

Long-Term Neuropsychiatric Disorders on Efavirenz-Based Approaches

Quality of Life, Psychologic Issues, and Adherence

Carmina R. Fumaz, MA,* Jose A. Muñoz-Moreno, BS,* José Moltó, MD,* Eugènia Negredo, PhD,*
Maria José Ferrer, MA,† Guillem Sirera, PhD,† Núria Pérez-Alvarez, BS,* Guadalupe Gómez, PhD,‡
David Burger, PhD,§ and Bonaventura Clotet, PhD||

Background: Efavirenz has been associated with neuropsychiatric disorders, although little is known about its long-term toxicity.

Objective: To assess neuropsychiatric disorders and their relation to efavirenz plasma levels as well as quality of life, psychologic status, and adherence in HIV-infected patients on long-term efavirenz-based antiretroviral therapy.

Methods: Cross-sectional study comparing 60 patients on an efavirenz-based approach (EFV group) and 60 patients on a protease inhibitor-containing regimen (PI group) for at least 1 year. Adverse events, efavirenz plasma levels, quality of life, psychologic status, and adherence were assessed.

Results: The mean time on treatment was 91.1 ± 39.5 weeks in the EFV group and 119.9 ± 67.4 weeks in the PI group. Mild dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence were reported more frequently in the EFV group than in the PI group ($P < 0.05$). Forty-nine of 60 patients presented with therapeutic efavirenz plasma levels (range: 1.0–4.0 mg/L). Efavirenz plasma levels were similar in subjects with and without neuropsychiatric disorders. No

significant differences were found between the EFV group and the PI group regarding quality of life and psychologic status. Sixty percent of patients in the EFV group and 55% in the PI group reported adherence $\geq 95\%$.

Conclusions: Mild and clinically tolerable neuropsychiatric disorders may persist in patients after a mean of 2 years using an efavirenz-based approach. Quality of life and psychologic status remained good in both study groups. Interventions to enhance long-term adherence should be applied in clinical practice.

Key Words: efavirenz, long-term neuropsychiatric disorders, plasma levels, quality of life, psychologic status, adherence

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The suppression of HIV replication using highly active antiretroviral therapy seems to require the lifelong maintenance of such therapy. Chronic adherence may become deeply complicated, particularly when patients do not perceive any symptom associated with the illness¹ and when the medication needs to be taken in such a strict fashion.² Moreover, another important obstacle to proper therapeutic adherence is the presence of adverse events.³ It seems clear that antiretroviral therapy may somehow limit a patient's quality of life,^{4,5} becoming a main reason for treatment discontinuation.⁶

After the commercialization of efavirenz as a new antiretroviral drug for the control of HIV infection,⁷ its use was associated with the onset of neuropsychiatric disturbances.⁸ Such disorders are usually mild and transient and generally disappear within a few weeks.⁸ However, token cases of psychosis, major depression, and suicidal ideation have also been described.^{9,10}

With the exception of a few studies, the assessment of efavirenz toxicity has focused on the short-term follow-up.^{11,12} In our experience, 13% of patients reported persistent neuropsychiatric disorders 1 year after starting efavirenz treatment.¹³ Nevertheless, data on long-term efavirenz toxicity are still scarce.^{14,15} This study assesses the prevalence of neuropsychiatric disorders among patients taking efavirenz for more than 1 year.

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From the *Lluita contra la SIDA Foundation, HIV Unit-Germans Trias i Pujol Hospital, Autonomous University of Barcelona, Barcelona, Spain; †HIV Unit-Germans Trias i Pujol Hospital, Barcelona, Spain; ‡Statistics and Operations Research Department, Polytechnic University of Catalunya, Barcelona, Spain; §Department of Clinical Pharmacy, University Medical Centre Nijmegen, Nijmegen, The Netherlands; and ||IrsiCaixa Foundation, Hospital Germans Trias i Pujol Hospital, Barcelona, Spain.

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Reprints: Carmina R. Fumaz, Lluita contra la SIDA Foundation, Hospital Germans Trias i Pujol, Ctra. de Canyet s/n, 08916 Badalona, Barcelona, Spain (e-mail: cfumaz@ns.hugtip.scs.es).

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METHODS

Study Design, Population, and Recruitment

This is a cross-sectional comparative study performed at the outpatient HIV clinic of a university hospital. Interviews were conducted from October 2002 through May 2003.

To be eligible, patients had to have been receiving a stable efavirenz (EFV group) or a protease inhibitor–based (PI group) antiretroviral regimen for at least 1 year. Other inclusion criteria were being 18 years of age or older and the absence of current opportunistic infections or acute illnesses. Patients were not to have a previous history of depression, schizophrenia, or other psychotic or personality disorders (classified according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) and not be taking psychiatric medication at the time of recruitment to the study.

All patients meeting the inclusion criteria were approached before their visit to the clinician. They were asked to participate in the study and to be interviewed by a psychologist trained in HIV. All the subjects agreed to participate, and they gave their informed consent before enrollment.

Study Objectives

The primary end point of the study was to assess the prevalence of neuropsychiatric disorders. Secondary end points targeted determining the relation between neuropsychiatric disorders and efavirenz plasma levels and assessing patients' quality of life, psychologic status, and adherence to treatment. The relation between adherence and other significant variables was also assessed.

Measurements

Demographic and clinical variables were recorded for each patient. Adverse events within the 4 weeks before the visit were recorded by means of a structured interview described elsewhere.¹³ Fatigue and sexual dysfunction were added to the original version of the questionnaire, because both may be present in a significant proportion of HIV-infected patients according to recent literature.^{5,16,17}

Blood samples were taken between 8:00 and 9:00 AM from patients in the EFV group to determine efavirenz plasma levels. All subjects followed a treatment schedule in which efavirenz was prescribed to be taken at night. The concentration of efavirenz was determined by reverse-phase high-performance liquid chromatography using a validated method.¹⁸

Quality of life was assessed with the Medical Outcomes Study-HIV (MOS-HIV) questionnaire.¹⁹ This tool consists of 35 questions and provides information on several dimensions of health: general health perception, pain, physical functioning, role functioning, social functioning, mental health, energy/fatigue, health distress, cognitive function, quality of life, and transitory health. The MOS-HIV scores are assigned on a scale of 0 to 100, where higher scores indicate better health.

Psychologic status was evaluated with the Profile of Mood State (POMS-A), a 15-item questionnaire that measures 5 affective states (depression, vigor, anger, tension, and

fatigue) and includes a total mood disturbance score (range: –12 to 48). The total mood disturbance score is a summary of the 5 subscales, with vigor weighted negatively. The higher the total score, the greater is the degree of mood disturbance.^{20,21}

Other psychologic variables assessed were effort to follow the treatment schedule^{13,22}; self-efficacy (a person's belief about his or her perceived capacity to follow the treatment schedule)^{23,24}; and limitation as a result of adverse events, health beliefs, and worry and limitation as a result of lipodystrophy.²⁵ All these were evaluated using 10-point visual analogue scales.

Adherence was self-reported by the patients and calculated as the percentage of missing doses within the previous 2 weeks.²² Appropriate adherence was defined as the consumption of at least 95% of the medication prescribed.²⁶ Data on intake condition compliance were also registered, and a percentage was calculated with the number of doses not consumed as prescribed within the previous 2 weeks.

Statistical Analysis

Continuous variables were analyzed using the Kolmogorov-Smirnov test to assess for normal distribution. Because they did not follow a normal distribution, variables were described by median (interquartile ranges) and compared using the Mann-Whitney nonparametric test. For the discrete variables, proportions (number of patients) were given and the χ^2 or Fisher exact test (as appropriate) was used. Probability values shown in the adverse events study represent single-variable comparisons, to wit, the probability of statistical significance (0.05 confidence limit) when comparing 1 variable between 2 groups. To correct for multiple comparisons, the threshold for statistical significance of the variables tested in this study was calculated to be 0.0022 according to the Sidak or Kimball correction, where the formula is $P = 1.00 - 0.95^{(1/N)}$, with N being the number of parameters. The relation between time on treatment and adherence was assessed with the Spearman nonparametric test.

To assess the contribution of the different variables of the study to adherence (<95% or $\geq 95\%$), the statistically significant variables in the univariate analysis were included in a multivariate stepwise logistic regression model.

The estimated sample size to detect a difference in adverse event rates between groups of at least 8%¹³ included 60 patients per study arm to reach a 99% power and a 2-sided significance level of 5%.

Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL).

RESULTS

A total of 120 HIV-infected subjects met the inclusion criteria and were recruited to the study. There were no significant differences between groups with regard to baseline sociodemographic and clinical characteristics (Table 1). Patients in the PI group had been on the same regimen for a longer time ($P = 0.004$) and had a higher CD4 cell count ($P = 0.02$) than subjects in the EFV group. Nevertheless, the percentage of patients with a CD4 cell count lower than 200 cells/mm³ was similar between groups ($P = 0.67$).

TABLE 1. Baseline Sociodemographic and Clinical Characteristics of the Patients

| Characteristics | EFV Group (n = 60) | PI Group (n = 60) | P |
|-------------------------------------|-----------------------|----------------------|-------|
| Age (y)* | 41.4 (±8.05) | 39.2 (±7.7) | 0.15 |
| Sex | | | 0.54 |
| Male | 45 (75) | 42 (70) | |
| Female | 15 (25) | 18 (30) | |
| Race† | | | 1 |
| White | 58 (96.6) | 59 (98.3) | |
| Gypsy | 2 (3.3) | 1 (1.6) | |
| Job situation† | | | 0.19 |
| Employed | 33 (55) | 32 (53.3) | |
| Temporal sick leave | 4 (6.7) | 2 (3.3) | |
| Definitive sick leave | 17 (28.3) | 12 (20) | |
| Unemployed | 6 (10) | 14 (23.3) | |
| Risk population† | | | 0.82 |
| Men who have sex with men | 19 (31.7) | 18 (30) | |
| Injection drug use | 18 (30) | 17 (28.3) | |
| Heterosexual | 18 (30) | 16 (26.7) | |
| Hemophilia | 1 (1.7) | 1 (1.7) | |
| Unknown | 4 (6.7) | 8 (13.3) | |
| Years of HIV infection* | 8.7 (±5.5) | 8.9 (±3.6) | 0.68 |
| Weeks on current HAART* | 91.1 (±39.5) | 119.9 (±67.4) | 0.004 |
| CD4 count (cells/mm ³)* | 517 (±268) | 630 (±282) | 0.025 |
| Plasma HIV-1 RNA copies/mL* | 8845 (±44,533.3) | 4829 (±20,159.4) | 0.41 |
| HIV-1 RNA <80 copies/mL† | 44 (73) | 41 (68.3) | 0.58 |
| Substance abuse† | 16 (26.7) | 18 (30) | 0.68 |
| Methadone† | 6 (10) | 7 (11.7) | 0.54 |
| HCV coinfection† | 15 (25) | 21 (35) | 0.23 |
| Interferon therapy† | 1 (1.7) | 1 (1.7) | 1 |
| Lipodystrophy† | 32 (53.3) | 24 (40) | 0.14 |

*Mean (standard deviation).

†n (%).

HAART, highly active antiretroviral therapy; HCV, hepatitis C virus.

The most used protease inhibitors in the PI group were nelfinavir (35%), followed by indinavir plus ritonavir (30%) and lopinavir plus ritonavir (21%).

Central Nervous System Disorders and Other Adverse Events

Fifty-four percent of patients in the EFV group and 27% in the PI group reported that they had at least 1 neuropsychiatric disorder within the 4 weeks before the visit ($P = 0.002$). Patients in the EFV group reported a significantly higher prevalence of dizziness, sadness, mood changes, irritability, lightheadedness, nervousness, impaired concentration, abnormal dreams, and somnolence. Conversely, there were no differences with regard to other adverse events evaluated (Table 2). No patient reported irrational thoughts, hallucinations, or depersonalization.

Efavirenz Plasma Levels

Efavirenz plasma levels were determined in patients in the EFV group after an average sampling time of 12.72 ± 2.90

TABLE 2. Adverse Events in the Study Groups

| Adverse Events | EFV Group n (%) | PI Group n (%) | P |
|----------------------------|--------------------|-------------------|------------------|
| Dizziness | 13 (21.7) | 3 (5) | 0.008 |
| Nephrolithiasis | — | 4 (6.7) | 0.118 |
| Polineuropathy | 15 (25) | 11 (18.3) | 0.402 |
| Perioral paresthesia | — | 1 (1.7) | 0.999 |
| Gastrointestinal disorders | 11 (18.3) | 18 (30) | 0.122 |
| Fatigue | 22 (36.7) | 15 (25) | 0.185 |
| Difficulty in erection | 12 (20) | 11 (18.3) | 0.817 |
| Loss of libido | 14 (23.3) | 11 (18.3) | 0.530 |
| Headaches | 14 (23.3) | 8 (13.3) | 0.170 |
| Sadness | 22 (36.7) | 9 (15) | 0.008 |
| Mood changes | 16 (26.7) | 7 (11.7) | 0.041 |
| Irritability | 18 (30) | 6 (10) | 0.007 |
| Euphoria | 2 (3.3) | 1 (1.7) | 0.157 |
| Lightheadedness | 17 (28.3) | 5 (8.3) | 0.005 |
| Nervousness | 18 (30) | 7 (11.7) | 0.015 |
| Impaired concentration | 16 (26.7) | 7 (11.7) | 0.041 |
| Abnormal dreams | 29 (48.3) | 1 (1.7) | <0.001 |
| Difficulty in sleeping | 17 (28.3) | 11 (18.3) | 0.213 |
| Somnolence | 15 (25) | 6 (10) | 0.034 |
| Nausea | 9 (15) | 6 (10) | 0.427 |

Statistically significant differences in univariate comparisons between the EFV group and the PI group are shown in bold.

hours since the last dose. The concentration of efavirenz ranged from 0.64 to 6.0 mg/L. Five and 6 patients had plasma levels less than 1.0 mg/L and greater than 4.0 mg/L, respectively. Mean efavirenz plasma levels were not significantly different between subjects with (2.5 ± 1.1) and without (2.7 ± 0.7) neuropsychiatric disorders ($P = 0.66$). Similarly, there was no association between the presence of neuropsychiatric disorders and efavirenz plasma levels greater than 4.0 mg/L.

Quality of Life

There were no significant differences between groups regarding quality of life. The aspects of quality of life that patients perceived as worst were general health perceptions (EFV group: median = 50 [interquartile range: 32.5–65] vs. PI group: median = 55 [35–75]), transitory health (EFV group: median = 50 [50–75] vs. PI group: median = 50 [50–75]), mental health (EFV group: median = 68 [56–84] vs. PI group: median = 72 [56–80]), and energy/fatigue (EFV group: median = 70 [52.5–80] vs. PI group: median = 75 [55–85]). Conversely, role functioning (EFV group: median = 100 [100] vs. PI group: median = 100 [100]) and social functioning (EFV group: median = 100 [70–100] vs. PI group: median = 100 [80–100]) were the areas best perceived by the patients.

Psychologic Status

In the EFV group, the median POMS-A total score was 4 (interquartile range: –5 to 13), whereas the median score was 3 (–4 to 11) ($P = 0.9$) in the PI group. There were no differences in any of the subscales: depression (1 [0–5] vs. 1 [0–3]), vigor (7 [4–9] vs. 7 [4.5–8.5]), anger (1 [0–4] vs. 1

[0–3]), tension (3 [1–6] vs. 3 [1–5]), and fatigue (3 [1–6] vs. 3 [0–5.5]) between the EFV and PI groups, respectively.

Comparison data between groups were not statistically significant with regard to the other psychologic variables assessed: effort to follow to the treatment schedule (1 [interquartile range: 0–3] vs. 1 [0–5]), self-efficacy (10 [9–10] vs. 10 [9–10]), limitation because of adverse events (4 [2–7] vs. 4 [0–5]), health beliefs (7 [5.2–9] vs. 8 [7–10]), and worry and limitation because of lipodystrophy (8 [2.5–9] vs. 5 [2–6.7]) and 4 [0–7] vs. 3 [0–7.2]) in the EFV and PI groups, respectively.

Adherence

Median adherence in medication intake was 100 (interquartile range: 89.3–100) and 98.9 (87.1–100) ($P = 0.8$) in the EFV and PI groups, respectively, and 100 (93.3–100) and 100 (93.3–100) ($P = 0.8$) in compliance intake conditions. Sixty percent of patients in the EFV group reported an adherence $\geq 95\%$, whereas this percentage was 55% in the PI group ($P = 0.5$).

In the univariate analysis, the variables associated with adherence were age (odds ratio [OR] = 1.06, 95% confidence interval [CI]: 1.01–1.12; $P = 0.02$), substance abuse (OR = 3.13, 95% CI: 1.01–1.12; $P = 0.007$), and effort to follow the treatment schedule (OR = 0.85, 95% CI: 0.74–0.98; $P = 0.03$).

TABLE 3. Relations of the Variables Assessed in the Study and Adherence: Univariate Logistic Regression Model

| Variables | P | OR | 95% CI |
|--|-------|------|------------|
| Group of treatment | 0.45 | 1.32 | 0.63–2.76 |
| Sex | 0.67 | 1.19 | 0.52–2.70 |
| Age | 0.02 | 1.06 | 1.01–1.12 |
| Weeks on treatment | 0.38 | 0.99 | 0.99–1.003 |
| Years of diagnosis | 0.32 | 0.96 | 0.88–1.04 |
| Job situation | 0.58 | 0.75 | 0.25–2.25 |
| Substance abuse* | 0.007 | 3.13 | 1.36–7.19 |
| HCV coinfection | 0.75 | 1.13 | 0.51–2.53 |
| Interferon treatment | 0.78 | 1.46 | 0.09–24.05 |
| Methadone | 0.19 | 2.21 | 0.66–7.46 |
| Lipodystrophy symptoms | 0.37 | 0.71 | 0.34–1.49 |
| Grade of worry because of lipodystrophy | 0.73 | 0.97 | 0.82–1.14 |
| Grade of limitation because of lipodystrophy | 0.84 | 0.98 | 0.84–1.15 |
| Effort to follow treatment schedule* | 0.03 | 0.85 | 0.74–0.98 |
| Self-efficacy | 0.07 | 1.25 | 0.98–1.59 |
| Health beliefs | 0.91 | 0.99 | 0.82–1.18 |
| Presence of adverse events | 0.59 | 1.25 | 0.54–2.87 |
| Limitation because of adverse events | 0.46 | 1.06 | 0.90–1.25 |
| POMS-A total | 0.15 | 0.97 | 0.94–1.009 |
| Quality of life domain | 0.13 | 1 | 0.99–1.03 |
| Transitory health domain | 0.31 | 1 | 0.99–1.02 |

*In the multivariate analysis, only substance abuse and effort to follow treatment schedule were significantly associated with adherence.
HCV, hepatitis C virus.

A trend toward significance was found in self-efficacy (OR = 1.25, 95% CI: 0.98–1.59; $P = 0.072$; Table 3).

On considering all the patients, we observed an inverse correlation between time on treatment and adherence ($r = -0.021$), which indicated that adherence decreased when time on treatment was longer. When both groups were analyzed separately, however, this correlation was only observed in the PI group ($r = -0.118$).

In the multivariate analysis, only substance abuse (OR = 3.38, 95% CI: 1.44–7.95; $P = 0.005$) and effort to follow the treatment schedule (OR = 0.84, 95% CI: 0.73–0.97; $P = 0.022$) were predictors of adherence $\geq 95\%$.

DISCUSSION

Our results show that neuropsychiatric disorders persist in more than half of HIV-infected patients on long-term efavirenz therapy. It is important to emphasize that these neuropsychiatric disturbances are usually mild and clinically tolerable, however.

To our knowledge, information provided about efavirenz and neuropsychiatric disorders has only been based on short-term follow-up.^{11,27} These disturbances have been reported to disappear, commonly, after a few weeks.²⁸ Nevertheless, some studies have suggested the need for more prolonged monitoring among patients receiving efavirenz.¹⁴ This would make it possible to assess the real prevalence of these adverse events as well as to provide psychologic support if needed.

In our study, which compares subjects on efavirenz versus protease inhibitor–based approaches, we have observed that neuropsychiatric disorders may persist after a mean of 2 years on efavirenz therapy. As in the literature,^{8,29} abnormal dreams, sadness, irritability, nervousness, lightheadedness, and difficulty in sleeping were the most frequent adverse events reported in the EFV group. In addition, although these disturbances may be related to individual psychologic factors, the differences found between the 2 study groups leads us to consider that efavirenz may play a key role in their maintenance.

The appearance and maintenance of neuropsychiatric disorders have been related to inadequate high efavirenz plasma levels.^{30,31} Nevertheless, we found no relation between efavirenz plasma levels and the presence of neuropsychiatric disorders in this study. Moreover, most patients in our study had efavirenz plasma levels between 1.0 and 4.0 mg/L, which has been suggested as the therapeutic range for efavirenz.³⁰ A possible explanation for this discordance is the cross-sectional nature of this study. Patients who had previously discontinued efavirenz because of moderate and severe adverse events and who might have had efavirenz plasma levels greater than the upper limit of the therapeutic interval were not included in the study. This limitation should be considered, and longitudinal studies on this issue are called for.

As was previously suggested,^{5,16} an important proportion of our patients in both study groups reported fatigue. A detailed analysis of this symptom shows that several factors, such as the psychologic impact of this chronic disease on patients' emotional status, may be even more relevant than the antiretroviral therapy itself. Thus, antiretroviral treatment

should not be regarded as the sole reason for the presence of fatigue. Other disturbances commonly reported by patients in both groups included sexual dysfunction. This type of dysfunction has been associated with the use of antiretroviral agents, although, once again, HIV infection itself³² and psychologic factors may play important roles.³³

Overall, patients in both groups reported a similar good quality of life, psychologic, and health status. The effort made to follow the treatment schedule was low among our patients, and subjects perceived themselves as efficient enough to follow the treatment schedule properly. This health perception resulted in more than half of our patients being employed and able to maintain an active life at the time of this study, with the positive social and economic consequences that may be derived from this.

Just like other data on adherence in clinical practice,³⁴ only 60% of patients in the EFV group and 55% in the PI group reported an adherence $\geq 95\%$. We chose self-reporting as the method for assessing adherence because it has shown a good correlation with drug plasma levels.²² Nevertheless, although self-reporting has the advantages of simplicity, speed, and viability of use, it may overestimate real data. Thus, the low levels of adherence observed in our study might be even lower. Interestingly, we observed an inverse relation between time on treatment and levels of adherence among the patients in the PI group. As has been suggested in other studies,³⁵ time may become an important factor in preventing proper adherence to treatment, particularly when regimens include a large number of pills that are taken several times per day.³⁶ In our opinion, interventions to enhance adherence should focus not only on the beginning of therapy but throughout the maintenance period. Chronic treatments involve physical and emotional fatigue, and this may result in a dangerous relaxation in medication intake. Numerous studies have tried to establish a “stereotype” of the adherent patient. To date, however, there is only consensus on a few factors that may be associated with better compliance. Just like other studies,^{22,37} we found that the variables of younger age, substance abuse, and a greater effort to follow the treatment schedule were significantly associated with inadequate adherence.

To conclude, according to our data, neuropsychiatric disorders may persist in the long term in a significant proportion of patients on efavirenz treatment. These disturbances were mild and clinically tolerable and did not impair patients' quality of life and psychologic status. Because adherence decreased with time, interventions to enhance long-term compliance should be applied in clinical practice.

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