients who initiate ART.[13-18] This recovery of function suggests that the underlying mechanism includes an alteration of neuronal

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e-Pub ahead of print on March 17, 2010, at www.neurology.org.

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Study funding: Supported in part by the NIH/NIAID (AI-68636 to AIDS Clinical Trials Group and AI068634 to the Statistical and Data Management Center) and by the General Clinical Research Center Units funded by the National Center for Research Resources.

Disclosure: Author disclosures are provided at the end of the article.

Presented in part at the 14th Conference on Retroviruses and Opportunistic Infections, Oral Abstract 113, Los Angeles, CA, February 25–28, 2007.

function prior to actual cell death. Since CNS viral replication is known to occur from the initial days of infection, it is likely that neuronal function is being impaired in the long asymptomatic period of HIV infection, resulting in subclinical cognitive impairment.

Since neurocognitive functioning improves with ART, we hypothesized that neurocognition would get worse in patients who discontinue treatment. We sought to evaluate neurocognitive functioning after treatment interruption (TI) in a population who had early treatment initiation. We also sought to evaluate potential neurocognitive improvement on ART in those patients who resumed ART, following a TI.

METHODS AIDS Clinical Trials Group (ACTG) 5170 was a multicenter, observational, prospective, 2-step study in asymptomatic HIV-infected subjects who wished to discontinue ART in the United States.[11] In step 1, eligible subjects elected to stop antiretroviral therapy; in step 2, patients from step 1 reinitiated antiretroviral therapy. This study design provided a Class III level of evidence.

Standard protocol approvals, registrations, and patient consents. This study, ACTG A5170, is registered with ClinicalTrials.gov under the identifier NCT00050284. The study was approved by the institutional review boards at each site. All subjects gave written consent prior to enrollment.

Subjects. Subjects were included for step 1 if they had confirmed HIV-1 infection, age >12 years, CD4 count >350 cells/mm^3 immediately prior to first ART, CD4 count >350 cells/mm^3 and plasma HIV-1 RNA viral load (VL) <55,000 copies/mL at screening, currently receiving ART with ≥2 drugs for ≥6 months, and a Karnofsky score ≥70. Subjects were excluded if they had a prior Centers for Disease Control and Prevention category B or C event, active drug or alcohol use, or serious medical condition that would negatively impact participation in the protocol. Complete inclusion and exclusion criteria have been reported in the primary study report.[11]

Study design. Subjects who underwent TI upon entry to step 1 were followed for up to 96 weeks. Neurocognitive assessments were conducted every 24 weeks. Subjects were eligible for step 2 if subject or provider desired to reinitiate ART, and were followed for at least 24 weeks, or 96 weeks from step 1 entry (whichever was longer). The protocol strongly recommended that subjects resume ART if the CD4 cell count fell to ≤250 cells/mm^3.

The neurocognitive examination consisted of Trail-Making Test A & B[19] and the Wechsler Adult Intelligence Scale–Revised Digit Symbol subtest.[20] These tests are sensitive in detecting both HIV-related neurocognitive changes[21,22] and antiretroviral effects upon CNS functions.[13] The raw test score of each measurement was standardized using demographic-adjusted normative means, which adjust for gender, age, education, and ethnicity (Caucasian and African American).[23] A standardized z score was calculated by subtracting the appropriate normative mean from the raw score then dividing by the appropriate normative SD for each test. A neuropsychological summary score (NP) was created for the analyses, by averaging the z scores across the 3 tests. Neurocognitive impairment was defined as 1 SD below the mean on 2 of the 3 tests or 2 SDs below the mean on 1 of 3 tests. Sustained impairment required subjects to meet the impairment criteria for 2 consecutive visits.

Table 1 Demographics at baseline

Characteristics	Values
Sex, n (%)	
Male	138 (83)
Female	29 (17)
Race/ethnicity, n (%)	
White non-Hispanic	108 (65)
Black non-Hispanic	31 (19)
Hispanic	24 (14)
Asian, Pacific Islander	4 (2)
Age, y	
Median (Q1–Q3)	42 (36–49)
IV drug use, n (%)	
Never	153 (92)
Previously	14 (8)
Currently	0 (0)

The changes in NP score from the baseline to weeks 24, 48, 72, and 96 in step 1 and step 2 were analyzed using t test for paired data. The linear and quadratic trends of the NP scores in both steps were examined using generalized estimating equation embedded in SAS PROC GENMOD procedure (Cary, NC). To take into account the practice effect and possible informative dropout, study week and the dropout time were included in the regression model as covariates.[24] In addition, 2 sensitivity analyses were performed using the t test for paired data. In one analysis, we compared the change in NP score after week 48 when the practice effect was considered to be leveled out. In the other analysis, we repeated the above analyses by only including subjects who completed the 96 weeks of follow-up without resumption of ART. Subgroup analyses assessing the effect of efavirenz (EFV) (Sustiva, Princeton, NJ, Bristol-Myers Squibb), ABC (Ziagen, GSK, RTP, NC), ZDV (Retrovir, GSK), D4T (Zerit, BMS, New York, NY), and baseline HIV RNA category (>50 cps/mL vs ≤50 cps/mL) in step 1 were performed. All tests were 2-sided. The p values were not adjusted for multiple tests and $p < 0.05$ was considered significant.

RESULTS **Study population.** Demographics characteristics of the 167 subjects enrolled are presented in tables 1 and 2. The median duration of ART prior to TI was 4.5 years, and the median duration of follow-up was 96 weeks after TI and 45 weeks after reinitiation of ART. A total of 144 subjects completed the study, including 102 who remained off ART for 96 weeks. A total of 137 (82%) subjects had VL ≤400 copies/mL at entry. The immunologic and virologic outcomes are detailed elsewhere.[11]

Improved neurocognition when stopping antiretrovirals. Mean NP scores increased when subjects stopped ART (figure 1). Significant mean NP score

Table 2 Disease and treatment characteristics at baseline

Characteristics	Values
Preentry CD4 cell count, cells/mm^3	
Median (Q1–Q3)	833 (668–989)
≤500	12 (7%)
>500	155 (93%)
Preentry HIV-1 viral load level, copies/mL	
Median (Q1–Q3)	<50 (<50–146)
≤50	106 (64%)
≤400	137 (82%)
51–200	24 (14%)
201–400	7 (4%)
401–5,000	23 (14%)
5,001–55,000	5 (3%)
>55,000	2 (1%)
Nadir CD4, cells/mm^3	
Median (Q1–Q3)	436 (375–510)
Less than 350	23 (14%)
351–400	35 (21%)
401–450	33 (19%)
451–500	30 (18%)
Over 500	45 (27%)
Not available	1 (1%)
Pre-ART viral load level, copies/mL	
Median (Q1–Q3)	22,611 (6,299–62,131)
Less than 400	2 (1%)
401–5,000	26 (16%)
5,001–20,000	30 (18%)
20,001–55,000	30 (18%)
Over 55,000	32 (19%)
Not available	47 (28%)
Time on ART, y, median (range)	4.5 (0.5–15)
Total no. ARTs, median (range)	3 (2–9)
Nucleoside-based regimen	39 (23%)
Non-nucleoside-based regimen	60 (36%)
Protease inhibitor–based regimen	62 (37%)
Non-nucleoside/protease combination	6 (4%)

Abbreviation: ART = antiretroviral therapy.

improvements of 0.22, 0.39, 0.53, and 0.74 were found at weeks 24, 48, 72, and 96 (all $p < 0.001$) (see table 3). The effect sizes (d) associated with the observed changes ranged from medium (0.37 at 24 weeks) to large (1.08 at 96 weeks). Sensitivity analysis including only the 95 subjects who stayed in step 1 for 96 weeks gave similar results.

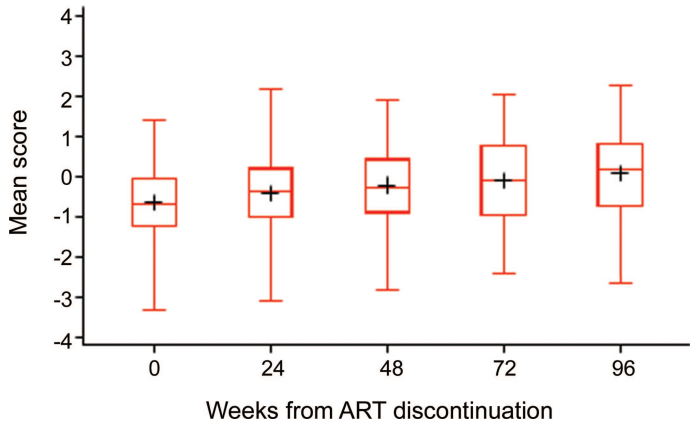
Subsequent analyses were undertaken to better understand the unexpected results. Practice or learning effects are known to occur with test-retest in neurocognitive studies, tend to diminish with repeated testing, and level out at the third repeated assessment.[24] Therefore, analyses were undertaken that examined changes at the third assessment on (48 weeks and after). From week 48 to 72, the 107 subjects had NP score improvements of 0.11 ($p < 0.05$); from week 48 to 96, the 95 subjects had NP score improvements of 0.33 ($p < 0.0001$). Practice or learning effect does not seem to account for the improving performance off antiretroviral therapy.

No neurocognitive improvements with ART resumption. Forty-two subjects restarted ART and enrolled in step 2. There were no significant improvements in NP scores (figure 2). From ART resumption to week 24 on ART, NP scores improved 0.08 in the 37 subjects with data available; at week 48 of ART resumption, the mean improvement in NP scores was 0.09 in the 25 subjects still on study; at week 72 of ART resumption, NP scores decreased by 0.06 in the 10 subjects still on study; and at week 96 of ART resumption, the mean improvement in NP scores was 0.48 in the four subjects still on study at that time.

Neurocognitive impairment. For subjects stopping antiretroviral therapy (step 1), 68 out of 166 with baseline results were impaired (41%). There were 41 of 167 (25%) subjects with sustained impairment at some point during step 1. There were 40 out of 166 with impairment at baseline but who later became unimpaired on step 1 (24%). For subjects who resumed ART on step 2, 9 out of 39 subjects were impaired at baseline (23%). There were 9 of 41 with sustained impairment at some point during step 2 (22%). There were 3 out of 39 with impairment at step 2 baseline but who later became unimpaired (8%).

Informative dropout. We were concerned that potential dropout of impaired subjects during step 1 created the appearance of improved neurocognitive scores over the course of step 1. Therefore, we compared the NP scores in step 1 between subjects who stayed on step 1 for 96 weeks to those who later went to step 2. Between-group comparisons at week 24, 48, and 72 found no significant differences between these subjects (all $p > 0.17$, data not shown, comparison at week 96 was not done because of insufficient data). This suggests that the increases in performance were not due to informative dropout. Among the subjects reinitiating ART, we also compared the baseline NP scores at step 1 to the baseline NP scores at step 2. Of the 39 subjects who had NP scores at entry to both step 1 and step 2, there was a mean

Figure 1 Plot of mean neuropsychological summary score following treatment interruption



increase of 0.34 ($p < 0.001$) at step 2 baseline compared to step 1 baseline.

In the regression analysis that simultaneously modeled the change in NP score and time of dropout using generalized estimating equation, the time of dropout was not significant in step 1, and was marginally significant in step 2. However, the dropout effect was estimated to be −0.19 for every 24 weeks, suggesting that subjects who dropped out of step 2 early had a greater 0.19 increase in NP score from baseline compared with those who dropped out 24 weeks later.

Neurocognition and virologic/immune system outcomes. To assess potential differences related to HIV VL, we stratified the sample into those with baseline HIV RNA below (n = 89) and at or above 50 cps/mL (n = 50). No differences in neurocognitive functioning were found between the HIV RNA VL groups at 24, 48, 72, or 96 weeks. Sensitivity analyses restricting the sample to only those who completed 96 weeks off ART found similar results with no differences over time between the 2 groups. To assess the effect of immune system functioning, we stratified the group by using the median nadir CD4+ cell count (436) into those below (n = 70) and above (n = 69). Those below had mean lower NP scores (0.29) at week 72 than those above the median (0.69). In the sensitivity analyses restricting the sample to those who remained off ART for 96 weeks, we found a trend only ($p = 0.08$).

Table 3 Change in NP scores from baseline after TI (step 1) and ART resumption (step 2)

Step	Week	Mean	No.	SD	t Test	p
1	24	0.22	139	0.59	4.41	<0.0001
1	48	0.39	131	0.64	7.04	<0.0001
1	72	0.53	110	0.76	7.25	<0.0001
1	96	0.74	95	0.68	10.55	<0.0001
2	24	0.08	37	0.51	0.95	NS
2	48	0.09	25	0.46	0.98	NS
2	72	−0.06	10	0.50	−0.36	NS
2	96	0.48	4	0.84	1.13	NS

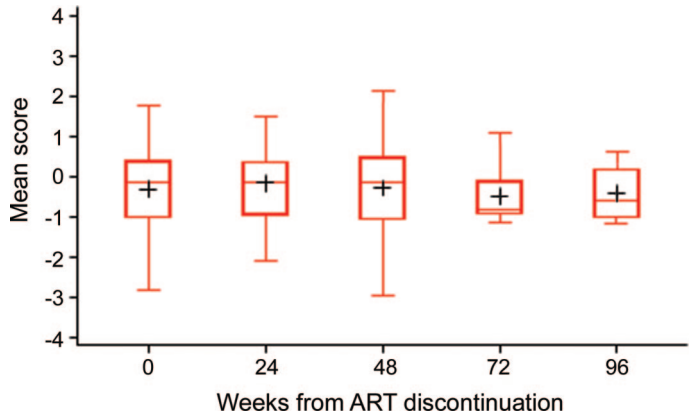
Abbreviations: ART = antiretroviral therapy; NP score = neuropsychological summary score; TI = treatment interruption.

Neurocognition and EFV, ABC, ZDV, and D4T. Previous studies have found that neurocognitive side effects were associated with the use of EFV.[25] We stratified the sample by EFV use to see if there were differences in neurocognitive improvement between the groups. Significant increases were noted in both subgroup analyses of subjects discontinuing EFV-containing regimens (baseline n = 40; NP −0.77) and non-EFV-containing regimens (baseline n = 126; NP −0.62). For the non-EFV group subjects, the mean NP score improved 0.14, 0.34, 0.50, and 0.67 over weeks 24, 48, 72, and 96 ($p < 0.05$); and for the EFV group subjects, the mean NP score improved 0.38, 0.59, 0.77, and 0.96 over weeks 24, 48, 72, and 96 ($p < 0.001$). The difference in mean NP scores between the 2 groups was significant ($p = 0.024$, Wei-Johnson test). Although there was some evidence of greater neurocognitive improvement in subjects discontinuing EFV-based regimens, both EFV and non-EFV groups showed significant increases in mean neurocognitive scores at each week compared to baseline. Similar analyses for subgroups who reported stopping ZDV (n = 74) and those not on ZDV (n = 65); stopping D4T (n = 49) and those not (n = 90); and stopping ABC (n = 36) and those not (n = 103) did not find differences in neurocognitive functioning over weeks 24, 48, 72, and 96 between these subgroups.

DISCUSSION HIV enters the CNS within days of initial infection, and is resident within the CNS throughout the prolonged asymptomatic period of HIV infection. CNS damage is thought to be associated with HIV viremia and inflammatory responses.[26,27] It is known that highly active antiretroviral therapy (HAART) improves neurocognitive functioning.[13,14,28-30] We expected that neurocognitive functioning would become worse when patients stopped taking antiretroviral therapy. Contrary to our hypothesis, neurocognitive functioning significantly improved after patients stopped treatment. This improvement continued over the course of the 96-week follow-up of the study among the patients remaining off ART. Based on the effect sizes, the magnitude of the observed improvement is likely to be clinically meaningful.

Why might this have occurred in this healthy population stopping antiretroviral therapy? There are several potential explanations. It is possible that these

Figure 2 Plot of mean neuropsychological summary score following treatment resumption



patients had subtle CNS drug-related toxicity that improved when treatment was stopped. It is known that repeated neuropsychological assessment can result in practice or learning effects, where improvement in functioning is due to practice or learning. However, studies have shown that practice or learning effects level off after 3 assessments.[24] We assessed whether the observed improvement could be attributed to practice or learning effects. We observed continued improvement from 48 weeks out (third testing) on the study, indicating that the improvements are not likely to be solely attributed to practice or learning effects. It is possible that the follow-up period on study was not long enough to document changes. However, this seems unlikely since the median duration of follow-up was 96 weeks, a duration 4 times longer than those associated with improvement when starting antiretrovirals. Although unlikely, it is possible that prior antiretroviral regimens did not have benefit on the CNS. Antiretrovirals thought to enter the CNS were widely represented in the baseline ART regimens.[28] It is also possible that there was a patient selection bias, so that subjects who elected to stop antiretrovirals were somehow more likely to have neurocognitive improvement. It may also be that the brief neuropsychological battery was not sensitive enough to detect declines. However, significant improvements were detected, indicating that the battery was sensitive enough in this study. Although brief, these tests have been found to be sensitive[21,22] and specific[31] in detecting HIV-related neurocognitive changes.

We also noted a lack of substantial neurocognitive improvement with resumption of ART. Neurocognitive improvement with initiation of HAART has been documented in many studies of patients who were naïve or failing current therapy. However, these studies were of patients who initiated treatment later in the disease course. Patients later in the disease may have greater inflammation within the CNS, or greater VL, and therapeutic intervention may have a greater benefit. As the virus is present in the CNS early in the disease process, it is likely that a threshold of neuronal damage must be reached for subclinical and clinical findings to be demonstrable. Once the viral replication has exceeded this threshold, clinical findings are readily apparent. Early in disease, cognitive reserves may allow for continued near-normal functioning. Treatment initiation at this early stage of disease may not result in the acute cognition gains that have been found with treatment at later disease stages.[32]

There was fluctuation in the level of impairment observed during this study. At baseline, 41% of the subjects were impaired, the majority of whom (59%) later became unimpaired. Twenty-five percent of subjects had sustained impairment off treatment at some point, and a similar number (22%) of those who resumed ART had sustained impairment at some point. These findings are similar to a much larger study, the ACTG Linked Longitudinal Randomized Trial, which utilized the same brief neuropsychological battery and assessed 1,160 subjects.[33] It is well-known that there are cognitive side effects of EFV,[25] which could have played a role in this study. Due to these cognitive side effects, those subjects on EFV regimens might be expected to have greater neurocognitive improvement than those with non-EFV regimens. We investigated the potential cognitive side effect implications for this study by stratifying subjects into those who had been on an EFV-containing regimen vs those who had not. When comparing between the EFV and non-EFV groups, we found that the EFV group had greater improvement than the non-EFV group. We also found that both groups had significant cognitive improvement at all time points after discontinuing antiretroviral treatment. When other agents with possible impact on the CNS such as ZDV, ABC, and D4T were analyzed, there were no differences between groups who stopped regimens with these agents over time. We also investigated the relationship of VL and immune functioning to neurocognition in these patients as they stopped treatment. We found no relationship between neurocognitive functioning and baseline VL. There was a relationship with nadir CD4, but only at one time point.

There are several limitations to the present study that could be addressed in future studies investigating neurocognition and treatment interruption. We were unable to include an HIV+ untreated control group with similar disease severity in the current study, which may have allowed a more precise determination of the practice/learning effects. We did not assess for depression, anxiety, or substance abuse, al-

though these were exclusionary criteria at diagnostic levels. We found improved neurocognitive functioning in this unique cohort of subjects who initiated antiretroviral treatment prior to immune impairment, and then later discontinued therapy. We were not able to attribute these results to practice and learning effects or the selective reinitiation of ART. It is possible that subtle antiretroviral toxicity may underlie the improvements measured after ART was stopped. Contrary to prior studies, significant neurocognitive improvement was not observed with resumption of ART in this unique cohort. This lack of observed improvement may be related to the earlier initiation of ART, where benefits occurred in other studies at a later disease stage, but may also be due to limited power. With the recent suggestion that earlier initiation of ART may improve clinical outcomes, the effect of ART as compared to that of unchecked HIV replication on neurocognitive function will require careful prospective study.[34]

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Zhaohui Su and Dr. Scott Evans.

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ACKNOWLEDGMENT

The A5170 study team thanks the patients who participated in 5170.

DISCLOSURE

Dr. Robertson has received funding for travel and speaker honoraria from GlaxoSmithKline, Boehringer Ingelheim, and Abbott, and research support from the NIH (NIAID 1U01AI068636 [NIMH PI], NIMH R01 MH067751 [Co-I], NINDS 5 U01 NS032228 [Co-I], and NIMH R01 MH081772 [Co-I]). Dr. Su reports no disclosures. Dr. Margolis serves on the editorial boards of the *Journal of Virology* and *AIDS*; has received speaker honoraria from Abbott, Gilead Sciences, Inc., Monogram Biosciences, Roche, GlaxoSmithKline, Boehringer Ingelheim, Merck Serono, Biotron Ltd., Trimeris, Inc., International AIDS Society USA, IAS-USA, and University of North Carolina Center for AIDS Research, UNC CFAR; serves on speakers' bureaus for Virco Pharmaceuticals L.L.C., Bristol-Myers Squibb, and Merck Serono; has received research support from Merck Serono, Bristol-Myers Squibb, the NIH (5 U01-AI067854-04 [Co-I], 5 U01 AI069423-03 [Co-I], NIAID 1 R01 MH085597-01A1 [PI], NIAID 1U19AI082608-01 [PI], NIAID 5 T32 AI007151-31 [PI], and NIAID 1 R34 AI084553-01 [PI]), and amfAR; and holds stock in Gilead Sciences, Inc. A. Krambrink reports no disclosures. Dr. Havlir serves on the editorial board of *AIDS* and *EJIAS*; and receives research support from the NIH (NIAID U01 AI069502 [PI], NICHD P01 HD059454 [PI], NIAID K24 AI51982 [PI], NIAID T32 AI060530 [PI], NIAID P30 AI27763 [Co-I], NIAID U01 AI062677 [PI], NIAID R01 AI051219 [Co-I]); CDC/Elizabeth Glaser Pediatric AIDS Foundation U62 CCU123541 [PI]; Adamas Pharmaceuticals ADS-TCAD-PO206 [PI]; and Abbott (drug donation for NIH funded study; Dr. Evans serves on scientific advisory boards for Genentech, Inc. and the HIV Neurobehavioral Research Center; serves as Guest Editor for the *Drug Information Journal*, Associate Editor for *Case Studies in Business, Industry, and Government,* and Academic Editor of *PLoS Clinical Trials*; has received honoraria from the NIH, the American Statistical Association, and the FDA for educational activities; serves as a consultant for CIS Biotech, Genentech, Inc., and Pfizer Inc.; serves on an advisory board for the FDA; and receives research support from the NIH (Statistical Center Support). Dr. Skiest has served on speaker's bureaus or received honoraria from for Gilead Sciences, Inc., Tibotec Therapeutics, GlaxoSmithKline, Bristol-Myers Squibb, and Merck; and receives research support from Gilead Sciences, Inc., Tibotec Therapeutics, Merck, Serono, Roche, GlaxoSmithKline, Pfizer, and the Schering-Plough Research Institute.

Received June 26, 2009. Accepted in final form February 2, 2010.

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