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Impact of Efavirenz on Neuropsychological Performance and Symptoms in HIV-Infected Individuals

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Background: **Efavirenz is a commonly used antiretroviral drug that causes neurologic side effects in more than 50% of patients.**

Objective: **To characterize efavirenz-associated neurologic symptoms in a randomized, controlled study of initial antiretroviral treatment.**

Design: **Substudy of a randomized, double-blind, controlled trial of combination antiretroviral regimens (A5095) that was performed between March 2001 and January 2002.**

Setting: **Multicenter academic clinical trial units.**

Participants: **HIV-infected patients who were initiating therapy in the context of a controlled trial.**

Measurements: **Neuropsychological performance measures, including the Digit Symbol Substitution Test and the Trail Making Test (Parts A and B); symptom questionnaires; standardized assessments of sleep quality, anxiety, and depression; and efavirenz plasma concentrations.**

Results: **Twenty of 303 (6.6%) enrolled participants prematurely discontinued the study. Neuropsychological performance improved in both groups over time without significant differences between patients who were receiving efavirenz and those who were not. The efavirenz group experienced more neurologic symptoms at week 1 ($P < 0.001$) but not at weeks 4, 12, or 24. A sleep index revealed that participants receiving efavirenz had more "bad dreams" during the first week of therapy ($P = 0.038$). No significant changes in anxiety or depressed mood were noted. Changes in efavirenz-associated neurologic symptoms were correlated to efavirenz plasma concentrations at week 1 but not at later time points. Twelve (6%) patients receiving efavirenz stopped taking the drug before the end of the study because of central nervous system symptoms.**

Limitations: **Participant selection may have been biased in favor of patients with fewer psychiatric complications. The study design permitted substitution of a new drug in place of efavirenz in cases of treatment-limiting toxicity.**

Conclusions: **In a large controlled trial, efavirenz use was associated with neurologic symptoms distinct from depression and anxiety that began early in therapy but resolved by week 4. Improvement in neuropsychological performance was comparable in patients who were receiving efavirenz and those who were not.**

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Trial ACTG A5097s.

*For members of the A5097s Study Team, see the Appendix, available at www.annals.org.

Efavirenz is a non-nucleoside reverse transcriptase inhibitor approved for treatment of HIV infection. The drug is potent, is generally well tolerated, and can be administered once daily, making it a preferred treatment option for HIV infection (1, 2). The most commonly reported adverse effect with efavirenz is neurologic toxicity, with more than 50% of patients reporting symptoms in open-label studies (1, 3). Our randomized, controlled study prospectively characterized aspects of the neurologic toxicity of 3 protease inhibitor–sparing antiretroviral regimens for the initial treatment of HIV infection.

METHODS

This investigator-initiated trial was a substudy of the AIDS Clinical Trials Group study A5095, a randomized, double-blind trial of 3 antiretroviral regimens: zidovudine and lamivudine in combination with efavirenz; abacavir; or abacavir and efavirenz in combination (4). For simplicity, we will refer to 2 groups: patients who received efavirenz (with or without abacavir) and those who did not. Randomization was performed centrally without reference to center. The study was supported by the National Institutes of Health (NIH) and was approved by the institutional review boards at each of the participating institutions, with each patient providing informed consent to participate in the substudy. All patients at sites taking part in the substudy were invited to participate before randomization for the parent study (**Figure 1**). Unblinding and within-class substitutions were allowed in cases of treatment-limiting toxicity (we substituted stavudine for zidovudine, didanosine for abacavir, and nevirapine for efavirenz). Participants had not previously received antiretroviral therapy, and their baseline plasma HIV-1 RNA levels were greater than 400 copies/mL. Parent study A5095 enrolled 1147 participants, of whom 303 at 36 clinical trials units volunteered to participate in the additional evaluations for

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A5097s. Participants were recruited between March 2001 and January 2002.

The primary measures of neuropsychological performance were the Trail Making Tests (Parts A and B) and the Digit Symbol Substitution Test (part of the Wechsler Adult Intelligence Scale III [5]). A summary neuropsychological *Z* score (NPZ3) was derived from the sum of the scores from these 3 tests and standardized for age. Positive scores indicated above-normal function, whereas negative scores indicated below-normal function. The entire score was coded as missing if any component of the NPZ3 was not available. The Neurologic AIDS Research Consortium 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 and tracking. Neuropsychometric measures were collected at baseline and at weeks 1, 4, 12, and 24. Testing was performed at each time point to assess symptoms that might be associated with efavirenz use, sleep disorders, anxiety, depression, and history of drug abuse. The instruments are summarized in **Table 1.** The symptom questionnaire developed for this study is shown in the **Appendix Figure** (available at www.annals.org).

Whole blood was collected from all participants to determine efavirenz trough concentrations in plasma (13). These data were used to explore relationships between drug exposure and other variables that were evaluated in the study.

Context

Neurologic toxicity is the most commonly reported adverse effect of the antiretroviral drug efavirenz.

Contribution

In this substudy of a randomized, controlled trial, 12 of 200 (6%) HIV-infected individuals discontinued treatment with efavirenz because of central nervous system symptoms or mood disorders versus 0 of 103 individuals (0%) who were not receiving the drug. Although patients taking efavirenz had more neuropsychological symptoms, such as bad dreams, in the first week of therapy, no statistically significant neuropsychological differences were found at weeks 4, 12, and 24.

Implications

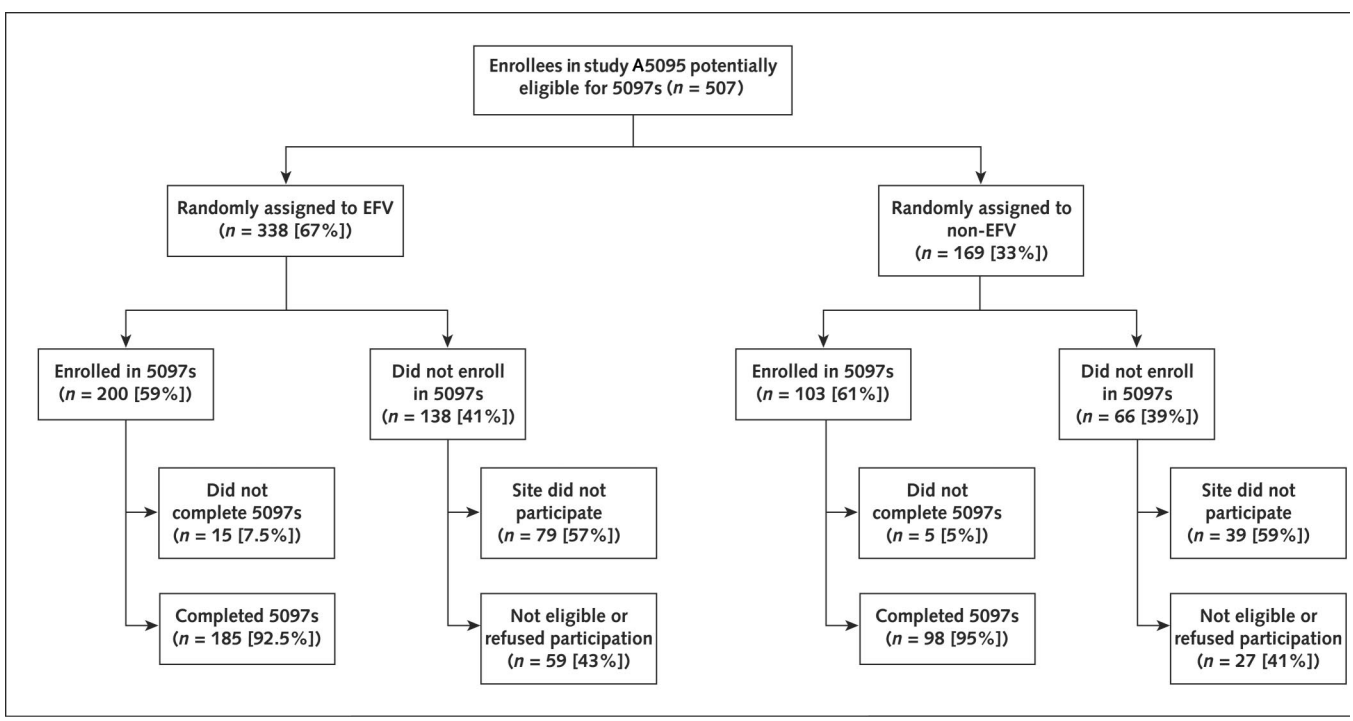
Some adverse neuropsychological effects associated with efavirenz are probably transient.

—The Editors

Statistical Analysis

Our substudy was designed to compare neurologic changes from baseline in patients who received efavirenz with changes in those who did not. The study had 90% power to detect a standard deviation of 0.4 for change in the summary neuropsychological performance score from baseline to week 1.

Figure 1. **CONSORT diagram of substudy 5097s.**



CONSORT = Consolidated Standards of Reporting Trials; EFV = efavirenz.

Table 1. **Testing Instruments**

Test	Domains Evaluated	Administrator	Range of Scores	Threshold
Neuropsychological *Z* score				
Trail Making Test, Part A*	Visuomotor tracking, cognitive sequencing	Interviewer	Time in seconds to complete	–
Trail Making Test, Part B*	Visuomotor tracking, cognitive sequencing	Interviewer	Time in seconds to complete	–
Digit Symbol Substitution Test (Wechsler Adult Intelligence Scale)†	Response speed, visuomotor coordination, conceptual tracking	Interviewer	0–133 in 90 seconds	–
Subject Experience Questionnaire	Efavirenz-related symptoms, non–efavirenz-related symptoms	Self	0–136 (34 questions, scale 0–4)	Continuous variable
Pittsburgh Sleep Quality Index‡	Sleep experience	Self	0–21	≥5: Poor sleep
State–Trait Anxiety Inventory§	Anxiety	Self	0–80	≥40
Center for Epidemiologic Studies Depression Scale‖	Depression	Self	0–60	≥16

*From references 6, 7.
† From references 8, 9.
‡ From reference 10.
§ From reference 11.
‖ From reference 12.

We presented descriptive statistics for the study sample and used nonparametric tests to determine treatment differences. Using the nonparametric methods of Hodges and Lehmann (14) and Proc-StatXact software, version 4.0.1 (Cytel Software Corp., Cambridge, Massachusetts), we estimated treatment differences for continuous outcomes with corresponding exact confidence intervals. Generalized estimating equation modeling (a regression method) and the Wei-Johnson test (a nonparametric method for analyzing incomplete 2-sample data) (15) were used to compare treatment groups longitudinally; both methods assumed that data were missing completely at random. We used the Spearman correlation coefficient, a rank-based method that is robust to extreme observations, to evaluate correlations. All significance testing was performed at an α level of 0.05 with no adjustment for multiple testing. All reported P values were 2-sided. To assess the potential effect of any missing data, we performed multiple imputation, analyzed 2 "worst-case" scenarios (**Appendix Table 1** and **Appendix Table 2**, available at www.annals.org), and conducted an "as-treated" analysis that excluded patients who discontinued efavirenz therapy. We used SAS software (SAS Institute, Inc., Cary, North Carolina) to perform statistical analyses. Test sources included Elsevier Science (Oxford, United Kingdom) for the Pittsburgh Sleep Quality Index, Mind Garden (Redwood City, California) for the State-Trait Anxiety Inventory for Adults, and the National Institute of Mental Health (Bethesda, Maryland) for the Center for Epidemiologic Studies Depression Scale.

Role of the Funding Sources

This investigator-initiated protocol was supported by the NIH. Drugs used in the study were donated by pharmaceutical companies whose representatives participated in team discussions. The study was monitored by NIH-contracted monitors and was supervised by a data safety monitoring committee that was appointed by the National Institute of Allergy and Infectious Diseases. The NIH-supported biostatistical team working with the AIDS Clinical Trials Group and the Neurologic AIDS Research Consortium performed the statistical analyses. The protocol team, led by the first author, had final responsibility for the study protocol, case report forms, statistical analysis plan, progress of the study, analysis, and reporting of the data, regardless of outcome. The final version was the sole responsibility of the authors. The team had full access to the data files of the study.

RESULTS

Baseline Evaluations

Recruitment characteristics are displayed in **Figure 1;** demographic characteristics of the study participants are presented in **Table 2**. The treatment groups were balanced at baseline with respect to demographic characteristics, neuropsychological measures, and responses to the symptom questionnaire. The sleep disturbance component of the global sleep index demonstrated a baseline difference; the patients who eventually received efavirenz had marginally more sleep disturbances ($P = 0.048$) (data not shown). Other components of the sleep index, including quality, latency, duration, efficiency, use of sleeping medication, and daytime dysfunction, were similar between groups. Alcohol abuse, drug use, and affective disturbances were infrequent and similar for both groups.

Disposition of Study Participants

The study allowed for drug substitution from the same class of antiretroviral agents in cases of treatment-limiting toxicity. **Table 3** summarizes the modifications that occurred and the respective reasons. **Appendix Table 3** (available at www.annals.org) gives further details of timing of modifications and the ethnicity of the individuals. Primary

end point data (the change in NPZ3 from baseline to week 1) were observed in 283 of the 303 (93.4%) participants.

Prospective Evaluations

Median NPZ3 scores improved in both groups during the study, with the greatest change occurring in the first week of treatment (**Figure 2**). No statistically significant differences in changes in neuropsychological performance were observed between the groups at any time point. We conducted conventional longitudinal analyses to further investigate differences in neuropsychological scores between the treatment groups. On the basis of these analyses, we had insufficient evidence to conclude that there were treatment differences (generalized estimating equation modeling in which treatment was the only independent variable and an exchangeable correlation structure was assumed, $P = 0.176$; Wei-Johnson test, $P = 0.196$). Multiple sensitivity analyses were performed, including single and multiple imputation methods, as-treated analyses, and 2 forms of "worst-case" scenarios. Details of these analyses are shown in **Appendix Table 1** (available at www.annals.org). Multiple imputation and as-treated analyses generally provided similar results to observed data at specific weeks; however, the worst-case analyses at weeks 4, 12, and 24 displayed significant differences between groups. These results suggest that differences between groups might exist if the worst-case scenario were true, that is, if patients without data who were receiving efavirenz had worse psychological performance than everyone else in the study, and patients without data who were not receiving the drug had better psychological performance than everyone else in the study. Generalized estimating equation modeling with imputed data (multiple imputation and as-treated analyses) revealed no statistically significant differences (**Appendix Table 2**, available at www.annals.org).

Changes in results of the Trail Making component of the NPZ3 were similar between groups at all time points. In comparison, patients who were not receiving efavirenz displayed slightly greater improvement on the Digit Symbol Substitution Test at weeks 4 and 12 but not at weeks 1 or 24. Correlation analysis of efavirenz levels with measures of neuropsychological function showed a small but significant negative correlation at weeks 4 ($\rho = -0.31$; $P = 0.002$) and 12 ($\rho = -0.28$; $P = 0.012$), suggesting an association between lower NPZ3 scores and higher efavirenz concentrations. However, changes in NPZ3 performance that occurred with the initiation of efavirenz did not correlate to efavirenz concentrations.

Changes in responses to the efavirenz symptom questionnaire differed between the groups, but other systemic symptoms did not (**Figure 2**). At week 1, changes in the efavirenz symptom scores were significantly greater ($P < 0.001$) in the patients who received efavirenz than in those who did not, but differences between groups were not significant at the later time points. Sensitivity analyses using multiple imputations, worst-case scenarios, and best-case

Table 2. **Baseline Characteristics and Evaluations by Treatment Group**

Variable	Treatment		*P* Value
	Efavirenz ($n = 200$)	Non-Efavirenz ($n = 103$)	
Sex, *n* (%)			0.64*
Men	164 (82)	82 (80)	
Women	36 (18)	21 (20)	
Ethnicity, *n* (%)			0.72*
White	105 (53)	50 (49)	
Black	66 (33)	37 (36)	
Hispanic	24 (12)	13 (13)	
Asian	4 (2)	1 (1)	
Native American	1 (1)	2 (2)	
Age			0.35†
Median, *y*	37	38	
< 25 y, *n* (%)	11 (6)	3 (3)	
25–34 y, *n* (%)	60 (30)	29 (28)	
35–44 y, *n* (%)	89 (45)	48 (47)	
45–54 y, *n* (%)	35 (18)	18 (17)	
≥ 55 y, *n* (%)	5 (3)	5 (5)	
Intravenous drug use, *n* (%)			0.61*
Never	182 (91)	91 (88)	
Currently	1 (1)	0 (0)	
Previously	17 (9)	12 (12)	
HIV-1 RNA, log_{10} copies/mL			0.72‡
Median	4.72	4.76	
Q1, Q3§	4.39, 5.34	4.42, 5.45	
CD4 cell count, × 10^9 cells/L			0.82‡
Median	0.219	0.197	
Q1, Q3§	0.73, 0.379	0.89, 0.338	
Neuropsychological performance score‖			0.78‡
Missing, *n*	4	0	
Median	−0.09	−0.03	
Q1, Q3§	−0.82, 0.56	−0.91, 0.42	
Depression score¶			0.41‡
Missing, *n*	3	0	
Median	12	12	
Q1, Q3§	5, 21	4, 21	
Anxiety score**			0.25‡
Missing, *n*	1	1	
Median	54	56	
Q1, Q3§	42, 64	47, 64	
Sleep status score††			0.61‡
Missing, *n*	11	2	
Median	6	5	
Q1, Q3§	4, 9	3, 9	
Efavirenz symptom score			0.075‡
Missing, *n*	1	1	
Median	8	6	
Q1, Q3§	3, 16	3, 12	

* Exact test.
† Exact Wilcoxon test.
‡ Kruskal–Wallis test.
§ Q1 is 25th percentile and Q3 is 75th percentile.
‖ Neuropsychological performance *Z* score.
¶ Center for Epidemiologic Studies Depression Scale.
** Spielberger State–Trait Anxiety Score.
†† Pittsburgh Sleep Quality Index.

scenarios supported these results (**Appendix Table 1**, available at www.annals.org). Changes in efavirenz symptom scores were correlated with efavirenz trough plasma concentrations at week 1 ($P = 0.040$) but not at other time points.

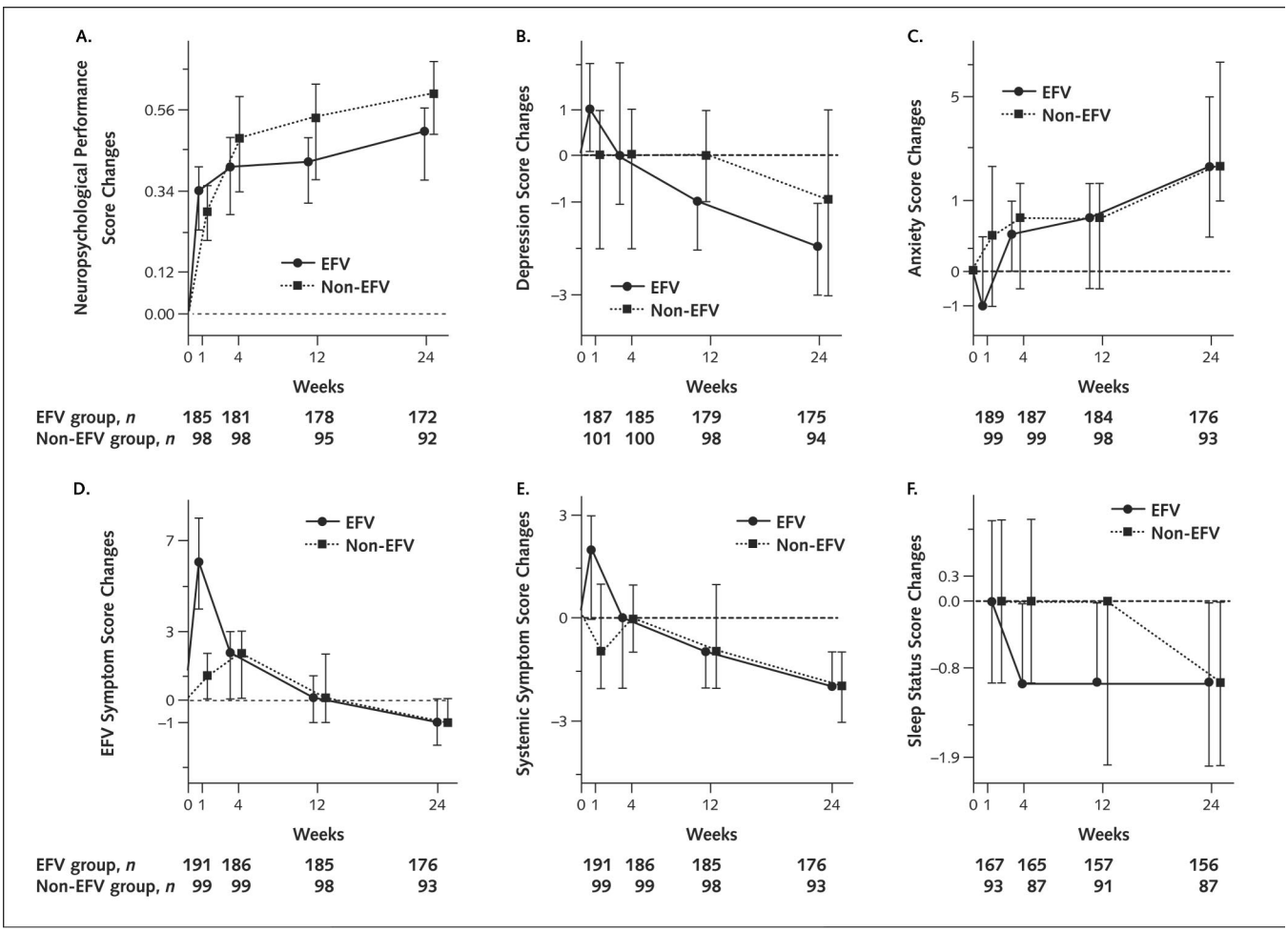
Sleep quality scores changed little over time. The efavirenz group had significantly greater "bad dream" score changes at week 1 ($P = 0.038$) but not at other time points. The patients who were not receiving efavirenz had significantly poorer sleep quality at week 4 ($P = 0.040$) (**Figure 2**). No significant correlations between efavirenz levels and sleep variables were detected.

All participants experienced substantial anxiety throughout the study; we observed clinically significant anxiety in greater than 80% of the patients at baseline and at each time point. Total anxiety scores increased in both groups. Changes in total anxiety scores from baseline were marginally different at week 1 ($P = 0.073$), with the patients receiving efavirenz experiencing fewer increases in anxiety. There was no significant difference with respect to changes in anxiety at weeks 4, 12, and 24. Neither absolute anxiety levels nor change in anxiety were significantly correlated to efavirenz levels.

Changes in depressed mood (**Figure 2**, **Table 3**) and high levels of depressive symptoms were similar between both groups. Efavirenz trough plasma levels correlated to absolute depression score at week 4 only, whereas changes in efavirenz levels did not correlate with changes in depression scores at any time point.

We collected information on use of concomitant medications (including sedative medications, such as benzodiazepines and barbiturates) that might have been added to treat efavirenz neurotoxicity. Of 200 patients receiving efavirenz, 5 (2.5%) used sedatives; 4 patients used them for a short time and 1 patient used them on a long-term basis. Thirteen of the 103 (13%) patients who were not receiving efavirenz used sedatives (10 patients used them for a short time whereas 3 used them on a long-term basis).

Figure 2. **Median changes from baseline over time and 95% CIs for each time point.**



Below each plot are the numbers of patients available to compute these measures. **A.** Change in neuropsychological performance over the duration of the study. **B.** Changes in depression from the Center for Epidemiologic Studies Depression Scale. **C.** Anxiety performance changes. **D.** Presumptive efavirenz (*EFV*)-related symptom score changes. **E.** Systemic symptom score changes. **F.** Change in sleep variables as measured by the Pittsburgh Sleep Quality Index. EFV = efavirenz.

Table 3. **Reasons for Modification of Treatment***

Variable	Group Receiving Efavirenz ($n = 200$)	Group Not Receiving Efavirenz ($n = 103$)	All Patients
Patients requiring modification of therapy, *n* (%)	42 (21)	17 (17)	59†
Reason for modification			
Central nervous system symptoms or mood disorders, *n* (%)	12 (6)	0 (0)	12†
Nonadherence, *n* (%)	9 (5)	3 (3)	12
Patient decision, *n* (%)	7 (4)	3 (3)	10
Rash or allergic reaction, *n* (%)	5 (3)	3 (3)	8
Prohibited medication, *n* (%)	4 (2)	1 (1)	5
Gastrointestinal symptoms, *n* (%)	2 (1)	2 (2)	4
Incarceration, *n* (%)	2 (1)	2 (2)	4
Virologic failure, *n* (%)	0 (0)	3 (3)	3
Pregnancy, *n* (%)	1 (1)	0 (0)	1

* Percentages are taken out of the total group sample sizes.
† Between-group comparison for all patients, $P = 0.44$; for central nervous system symptoms and mood disorders, $P = 0.010$. All other comparisons are not significant.

DISCUSSION

Neurologic adverse effects associated with efavirenz affect more than 50% of patients (3) and are different from those associated with other antiretroviral drugs. To our knowledge, this report provides the largest prospective, controlled study to evaluate efavirenz neurotoxicity.

A fundamental question is whether neurologic performance suffers when efavirenz therapy is initiated. We chose to use a modest battery of quantitative tasks that tap critical domains of motor persistence, sustained attention, response speed, visuomotor coordination, and conceptual shifting and tracking. We were reassured to find that neuropsychological performance improved similarly and differences never exceeded 0.2 NPZ3 score units between groups. The practical impact of differences of less than 0.5 NPZ3 score units is negligible. Most treatment trials for cognitive impairment seek power to detect an NPZ change of 0.5 or greater to be clinically significant. Our testing was limited and did not probe some elements of neuropsychological function, including memory and learning. Improvement in performance was demonstrated in previous studies evaluating other antiretroviral therapies, including efavirenz and nevirapine (16–20). Our results demonstrated that correlations between efavirenz trough blood concentrations and decreased absolute neuropsychological performance scores were small but statistically significant at weeks 4 and 12. These results were not confirmed with change in performance or with variables estimated from a population pharmacokinetic analysis (21).

The neurologic adverse effects associated with use of efavirenz are subjective in nature, and patients may be more likely to report symptoms if they are told of the possibilities before initiating treatment. Consequently, the nature, duration, and severity of these symptoms could only be isolated in a double-blind, controlled trial such as that performed here. Previous evaluations were limited to uncontrolled or open-label studies (1, 2). In our study, the subjective questionnaire was specifically designed to amplify the descriptive areas that were previously associated with efavirenz and compare them directly with a regimen that did not contain efavirenz. This study confirms the presence of a subjective neurologic syndrome starting soon after efavirenz initiation, as well as the distinctly transient nature of this event. In most participants, symptoms resolved within the first month; the most significant symptoms were found at day 7, so maximal effects possibly occurred even earlier and were already declining by the time our measurements were made. Smaller uncontrolled observations of efavirenz-related neurologic symptoms (22, 23) showed potential residual symptoms as late as 1 year, but the interpretation of these findings is difficult in the absence of blinded control observations. *Dizziness* is a term that was volunteered in previous studies of efavirenz toxicity (22), but the descriptor is notoriously ambiguous. Our questionnaire isolated the definition of dizziness as a sensation of movement associated with a transient neurovestibular symptom complex.

The option to substitute nevirapine or to withdraw from the study complicated analysis of our results. We carefully considered these confounding factors and performed confirmatory sensitivity analyses that excluded the participants who changed or discontinued efavirenz therapy. We confirmed that a relatively small subset of individuals had significant symptoms precluding use of efavirenz. Elective substitution of nevirapine for presumed efavirenz-associated toxicity occurred almost exclusively in the groups receiving efavirenz (**Table 3**), indicating that patients and clinicians could routinely recognize unique symptoms associated with efavirenz. Our data do not fully address the possibility that efavirenz-associated neurologic events could persist or occur later in therapy, but an analysis at later time points is planned.

The presence and severity of the subjective reports of adverse effects were hypothesized to be dose-dependent; therefore, we sought to correlate symptoms with plasma efavirenz drug concentrations. One previous report suggested that the neuropsychological side effects associated with efavirenz were associated with high serum drug concentrations (24). Our more extensive data are less supportive of such a correlation. The correlation between the

change in symptom score from baseline and the plasma concentration was significant only at week 1, whereas absolute symptom scores never correlated significantly with plasma efavirenz concentrations. Higher drug levels and the transient symptoms that we noted at week 1 have more recently been associated with the *CYP2B6* haplotype, which is more common in African-American patients (25). Although some researchers have urged dose modification to address the neuropsychological symptoms (22), our data suggest that dose modification is unlikely to be helpful.

Reports of sleep-related side effects have typified the efavirenz neurologic syndrome; therefore, careful prospective analysis of these symptoms was required (23). Landovitz and colleagues (26) conducted sleep index (Pittsburgh Sleep Quality Index) evaluations of 33 participants in a nonblinded trial that was augmented by polysomnography in 8 participants. As in our study, most of their patients slept poorly at baseline, and initiation of efavirenz therapy did not result in a change of sleep status. Development of bad dreams was confirmed in our study at week 1 but did not persist. Gallego and colleagues (27) described a larger unblinded evaluation of sleep in a study comparing 18 efavirenz-treated HIV-infected participants with 13 healthy, HIV-seronegative controls. Efavirenz use was associated with longer sleep latencies and shorter duration of deep sleep, and efavirenz plasma levels were higher in patients with insomnia or reduced sleep efficiency. Our double-blind, controlled analysis failed to replicate this finding. Selection bias in the report by Gallego and colleagues could have yielded results that appeared to differ from those of our large controlled evaluation.

Physicians, concerned that preexisting psychiatric disorders may be exacerbated by use of this drug, sometimes refrain from prescribing the agent because of anecdotal reports of serious psychiatric complications (28–30). Lochet and colleagues (23) described an uncontrolled evaluation of efavirenz-treated participants who demonstrated substantial anxiety (15.5%), mood disorders (19.3%), and suicidal ideation (9.2%). To better describe these risks, we provided a controlled, systematic evaluation of the impact of efavirenz on anxiety and on depression and found no evidence that efavirenz-based regimens resulted in excess anxiety or depression. This finding was consistent with a recent retrospective report that demonstrated no significant differences in neuropsychiatric disorders between 414 participants receiving efavirenz and 320 patients receiving nevirapine (31). Although other case reports suggested psychiatric deterioration (particularly mania) with efavirenz use (32–34), this deterioration has also been reported in untreated HIV-infected patients and as being associated with other antiretroviral therapies (35, 36).

Blanch and colleagues (33) conducted an open-label study of consecutive patients who initiated efavirenz therapy to examine possible risk factors for neurotoxicity. They found that patients were more likely to report neuropsychological symptoms if they had lower educational status, fewer central nervous system symptoms at baseline, better baseline physical status, higher baseline scores on the health transition subscale of the Medical Outcomes Study, and higher somatization scores. However, this study was marred by a significant selection bias and dropout rate.

Our study has several limitations. Because efavirenz was used in more than 1 group, the investigators may not have offered the parent study to some individuals with overt psychiatric histories. The study design further complicated the interpretation of the results by allowing substitution of nevirapine for efavirenz at an investigator's discretion. Statistical sensitivity analyses were required to interpret the potential impact of drug substitution and dropout on this substudy. We also recognize that only a limited battery of neuropsychological tests was employed; a more extensive set of tests might reveal more subtle abnormalities.

Our study supports current recommendations regarding efavirenz use: Transient, subjective neurologic effects are frequently experienced but are generally not severe, and forewarned patients may safely continue the drug and anticipate that the symptoms will resolve promptly. Initiation of any therapy for HIV infection, together with the stresses of living with a serious chronic illness, requires careful patient monitoring and support, including recognition of substantial anxiety and depression. Efavirenz, however, does not need to be avoided as a treatment for patients who are experiencing significant anxiety or depression.

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Statistical expertise: D.B. Clifford, S. Evans, Y. Yang, H. Ribaudo.

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Appendix

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Appendix Figure. **Sample participant questionnaire.**

QLW0038(A5097S)/01-10-01

SUBJECT EXPERIENCE QUESTIONNAIRE

NIAID ADULT AIDS CLINICAL TRIALS GROUP

Patient Number | Date of Patient Visit (mmm dd yy)

Protocol Number: A 5 0 9 7 S | Institution Code

Form Week | Key Operator Code

INSTRUCTIONS: Please answer the following questions by placing a "✓" in the appropriate box.

A. The following questions ask about experiences you might have had during the past week including today. Please check the box that describes how much you have had **each** experience.

	(Check one.)				
	Not At All	**A Little**	**Moderately**	**Quite A Bit**	**Extremely**
1. Vivid dream?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Fever?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Being off balance?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Chills or sweats?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Restless sleep?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. New weakness or tiredness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Nightmare?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Cough?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Felt like I was going to fall over?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Cold symptoms?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Headache?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Vomiting?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Waking up a lot?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14. Diarrhea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Weird dream?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16. Abdominal pain?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17. Felt like the room was spinning?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18. Muscle pain?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19. Had hangover type drowsiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

01-10-01

SUBJECT EXPERIENCE QUESTIONNAIRE

Patient Number ☐☐ ☐☐☐☐ ☐ Date of Patient Visit ☐☐☐ ☐☐ ☐☐ (mmm dd yy)

	(Check one.)				
	Not At All	**A Little**	**Moderately**	**Quite A Bit**	**Extremely**
20. Nausea?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21. Intense dream?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22. Shortness of breath?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23. Unsteady walking?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24. Don't feel well?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25. Felt light headed?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26. Wheezing?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
27. Trouble going to sleep?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
28. Rash?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Scary dream?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Bronchitis (coughing)?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Felt like I was spinning?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Sore throat?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
33. Had feeling of uneasiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
34. Flu-like illness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
35. Other experience?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Specify [30]: _____

Language: English ☐ E

01-10-01

Date Form Keyed (DO NOT KEY): ____ / ____ / ____

Appendix Table 1. **Neuropsychological Performance**

Sensitivity Analysis	Neuropsychological *Z* Score				Change in Efavirenz Symptom Score			
	Group Receiving Efavirenz	Group Not Receiving Efavirenz	95% CI by Hodges–Lehmann Method*	Wilcoxon *P* Value	Group Receiving Efavirenz	Group Not Receiving Efavirenz	95% CI by Hodges–Lehmann Method*	Wilcoxon *P* Value
Week 1								
Observed data								
Mean (SD), *n*	0.32 (0.55)	0.34 (0.47)			6.88 (12.3)	1.23 (9.27)		
Median, *n*	0.32	0.28	–0.097 to 0.111	0.90	6	1	3 to 7	<0.001
Range, *n*	–2.15 to 2.43	–0.93 to 2.31			–26 to 59	–36 to 43		
Multiple imputation†								
Mean (SD), *n*	0.32 (0.55)	0.35 (0.50)			6.90 (12.2)	1.39 (9.36)		
Median, *n*	0.32	0.28	–0.099 to 0.114	0.90	6	1	3 to 7	<0.001
Range, *n*	–2.1 to 2.43	–0.93 to 2.32			–26 to 59	–36 to 43		
Worst case 1‡								
Mean (SD), *n*	0.26 (0.65)	0.40 (0.58)			7.73 (14.2)	0.11 (11.1)		
Median, *n*	0.30	0.29	–0.149 to 0.073	0.51	6	1	3 to 8	<0.001
Range, *n*	–2.2 to 2.43	–0.93 to 2.70			–26 to 59	–36 to 43		
Worst case 2§								
Mean (SD), *n*	0.14 (0.84)	0.44 (0.63)			9.23 (16.2)	–0.21 (11.6)		
Median, *n*	0.28	0.30	–0.214 to 0.023	0.115	6	1	4 to 9	<0.001
Range, *n*	–2.2 to 2.43	–0.93 to 2.32			–26 to 59	–36 to 43		
As treated‖								
Mean (SD), *n*	0.32 (0.55)	0.34 (0.47)			6.57 (12.2)	1.23 (9.27)		
Median, *n*	0.32	0.28	–0.103 to 0.108	0.97	5	1	2 to 7	<0.001
Range, *n*	–2.2 to 2.43	–0.93 to 2.32			–26 to 59	–36 to 43		
Best case¶								
Mean, *n*					3.80 (15.8)	3.48 (14.4)		
Median, *n*					4	1	0 to 5	0.019
Range, *n*					–36 to 59	–36 to 59		
Week 4								
Observed data								
Mean (SD), *n*	0.46 (0.64)	0.54 (0.59)			1.83 (8.75)	2.76 (10.2)		
Median, *n*	0.38	0.47	–0.178 to 0.063	0.35	2	2	–3 to 1	0.40
Range, *n*	–2.6 to 2.66	–0.63 to 2.96			–28 to 23	–38 to 39		
Multiple imputation†								
Mean (SD), *n*	0.44 (0.64)	0.56 (0.63)			1.99 (8.64)	3.04 (10.5)		
Median, *n*	0.37	0.47	–0.203 to 0.039	0.184	2	2	–3 to 1	0.45
Range, *n*	–2.6 to 2.66	–0.63 to 2.96			–28 to 23	–38 to 39		
Worst case 1‡								
Mean (SD), *n*	0.36 (0.77)	0.59 (0.69)			2.96 (12.0)	2.02 (12.6)		
Median, *n*	0.34	0.47	–0.256 to –0.003	0.045	2	2	–2 to 2	0.78
Range, *n*	–2.6 to 2.66	–0.93 to 2.7			–28 to 59	–38 to 43		
Worst case 2§								
Mean (SD), *n*	0.17 (1.09)	0.65 (0.78)			5.83 (16.9)	1.25 (12.5)		
Median, *n*	0.32	0.48	–0.337 to –0.058	0.005	2	2	–1 to 3	0.46
Range, *n*	–2.6 to 2.43	–0.63 to 2.96			–28 to 59	–38 to 39		
As treated‖								
Mean (SD), *n*	0.45 (0.64)	0.54 (0.59)			1.97 (8.73)	2.76 (10.2)		
Median, *n*	0.38	0.47	–0.179 to 0.066	0.36	2	2	–3 to 1	0.49
Range, *n*	–2.6 to 2.66	–0.63 to 2.96			–28 to 23	–38 to 39		
Week 12								
Observed data								
Mean (SD), *n*	0.46 (0.77)	0.58 (0.53)			0.24 (9.11)	0.60 (7.79)		
Median, *n*	0.40	0.50	–0.217 to 0.018	0.097	0	0	–2 to 2	0.96
Range, *n*	–6.1 to 2.83	–0.44 to 2.43			–20 to 34	–20 to 37		
Multiple imputation†								
Mean (SD), *n*	0.43 (0.76)	0.61 (0.54)			0.41 (8.96)	0.49 (7.61)		
Median, *n*	0.39	0.51	–0.256 to –0.023	0.027	0	0	–2 to 2	0.94
Range, *n*	–6.1 to 2.83	–0.44 to 2.43			–20 to 34	–20 to 37		
Worst case 1‡								
Mean (SD), *n*	0.29 (1.19)	0.62 (0.61)			1.82 (13)	–0.43 (11.1)		
Median, *n*	0.37	0.50	–0.267 to –0.018	0.008	0	0	–1 to 3	0.45
Range, *n*	–6.1 to 2.83	–0.44 to 2.43			–20 to 59	–20 to 43		
Worst case 2§								
Mean (SD), *n*	–0.26 (2.17)	0.73 (0.71)			4.65 (17.8)	–1.2 (10.8)		
Median, *n*	0.33	0.53	–0.516 to –0.178	<0.001	0	0	0 to 4	0.096
Range, *n*	–6.1 to 2.83	–0.44 to 2.43			–20 to 59	–20 to 37		

Continued on following page

Appendix Table 1—**Continued**

Sensitivity Analysis	Neuropsychological *Z* Score				Change in Efavirenz Symptom Score			
	Group Receiving Efavirenz	Group Not Receiving Efavirenz	95% CI by Hodges–Lehmann Method*	Wilcoxon *P* Value	Group Receiving Efavirenz	Group Not Receiving Efavirenz	95% CI by Hodges–Lehmann Method*	Wilcoxon *P* Value
As treated‖								
Mean (SD), *n*	0.46 (0.77)	0.58 (0.53)			0.38 (9.09)	0.60 (7.49)		
Median, *n*	0.40	0.50	–0.213 to 0.024	0.119	0	0	–2 to 2	0.93
Range, *n*	–6.1 to 2.83	–0.44 to 2.43			–20 to 34	–20 to 37		
Week 24								
Observed data								
Mean (SD), *n*	0.58 (0.62)	0.65 (0.60)			–0.94 (8.75)	–0.46 (8.13)		
Median, *n*	0.47	0.59	–0.285 to –0.441	0.26	–1	–1	–2 to 1	0.64
Range, *n*	–1.2 to 3.13	–1.2 to 2.73			–29 to 26	–21 to 22		
Multiple imputation†								
Mean (SD), *n*	0.56 (0.57)	0.63 (0.59)			–0.65 (8.83)	–0.27 (8.05)		
Median, *n*	0.51	0.58	–0.175 to 0.071	0.41	–1	0	–2 to 1	0.67
Range, *n*	–1.2 to 2.65	–1.2 to 2.73			–29 to 26	–21 to 22		
Worst case 1‡								
Mean (SD), *n*	0.49 (0.66)	0.67 (0.65)			1.48 (13.1)	–0.98 (10.8)		
Median, *n*	0.41	0.57	–0.267 to –0.018	0.026	0	–1.0	–1 to 3	0.47
Range, *n*	–1.2 to 3.13	–1.2 to 2.73			–29 to 59	–36 to 43		
Worst case 2§								
Mean (SD), *n*	0.33 (0.84)	0.87 (0.86)			6.25 (21.2)	–3.9 (13.1)		
Median, *n*	0.40	0.64	–0.516 to –0.178	<0.001	0	–1.0	1 to 6	0.011
Range, *n*	–1.2 to 3.13	–1.2 to 2.73			–29 to 59	–36 to 22		
As treated‖								
Mean (SD), *n*	0.58 (0.53)	0.65 (0.60)			–0.9 (8.77)	–0.46 (8.13)		
Median, *n*	0.50	0.59	–0.199 to 0.078	0.35	–1	–1	–2 to 1	0.67
Range, *n*	–1.2 to 2.65	–1.2 to 2.73			–29 to 26	–21 to 22		

* Confidence interval for a nonparametric measure of the difference between distributions using the methods of Hodges and Lehmann.
† Multiple imputation for missing data calculated with SAS PROC MIXED software (SAS Institute, Inc., Cary, North Carolina).
‡ For the group receiving efavirenz, missing data were imputed by the worst observed result from the particular patient at any week. If data were not available for any week, then the worst result for the group was imputed. For the group that did not receive efavirenz, missing data were imputed by the best observed result from the particular patient at any week. If data were not available for any week, then the best result for the group was imputed.
§ Missing data for the group receiving efavirenz were imputed using the worst result for the group at each week. Missing data for the group that did not receive efavirenz were imputed with the best result for the group at each week.
‖ Excludes patients who discontinued therapy. Patients were only excluded from analysis for the weeks after therapy was discontinued.
¶ Missing data (and data for patients who discontinued treatment) were imputed with the best scores for the group receiving efavirenz. Missing data (and data for patients who discontinued treatment) were imputed with the worst scores for the group that did not receive efavirenz. These analyses were only conducted for the efavirenz symptom score at week 1 because these results were the only ones that were significant.

Appendix Table 2. **Results of Sensitivity Analysis by Generalized Estimating Equation Method***

Correlation Structure	Regression Estimate
Observed data	
Exchangeable, *n*	0.1763
AR(1), *n*	0.2987
Unstructured, *n*	0.3670
Multiple imputation	
Exchangeable, *n*	0.1345
AR(1), *n*	0.2944
Unstructured, *n*	0.3548
As treated	
Exchangeable, *n*	0.1608
AR(1), *n*	0.2635
Unstructured, *n*	0.3237

* AR(1) = Autoregressive (first order) correlation structure.

Appendix Table 3. **Status and Ethnicity of Patients Requiring Modification of Treatment***

Variable	Group Receiving Efavirenz, *n* (%)	Group Not Receiving Efavirenz, *n* (%)	All Patients, *n*	Timing of Efavirenz Discontinuation, *wk*†		
				Q1	Median	Q3
Central nervous system symptoms or mood disorder						
Changed to nevirapine						
White	6 (0)	0 (0)	6	3	7.5	18
Other ethnicity	4 (0)	0 (0)	4	0.5	3	9.5
Terminated treatment						
Other ethnicity	2 (0)	0 (0)	2	1	8	15
Nonadherence						
Terminated treatment						
White	5 (0)	1 (0)	6	2	3	13
Other ethnicity	3 (0)	2 (0)	5	12	20	21
Withdrew from study						
White	1 (0)	0 (0)	1	1	1	1
Patient decision						
Changed to nevirapine						
Other ethnicity	1 (0)	0 (0)	1	29	29	29
Terminated treatment						
White	3 (0)	1 (0)	4	1	7	20
Other ethnicity	3 (0)	2 (0)	5	15	16	17
Rash or allergic reaction						
Changed to nevirapine						
White	2 (0)	1 (0)	3	1	1	3
Other ethnicity	1 (0)	0 (0)	1	3	3	3
Terminated treatment						
White	0 (0)	1 (0)	1	15	15	15
Other ethnicity	2 (0)	1 (0)	3	1	1	2
Prohibited medication						
Terminated treatment						
White	2 (0)	1 (0)	3	0	1	24
Other ethnicity	1 (0)	0 (0)	1	10	10	10
Withdrew from study						
White	1 (0)	0 (0)	1	1	1	1
Gastrointestinal symptoms						
Changed entire regimen						
White	0 (0)	1 (0)	1	9	9	9
Terminated treatment						
White	0 (0)	1 (0)	1	0	0	0
Other ethnicity	2 (0)	0 (0)	2	4	11.5	19
Incarceration						
Terminated treatment						
Other ethnicity	1 (0)	2 (0)	3	5	21	25
Withdrew from study						
Other ethnicity	1 (0)	0 (0)	1	24	24	24
Virologic failure						
Changed to nevirapine						
Other ethnicity	0 (0)	1 (0)	1	32	32	32
Changed entire regimen						
White		1 (0)	1	24	24	24
Withdrew from study						
White	0 (0)	1 (0)	1	23	23	23
Pregnancy						
Changed to nevirapine						
Other ethnicity	0 (0)	0 (0)	1	20	20	20

* Percentages are derived from total group sample sizes.
† Q1 is 25th percentile and Q3 is 75th percentile.