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Long-Term Impact of Efavirenz on Neuropsychological Performance and Symptoms in HIV-Infected Individuals (ACTG 5097s)

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Abstract

Background—Efavirenz (EFV) is an antiretroviral (ARV) drug associated with neuropsychological effects. Limited data describing the long-term impact of EFV-based regimens on neuropsychological performance over more than 3 years are available.

Methods—We enrolled a subset of participants from a large initially EFV placebo-controlled trial of therapies for HIV subjects naïve to ARV treatment (A5095). Clinical follow-up continued for 184 weeks of study. Subjects were assessed with brief neuropsychological testing, a symptom questionnaire of EFV-associated symptoms, the Pittsburgh Sleep Index, Center for Epidemiologic Studies-Depression Scale, and an anxiety rating interview.

Results—Over 184 weeks on EFV, the median NPZ3 score in 86 evaluable patients improved from baseline by +0.5 ($p < .01$); all components improved, although higher EFV levels were associated with slightly lower responses. Overall symptom scores did not change, while EFV-associated CNS symptoms increased ($p = .01$). Median change of bad dream sleep scores and anxiety increased from the baseline while global depression score decreased.

Conclusions—In participants who continued EFV-based regimens, neuropsychological performance improvement from baseline was maintained over 3 years. EFV-based treatment was generally well tolerated, but small increases from baseline in EFV-associated symptoms, bad dreams, and anxiety were detected.

Keywords

anxiety; depression; efavirenz; HIV therapy; neuropsychologic effects; sleep

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for treatment of HIV disease. It is potent, generally well tolerated, and can be administered once a day, making it an attractive component of antiretroviral therapy for the initial treatment of people with HIV infection. Antiretroviral therapy using EFV is effective¹ and is listed among preferred HIV treatment options.² The most commonly reported adverse experience with EFV

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is central nervous system (CNS) toxicity, with more than 50% of patients reporting symptoms in open-label studies.^{1,3} An earlier report of the current study (AIDS Clinical Trials Group [ACTG] A5097s) prospectively characterized aspects of the 24-week neurological toxicity in the setting of a comparative, placebo-controlled study of three protease inhibitor (PI)-sparing antiretroviral regimens for the initial treatment of HIV infection.⁴ The study continued for a total of 184 weeks providing an opportunity to continue evaluation of the neurological implications of long-term therapy with EFV in a population with established baseline neuropsychologic function evaluation.

Methods

A5097s (NCT00013529) was a substudy of A5095, a randomized, double-blind trial of three antiretroviral regimens: zidovudine and lamivudine in combination with blinded (1) EFV; (2) abacavir and EFV; or (3) abacavir.⁵ The design and description of the 6-month blinded study have been reported.^{4,6} Unblinding of the triple nucleoside arm was performed in February 2003, after which patients continued on the same therapy in EFV-containing arms, whereas those in the triple nucleoside arm added a drug to their therapy or continued in study follow-up on a treatment of their choice. In late 2004, subjects still in follow-up on the A5095 parent trial consented to an additional 24 weeks of study at which time those subjects on the 5095 parent study who were previously enrolled in A5097s regardless of treatment status were approached to consent to an additional long-term neurological exam. Both studies then continued until the final evaluation in early 2005. Primary analysis for this report consists of the patients on continuous long-term EFV therapy at the conclusion of the study or at Week 184. Secondary analysis evaluates patients in whom no EFV was used during the entire study, those who added EFV at some point in the study, and those who had variable therapies in the course of the study.

The instruments used to measure neuropsychological performance were the Trail Making Tests (series A and B) and the Digit Symbol test (Wechsler Adult Intelligence Scale-Revised⁷). A summary neuropsychological composite score constructed from these three tests (NPZ3) is defined as the sum of three standardized (for age) test scores and is reported such that positive scores indicate above-norm function and negative scores indicate below-norm function. The entire score was coded as missing if any component of the NPZ3 was not available. The Neurologic AIDS Research Consortium (NARC) provided administrator training at each site. These tests assessed functioning in the areas of motor persistence, sustained attention, response speed, visuomotor coordination, and conceptual shifting/tracking. The neuropsychometric measures were collected at baseline and Week 184 or the final study visit for this report and Weeks 1, 4, 12, and 24 as part of the prior report to assess symptoms that might be associated with EFV using a specially designed questionnaire,⁴ the Pittsburgh Sleep Quality Index (PSQI),⁸ the State-Trait Anxiety Inventory for Adults,⁹ and the Center for Epidemiologic Studies-Depression (CES-D) scale.¹⁰

Whole blood for the determination of EFV trough concentrations in plasma was collected and analyzed,¹¹ and the data were used to explore relationships between drug exposure and other parameters collected in the study.

The primary analysis was conducted on the group of participants who were initially randomized to EFV and had long-term continuous therapy throughout the study. Changes from baseline were calculated by subtracting the value at baseline from the Week 184 or study discontinuation value. Baseline is defined as study entry. A positive difference thus indicated an increase from baseline while a negative difference denoted a decrease. Within-arm changes were assessed using Wilcoxon signed rank tests, and between-group comparisons were evaluated with Wilcoxon rank sum tests. Several hypothesis tests are conducted, each at a 0.05 significance

level, without adjustment for multiple comparisons. Thus, results should be interpreted cautiously. As this cohort represents a select group, we assessed the generalizability of the analysis of the long-term EFV cohort by comparing the baseline measures of this cohort to the cohort of participants that were randomized to EFV but did not have long-term follow-up data on EFV. Between-arm comparisons are considered secondary.

Results

Of the 303 patients randomized at baseline and included in the A5097s study, 200 were randomized to an EFV regimen, 170 of whom remained on A5095 (parent study) follow-up over the long-term. Of these, 117 consented to the long-term neuropsychological performance evaluation, including 86 subjects who remained on EFV throughout the study; these are the groups selected for the primary analysis (Figure 1). Of the remaining 91 participants who consented to the long-term neuropsychological evaluation, 37 were treated with several regimens through the study course, 21 were on EFV at study conclusion having switched to it during the course of the study, and 33 remained on non-EFV-containing regimens throughout the study. The groups are similar in baseline characteristics (Table 1) and are also similar to the demographics of the parent A5095 study.

We focus our analyses on summarizing results for the cohort that was randomized to EFV and remained on EFV long term unless otherwise stated. Mean neuropsychological performance as measured by the NPZ3 score was very close to normal at baseline but 25% of participants had $NPZ3 < 0.5$ and 16% had $NPZ3 < 1$, demonstrating some neuropsychological impairment at baseline. Improvement was seen at Week 184 in all groups compared to baseline performance (EFV-only group, $p < .01$) (Table 2). Each of the three component tests showed statistically significant improvement during the interval of the study. The prompt and sustained improvement of ~ 0.5 *SD* in the composite neuropsychological performance is displayed in Figure 2. Similar improvement was seen over the course of the study in those with no EFV therapy during the study. EFV trough drug levels and NPZ3 scores at the final visit were negatively correlated, suggesting a small but statistically significant negative impact of increasing levels of EFV on NPZ3 ($r = -0.29$, $p < .01$). Similar correlations were observed for each of the three component tests of the NPZ3 ($r = -0.27$, $p = .01$, for Digit Symbol; $r = -0.20$, $p = .06$, for Trail Making A; $r = -0.19$, $p = .08$, for Trail Making B). However, the change in neurological performance from baseline was not significantly correlated to serum EFV levels at the final visit ($r = -0.002$, $p = .99$).

Symptoms that have previously been associated with EFV such as dizziness, sense of being off balance, and changed sleep and dreaming were evaluated at Week 184 or the final visit. Figure 3 displays the pattern of symptom change previously associated with EFV use from the EFV symptoms questionnaire.⁴ The significant increase in these EFV-associated symptoms seen in the first week of therapy decreased toward baseline levels during the study but remained higher than baseline levels at the final visit (median change of 1 from a total possible score of 70; $p = .01$) (Table 3, Figure 3). EFV-associated symptoms were not significantly correlated with EFV serum trough levels measured at the final visit ($r = -0.10$, $p = .34$).

Sleep complaints had been prominently noted in random observations of EFV neuropsychological side effects and were systematically studied with the Pittsburgh Sleep Quality Index. This provides a global sleep quality score with results > 5 (range 0–21) suggesting poor quality sleep. Changes in global sleep scores over the study were not significant ($p = .14$), although the “bad dreams” question detected a mean increase of 0.29 increase (scale of 0 to 3) in this complaint ($p < .01$) after 184 weeks on therapy.

Symptoms of depressed mood were assessed with the CES-D with a range of 0–60; higher scores indicate more depression and a score of 16 is defined as suggesting clinical depression. There was statistically significant decrease in depression symptoms over the course of the study with the median score decline of 1.0 ($p = .03$). In the long-term EFV-treated group, the percent with CES-D scores >16 declined from 34.1% to 22.3% over the study.

Anxiety was also a symptom of concern measured by the State Anxiety Index.⁹ On an 80-point scale, anxiety increased from baseline by a median of 4 points at Week 184 with long-term EFV treatment ($p < .01$).

Although the emphasis of these analyses is on the longitudinal course of EFV-treated patients, Tables 2 and 3 provide the contrast with other groups in the study. When EFV-only treated patients are compared with those never receiving EFV, there are no statistically significant differences in the changes over the study; although there is some evidence that the EFV-associated symptoms are higher in EFV-treated subjects ($p = .06$).

Because the long-term EFV cohort represents a select group, we assessed the generalizability of the analyses of this cohort by comparing the baseline measures of this cohort to the cohort of participants that were originally randomized to EFV but did not have long-term follow-up data on EFV (due to a lack of consent, patient dropout, or a change to a non-EFV regimen) (Table 4 and 5). The long-term EFV cohort had statistically significant better baseline neuropsychological performance (NPZ, $p < .01$; Trail Making A, $p = .02$; Trail Making B, $p < .01$; Digit Symbol, $p < .01$) and overall better sleep score ($p = .04$) at baseline compared to those randomized to EFV but without long-term data on EFV. Differences were not identified with respect to the bad dream score, depression, age, gender, race, intravenous drug use, and disease status (HIV-1 RNA viral load and CD4 count) (Table 5).

To further assess the representativeness of the 86 participants upon which the primary evaluation of long-term follow-up on EFV is based, we evaluated the reasons that 114 participants who were randomized to EFV were not included in the long-term EFV cohort. These 114 participants consisted of three groups (Figure 1): (a) a group that permanently discontinued A5095 ($n = 30$), (b) a group that did not consent to long-term neurological follow-up ($n = 53$), and (c) a group that discontinued EFV during follow-up ($n = 31$). Of the 30 participants who prematurely discontinued A5095, the reasons were as follows: subject/parent unable to get to clinic (11), ACTU unable to contact subject/parent (8), withdrew consent prior to study completion (5), death (4), and not willing to adhere to requirements (2). Of the 53 who did not consent to long-term neurological follow-up, most consented to long-term follow-up in 5095 and 33 were still on EFV. Of the 31 participants who discontinued EFV during follow-up, the reasons were as follows: CNS/mood (11; 6 of which were prior to Week 24), virologic failure (6; all after Week 48), rash/allergic reaction (5; 4 of which were prior to Week 24), prohibited medication (2), subject decision (2), gastrointestinal complaint (1), noncompliance (1), pregnancy (1), other toxicity (1), and other (1).

Discussion

EFV is an effective, well tolerated, and widely used component of antiretroviral therapy. CNS complaints have been the most commonly reported side effects and most frequent causes for drug withdrawal. Because these complaints may also affect compliance with medications, ongoing attention is warranted. The present study provides one of the longest reported periods of monitoring of the neuropsychological effects of EFV with a known baseline description of symptoms and performance, spanning a mean period of observation of more than 3 years on continuous EFV therapy. If continuous use of this drug had neurotoxic effects, they might be expected to manifest over a long period such as monitored in this report.

Our initial placebo-controlled, blinded observations provided considerable reassurance that the complaints occurring in the first week of therapy are transient, declining to the level of the placebo-treated patients after 4 weeks on EFV. Other concerns that the drug effects might compromise neuropsychological performance or exacerbate anxiety, depression, or sleep complaints were not found in the placebo-controlled experience during 6 months of therapy.⁴

Longer term evaluation of these problems is warranted however, because these drugs typically are used for many years. Because of the systematic characterization of a large number of patients in our clinical trial, we were able to compare changes from baseline to over 3 years in >80 patients on continuous EFV therapy.

It is encouraging that neuropsychological responses remained improved throughout the 3 years of this study. Reports of significant proportions of patients in HIV clinics who are mildly impaired on neuropsychological testing might suggest that slow progression of disability might be occurring, even in treated patients.^{12,13} EFV has modest CNS penetration from the blood based on CNS Penetration Effectiveness scoring methods,¹⁴ and concerns about the efficacy of the drug for the CNS could be entertained on this basis; but our results are consistent with the report of Tashima¹⁵ suggesting that CSF and most likely CNS penetration is sufficient to block viral replication in the brain compartment and prevent neurocognitive deterioration that might be associated with incomplete control of the CNS HIV infection.¹⁵ An alternative consideration, that cognitive dysfunction might be a result of chronic neurotoxicity of drugs used as ARV, could also be considered. EFV would be a drug of concern given its known acute neurological side effects.⁴ Our finding that neurocognitive performance was maintained without decline over 3 years of therapy provides reassurance that chronic neurotoxicity of this therapy is unlikely in many patients. However, higher serum trough EFV drug concentrations were associated with a small, but statistically significant, decline in neuropsychological performance at 3 years.

The finding of a slight increase in our CNS symptoms score at the conclusion of the study is of interest. This instrument was designed to be highly sensitive to potential symptoms previously associated with EFV, such as dizziness or changes in sleep patterns. The significant increase in the symptom score from baseline was small and thus almost certainly of minimal clinical consequence, but it does corroborate the clinical experience that some individuals experience more extended neuropsychiatric changes over time than appreciated in the original blinded studies. This may result from the unblinded use of EFV, and the greater likelihood in open-label setting to note side effects known to be related to the drug. However, because those significantly bothered by the symptom likely electively stopped the drug, this confirms that at least some patients have mild, persistent symptoms arising from continued EFV use.

We were also able to re-evaluate association of neurological symptoms with EFV drug levels. Our initial findings suggested that neurological symptoms were not correlated with serum drug levels, at least after patients with intolerable side effects have been eliminated from ongoing evaluation.¹⁶ This contrasts with the suggestion of Marzolini et al¹⁷ who reported a relation with high drug levels and the development of clinical toxicity. However, their subjective report was far less quantitative than the sensitive scoring system that we used for the present study, while including a much smaller group of patients followed for less time. The elective discontinuation of EFV in those experiencing clinically significant symptoms, and potentially some who ostensibly stopped for administrative reasons, limits our ability to analyze the spectrum of toxicity that can occur with this drug and its association with serum concentration. Our findings may be compared with those of Rihs et al who recently reported a comparison of EFV-treated patients to a matched control group at 6 months into therapy.¹⁸

The outstanding finding in this report is the high levels of stress, anxiety, and unusual dreams in EFV-treated subjects. These investigators used the Depression Anxiety and Stress Scale (DASS), which differs from the State-Trait Anxiety Inventory for Adults⁹ and CES-D¹⁰ that we used. We did not have a specific measure for stress in our study but did find slight changes in bad dreams and anxiety. As in our report, Rihs et al found no differences in cognitive impairment between their EFV-treated groups and the comparator arm.

Although our experience is a substantial prospective observation of EFV use, it has limitations. First, the comparator triple-nucleoside arm with placebo EFV was stopped early due to inferior viral suppression, and consequently all treatment arms were unblinded. After this point, patients receiving EFV were aware they were taking this drug and knew of its reported side effects. Second, it is likely that the cohort that continued on EFV was affected by selection bias, because patients experiencing potential EFV side effects were allowed to switch to nevirapine or to withdraw from the study so as to use alternative therapies. Further, investigators likely did not offer study participation to patients they thought might have neuropsychological problems. Thus, the experience we record approaches the optimal response to antiretroviral therapy containing EFV, rather than providing a complete characterization of the tolerability of this drug. Third, our tools for measurement are not exhaustive, because we required practical measures that could be performed quickly, would be well tolerated, and could be administered by personnel who were not neuropsychologists. The measures we used evaluate several domains of neuropsychological functioning including motor persistence, sustained attention, response speed, visuomotor coordination, and conceptual shifting/tracking. However, memory and cognitive domains were not formally assessed.

Our results should be interpreted in light of the relatively normal status of the participants, whose mean neuropsychological performance was normal at baseline. Interpretation of our study requires caution, because we did not adjust for the multiplicity of tests and because of the non-random loss of subjects in follow-up. Interpretations of anxiety, sleep, and depression are not analyzed in relation to any other medical intervention that the patients may have received for these complaints. Our generalizability analysis suggests that patients with better cognitive status or sleep behavior at baseline were more likely to remain on EFV throughout the study. It is interesting that neither bad dreams nor depression at baseline were associated with excess drop-out in this experience. Finally, we measured only trough levels of EFV, whereas peak drug levels might have a different correlation with adverse events.

Nevertheless, this report provides a valuable description of the prospective use of EFV in a substantial group of patients. It substantiates the ability of EFV-based HAART to maintain stable and normal neuropsychologic function over more than 3 years at least for some patients. Given the concerns of a large number of cognitively impaired patients in our HIV clinics, it is reassuring to know that with optimal use of this common first-line therapy, stable or improved neurological performance is generally achieved for patients who are able to remain on EFV-based therapy.

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Appendix: ACTG A5097s Study Team

In addition to the authors, other members of the ACTG A5097s protocol team include the following: Sally Snyder, BS (Social and Scientific Systems, Silver Spring), Clinical Trials Specialist; Meredith Glicksman, MS (Washington University, St. Louis), protocol co-chair; Christina Lalama, MS (Harvard University, Boston), substudy statistician; Nicole Grosskopf, BS, Linda Millar, BS (Frontier Science & Technology Research Foundation), data managers; and Valery Hughes, NP (Cornell Clinical Trials Unit, New York), field representative.

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Figure 1.
CONSORT diagram.

Figure 2.
Median change (with Q1 and Q3) in NPZ3 score by group over time.

Figure 3.
Median change (with Q1 and Q3) in EFV-associated symptom score by group over time.

Table 1

Baseline demographics by group

	EFV only (n = 86)	Various regimens (n = 37)	Late long-term EFV (n = 21)	Non-EFV only (n = 33)	P
Age, years					
Mean (SD)	39.2 (9.2)	37.4 (7.2)	40.0 (8.1)	40.5 (8.7)	.50
Min, Max	20, 64	26, 53	24, 58	26, 61	
Gender					.43
Male	73 (85%)	26 (70%)	17 (81%)	26 (79%)	
Female	13 (15%)	11 (30%)	4 (19%)	7 (21%)	
Race					.22
White	45 (52%)	21 (57%)	9 (43%)	14 (42%)	
Black	28 (33%)	14 (38%)	9 (43%)	11 (33%)	
Hispanic	10 (12%)	2 (5%)	2 (10%)	7 (21%)	
Others	3 (4%)	0	1 (5%)	1 (3%)	
IV drug use					.55
Never	81 (94%)	33 (89%)	16 (76%)	30 (91%)	
Currently	1 (1%)	0	0	0	
Previous	4 (5%)	4 (11%)	5 (24%)	3 (9%)	
Education, years					
Mean (SD)	14.2 (2.8)	13.3 (2.6)	13.7 (2.7)	13.7 (2.1)	.34
Min, Max	9, 23	7, 18	8, 18	9, 19	
Baseline CD4 cell count					
Mean (SD)	305.2 (324.1)	222.49 (176.6)	301.7 (236.9)	270.4 (190.4)	.47
Min, Max	0, 2594	6, 697	24, 1005	7, 818	
Baseline log ₁₀ HIV-1 RNA					
Mean (SD)	4.81 (0.74)	4.91 (0.82)	4.83 (0.73)	4.86 (0.59)	.69
Min, Max	3.03, 6.63	2.77, 6.52	3.57, 6.37	4.00, 6.19	

Note: *p* value is for the EFV-only group versus the non-EFV group.

Table 2

Descriptive statistics of NPZ3 scores

	EFV only	Various regimens	Late long-term EFV	Non-EFV only	<i>p</i> ^a
Baseline NPZ3 score					
<i>N</i>	84	37	21	33	.07
Mean (<i>SD</i>)	0.04 (1.0)	-.49 (1.2)	-.04 (0.9)	-.25 (1.0)	
Median	0.25	-.16	0.13	-.05	
Min, Max	-4.1, 1.3	-4.1, 0.9	-2.6, 1.0	-3.0, 1.6	
Change of NPZ3 score					
<i>N</i>	81	33	21	33	.69
Mean (<i>SD</i>)	0.47 (0.6)	0.81 (0.9)	0.57 (0.7)	0.58 (0.9)	
Median	0.50	0.52	0.43	0.61	
Min, Max	-1.6, 2.0	-.62, 3.4	-1.1, 3.0	-1.2, 4.0	
<i>p</i> ^b	<0.01	<0.01	<0.01	<0.01	
Baseline TMA score					
<i>N</i>	84	37	21	33	.31
Mean (<i>SD</i>)	-.06 (1.4)	-.72 (1.5)	-.06 (0.9)	-.34 (1.5)	
Median	0.39	-.34	0.33	0.11	
Min, Max	-7.1, 1.6	-5.0, 1.3	-1.9, 1.3	-4.9, 1.4	
Change of TMA score					
<i>N</i>	81	33	21	33	.71
Mean (<i>SD</i>)	0.69 (1.0)	1.19 (1.3)	0.76 (0.6)	0.51 (1.2)	
Median	0.54	0.90	0.78	0.62	
Min, Max	-1.8, 4.2	-1.1, 4.2	-.31, 1.8	-2.0, 4.5	
<i>p</i> ^b	<0.01	<0.01	<0.01	<0.01	
Baseline TMB score					
<i>N</i>	84	37	21	33	.07
Mean (<i>SD</i>)	0.27 (1.0)	-.25 (1.5)	0.11 (1.6)	-.10 (1.2)	
Median	0.49	0.13	0.52	0.27	
Min, Max	-3.9, 1.9	-6.4, 1.2	-6.4, 1.4	-3.7, 1.6	
Change of TMB score					
					.06

	EFV only	Various regimens	Late long-term EFV	Non-EFV only	<i>p</i> ^a
<i>N</i>	81	33	21	32	
Mean (SD)	0.27 (1.0)	0.72 (1.4)	0.41 (1.8)	0.63 (1.2)	
Median	0.29	0.42	0.29	0.44	
Min, Max	-5.4, 2.9	-1.3, 5.8	-5.4, 5.8	-1.7, 4.1	
<i>p</i> ^b	<0.01	<0.01	<0.01	<0.01	.18
Baseline DSY score					
<i>N</i>	84	37	21	33	
Mean (SD)	-.09 (0.9)	-.49 (1.1)	-.17 (1.0)	-.32 (0.9)	
Median	-.01	-.37	0.11	-.37	
Min, Max	-2.8, 1.8	-3.4, 1.5	-2.2, 1.2	-2.1, 1.8	
Change of DSY score					
<i>N</i>	81	33	21	33	.48
Mean (SD)	0.45 (0.9)	0.51 (0.7)	0.54 (0.6)	0.60 (1.0)	
Median	0.43	0.26	0.52	0.52	
Min, Max	-2.2, 3.5	-1.2, 2.2	-.48, 2.1	-2.1, 3.4	
<i>p</i> ^b	<0.01	<0.01	<0.01	<0.01	

Note: TMA = Trail Making A, TMB = Trail Making B, DSY = Digit Symbol test.

^aWilcoxon rank sum test comparing EFV only group with non-EFV only group.

^bWilcoxon signed rank test for testing whether change from baseline is zero.

Table 3
Sleep, depression, anxiety, and EFV-associated symptom score change

	EFV only	Various regimens	Late long-term EFV	Non-EFV only	<i>p</i> ^a
Baseline sleep score					
<i>N</i>	81	33	20	31	0.76
Mean (<i>SD</i>)	5.99 (3.7)	6.42 (3.8)	6.35 (4.3)	5.74 (3.7)	
Median	5.00	6.00	4.50	5.00	
Min, Max	0.00, 17.0	0.00, 15.0	1.00, 16.0	1.00, 16.0	
Change of sleep score					
<i>N</i>	73	31	17	24	.32
Mean (<i>SD</i>)	-.63 (3.8)	-.10 (4.0)	-1.4 (4.4)	-1.5 (3.3)	
Median	0.00	0.00	-2.0	-2.0	
Min, Max	-11, 11.0	-10, 8.0	-13, 4.0	-8.0, 4.0	
<i>p</i> ^b	.14	.92	.31	.10	
Baseline depression score					
<i>N</i>	85	37	21	33	.89
Mean (<i>SD</i>)	12.2 (10.5)	13.3 (11.1)	13.8 (12.5)	11.8 (10.5)	
Median	9.00	9.00	9.00	9.00	
Min, Max	0.00, 45.0	0.00, 37.0	1.00, 46.0	0.00, 40.0	
Change of depression score					
<i>N</i>	84	34	21	32	.71
Mean (<i>SD</i>)	-2.1 (9.3)	3.26 (10.8)	-5.2 (13.6)	-1.4 (9.1)	
Median	-1.0	2.50	-2.0	-1.0	
Min, Max	-27, 25.0	-19, 30.0	-41, 18.0	-31, 27.0	
<i>p</i> ^b	.03	.13	.12	.32	
Baseline anxiety score					
<i>N</i>	86	37	21	33	.14
Mean (<i>SD</i>)	53.9 (12.8)	54.1 (11.7)	54.3 (12.4)	57.8 (10.7)	
Median	55.5	54.0	57.0	60.0	
Min, Max	18.0, 70.0	27.0, 70.0	18.0, 70.0	30.0, 70.0	
Change of anxiety score					
					.12

	EFV only	Various regimens	Late long-term EFV	Non-EFV only	<i>p</i> ^a
<i>N</i>	85	34	21	31	
Mean (<i>SD</i>)	4.46 (12.0)	-3.4 (14.9)	5.76 (12.1)	0.13 (10.5)	
Median	4.00	-2.5	2.00	2.00	
Min, Max	-32, 38.0	-56, 18.0	-11, 46.0	-27, 18.0	
<i>p</i> ^b	0.01	.27	.031	.51	
Baseline bad dream score					
<i>N</i>	83	33	21	32	.32
Mean (<i>SD</i>)	0.35 (0.7)	0.39 (0.8)	0.62 (1.1)	0.53 (0.9)	
Median	0.00	0.00	0.00	0.00	
Min, Max	0.00, 3.0	0.00, 3.0	0.00, 3.0	0.00, 3.0	
Change of bad dream score					
<i>N</i>	83	33	21	32	.14
Mean (<i>SD</i>)	0.29 (1.0)	0.52 (1.1)	-.05 (1.1)	-.16 (1.2)	
Median	0.00	0.00	0.00	0.00	
Min, Max	-2.0, 3.0	-2.0, 3.0	-3.0, 3.0	-3.0, 2.0	
<i>p</i> ^b	<0.01	.01	.97	.55	
Baseline EFV symptom score					
<i>N</i>	86	37	21	33	.87
Mean (<i>SD</i>)	7.44 (7.3)	11.9 (10.1)	10.7 (9.6)	7.09 (6.3)	
Median	5.00	9.00	7.00	5.00	
Min, Max	0.00, 32.0	0.00, 39.0	0.00, 34.0	0.00, 25.0	
Change of EFV symptom score					
<i>N</i>	85	34	21	32	.06
Mean (<i>SD</i>)	2.99 (10.3)	1.09 (9.0)	-1.6 (8.9)	-.34 (6.7)	
Median	1.00	-.50	0.00	-1.0	
Min, Max	-21, 42.0	-16, 24.0	-21, 10.0	-16, 23.0	
<i>p</i> ^b	.01	.68	.71	.49	

^aWilcoxon rank sum test comparing EFV only group with Non-EFV only group.

^bWilcoxon signed rank test for testing whether change from baseline is zero.

Table 4
Baseline neuropsychological characteristics among different arms

	Arm 1 (n = 86)	Arm 2 (n = 114)	Arm 3 (n = 33)	Arm 4 (n = 70)	p ^a	p ^b
Baseline NPZ3 score						
N	84	112	33	70		
Median	0.25	-.25	-0.05	0.002	<.01	.83
Q1, Q3	-0.42, 0.74	-0.95, 0.31	-1.06, 0.37	-0.68, 0.47		
Baseline TMA score						
N	84	112	33	70		
Median	0.39	-.13	0.11	-0.001	.02	.97
Q1, Q3	-0.68, 0.79	-0.91, 0.56	-1.24, 0.68	-0.91, 0.68		
Baseline TMB score						
N	84	112	33	70		
Median	0.49	0.11	0.27	0.18	<.01	.79
Q1, Q3	0.03, 1.00	-1.03, 0.52	-0.64, 0.68	-0.63, 0.74		
Baseline DSY score						
N	84	112	33	70		
Median	-0.01	-0.48	-0.37	-0.09	<.01	.68
Q1, Q3	-0.73, 0.66	-1.26, 0.20	-0.94, 0.12	-0.94, 0.52		
Baseline sleep score						
N	82	107	32	69		
Median	5.00	6.00	5.00	6.00	<.05	.29
Q1, Q3	3.00, 8.00	4.00, 11.00	3.50, 7.50	3, 10		
Baseline anxiety score						
N	86	113	33	70		
Median	55.5	53	60	53	.15	.04
Q1, Q3	45, 64	40.5, 62	51, 68	43, 62		
Baseline log₁₀ HIV-1 RNA	4.81 (0.74)	4.89 (0.73)	4.86 (0.59)	4.89 (0.77)	.45	.81
Baseline CD4 count	305.2 (324.1)	230.6 (191.0)	270.4 (190.4)	244.9 (225.7)	.08	.29

Note: Arm 1: randomized to EFV and continued EFV with long-term data; Arm 2: randomized to EFV but do not have long term data on EFV; Arm 3: randomized to non-EFV and continued on non-EFV with long term data; Arm 4: randomized to non-EFV but do not have long term data on non-EFV.

^aWilcoxon rank sums test between Arm 1 and Arm 2.

^bWilcoxon rank sums test between Arm 3 and Arm 4.

Table 5
Baseline demographics by different arms

	Arm 1 (n = 86)	Arm 2 (n = 114)	Arm 3 (n = 33)	Arm 4 (n = 70)	p
<i>Age, years</i>					
Mean (SD)	39.2 (9.2)	36.4 (7.8)	40.5 (8.7)	37.7 (8.0)	.44
Min, Max	20, 64	21, 67	26, 61	19, 61	
<i>Gender</i>					
Male	73 (85%)	91 (80%)	26 (79%)	56 (80%)	.78
Female	13 (15%)	23 (20%)	7 (21%)	14 (80%)	
<i>Race</i>					
White	45 (52%)	60 (53%)	14 (42%)	36 (51%)	.71
Black	28 (33%)	38 (33%)	11 (33%)	26 (37%)	
Hispanic	10 (12%)	14 (13%)	7 (21%)	6 (9%)	
Others	3 (4%)	2 (1%)	1 (3%)	2 (3%)	
<i>IV drug use</i>					
Never	81 (94%)	101 (89%)	30 (91%)	61 (87%)	.41
Currently	1 (1%)	0	0	0	
Previous	4 (5%)	13 (11%)	3 (9%)	9 (13%)	
<i>Education, years</i>					
Mean (SD)	14.2 (2.8)	13.3 (2.3)	13.7 (2.1)	13.2 (2.6)	.19
Min, Max	9, 23	7, 18	9, 19	4, 19	
<i>CD4 count</i>					
Mean (SD)	305.2 (324.1)	230.6 (191.0)	270.4 (190.4)	244.9 (225.7)	.22
Min, Max	0, 2594	3, 802	7, 818	3, 1005	
<i>log₁₀ HIV-1 RNA</i>					
Mean (SD)	4.81 (0.74)	4.89 (0.73)	4.86 (0.59)	4.89 (0.77)	.86
Min, Max	3.03, 6.63	2.70, 6.52	4.00, 6.19	3.05, 6.62	

Note: Arm 1: randomized to EFV and continued EFV with long-term data; Arm 2: randomized to EFV but do not have long term data on EFV; Arm 3: randomized to non-EFV and continued on non-EFV with long term data; Arm 4: randomized to non-EFV but do not have long term data on non-EFV. *p* value is overall test among four arms.