Dream changes following initiation of efavirenz treatment

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Introduction

Efavirenz is a potent antiretroviral drug for HIV infection but neuropsychological toxicity is reported in around 20 to 50% of patients. One of the most common effects reported is sleeping disturbances including nightmares and vivid dreams. There have been quantitative studies reported on the influence of efavirenz on sleep architecture. In most studies, a questionnaire performed after the night of the study was used to assess dream changes. Retrospective self-reports significantly underestimate current nightmare and bad dream frequency when compared to other methods. Qualitative studies focusing on the possible impact of
efavirenz on dream content are lacking. We endeavoured to assess the possible influence of efavirenz treatment on the length of dreams, the thematic of the oniric scenes and the emotional content of dreams.

### Patients and method

This was a pilot study. Ten HIV patients currently on follow-up in our clinic who consecutively started efavirenz treatment were studied before and after starting efavirenz treatment; thus, they were their own controls, a previously used design.\(^5\) Inclusion criteria were to be older than 18 years, to start efavirenz treatment for any reason and to signed informed consent form. Exclusion criteria were patients with previously known psychiatric disorders or psychiatric treatment, any neurological disorder that could influence dreaming and sleep alterations. The Ethical Hospital Institutional Committee Board approved the study.

Clinical and epidemiological variables were taken into account. All the patients fulfilled a structured questionnaire designed by one of the authors (JAP) as a general assessment of sleep disorders symptoms.\(^7\) A nocturnal polysomnogram (PSG) study was performed before starting efavirenz and within two weeks after treatment. A blood sample was obtained just before the second polysomnographic study to assess efavirenz plasma levels.

The PSG was performed recording electroencephalogram, electrocardiogram and continuous finger pulse oxymetry. Sleep stages were scored visually according to standard criteria. Standard methods of PSG recording and scoring were used and we used validated techniques previously used to evaluate dreaming.\(^8\)

We intended to study dream content of both the first and last REM sleep periods: The REM sleep period occurring after 5:00 am was considered the last REM period. We studied REM sleep because during such a sleep stage dreams are more frequently reported and remembered, and dream content is more vivid and emotional, whereas dreaming arising from other sleep stages tend to be formed by short, fragmented oniric scenes. Otherwise, nightmares are acknowledged as a REM sleep processes.

In each study subjects were awakened by calling their names 5-10 minutes after the beginning of the first and last REM sleep periods. Once fully awake, subjects were asked: “Were you dreaming?” If so, “could you please tell me what actually were you dreaming before I woke you up?” Once the patient spontaneously related the content of the dream, we asked again twice: “Do you remember anything else?”. All the questions and responses were audio taped for later analysis. After each awakening subjects were allowed to fall sleep again.

Reports, when present, were written and later analyzed by the investigators, who were unaware if the PSG was performed before or after the efavirenz treatment. To evaluate the measure of the length of the dream we counted the number of words and the number of thematic units. A new thematic unit was considered if the setting, the activity or the main character of the dream changed.\(^8\) Emotional content of the dream were classified into four categories: violent/highly anxious, moderately anxious, pleasant and neutral. Dreams were considered violent/highly anxious whenever there was verbal or physical violence in the dream or when the subject reported an awful, stressful or highly emotional situation. When subjects upon awakening were not able to remember any details of the dream in spite of thinking that they had dreamt, we considered no dream recall and number of words was scored as null.\(^8\)

We compared the dream changes before and after efavirenz in each subject. For statistical analysis we used the Wilcoxon Signed Ranks Test to compare type of emotional content, Z-test (proportions) for overall emotional content, T Test for repeated measures for number of thematic units and words, Chi-squared or Fischer as appropriate for recall rate.

### Results

Eighteen PSG were performed in ten patients; 10 underwent the first PSG and 8 the second PSG. Reasons for withdrawal during the 2\(^{nd}\) PSG were an onset of severe diarrhoea and hospital admission in one patient and laboral reasons in the other (he started a night work). The results were essentially identical when the 2 patients with incomplete follow-up were excluded from the analysis.

Eight patients were male and two female. Mean age was 38.6 (10.9) years. Mean time from HIV diagnosis to antiretroviral treatment was 2.4 (4.3) years. Only 2 patients had received previous HAART without efavirenz, and their mean time on HAART before efavirenz use was 1.04 (2.2) years (Table 1). Mean CD4 cells at baseline was 247.1 (SD 167.1) c/mL and viral load 5.0 (SD 1.6) lg10 cp/mL. No patients were taking neuropsychiatric drugs and no one had previous sleeping abnormalities. Mean time on efavirenz treatment at the 2\(^{nd}\) PSG was 10.4 (5.4) days. Plasma levels of efavirenz extracted just before the PSG study were within therapeutic range in all the patients (Table 1).

After efavirenz treatment, several symptoms were self-reported by the patients: 4 of them reported anxiety, 2 impaired concentration, 1 diurnal somnolence and 1 insomnia. Sleeping disturbances were self reported in 3 patients. No patient had depressive symptoms. Patient number 7 suffered a self limited acute confusional syndrome one day after starting efavirenz treatment. Efavirenz was not stopped and the patient fully recovered in the following 48 hours.

PSG were essentially normal in all the subjects, apart from the two provoked interruptions to ask patients for their dreams. Nine patients recalled at least one dream in the baseline study when awakened in REM sleep. One patient reported dreaming only the first night and six patients reported dreaming both nights. No patient reported dreams only the second night. There were 16

<table>
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<th>Patient number</th>
<th>Days on efavirenz treatment at 2(^{nd}) PSG</th>
<th>Plasma levels efavirenz (1-4 μg/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>12</td>
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<td>d4T + ZTC + EFV</td>
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<tr>
<td>10</td>
<td>12</td>
<td>1.17</td>
<td>ZDV + ZTC + EFV</td>
</tr>
</tbody>
</table>

Level 1-4 μg/ml is the therapeutic range of efavirenz plasma levels.
D4T: stavudine; EFV: efavirenz; TDF: tenofovir; ZDV: zidovudine; 3TC: lamivudine.
Some patients recalled just one dream: 2 awakenings (43%) in the patients without treatment, and in 6 out of 14 patients with efavirenz treatment (p = 0.024) (Table 2). Some patients recalled just one dream: 2 in the first night and 4 patients in the second night.

There were no differences in the mean number of words per dream before and after efavirenz treatment (61.9 versus 47.5, p = 0.115) but the number of thematic units was higher before efavirenz than after (16 versus 8, p = 0.442). Emotional content is described in detail in Table 2. The proportion of dreams with no neutral emotional content (either pleasant or unpleasant) was higher after efavirenz treatment: 37.5% in the first night and 66.7% in the second night.

### Discussion

In this study, surprisingly, we have not found relevant abnormalities in dream patterns in patients taking efavirenz. It is conceivable that the higher proportion of emotional dreams after efavirenz treatment underlies the perception of the effects of efavirenz on dream quality. The artificial awakening in the laboratory of the present study has undercovered a substantial number of “neutral” dreams that may have been unnoticed in other studies.

Neuropsychiatric side effects of efavirenz may be related to its plasma levels. In our series, levels of efavirenz were within the therapeutical range in all patients, showing that the drug was present at the moment of the PSG study. Besides that, none of our patients had prior neuropsychiatric abnormalities, which may explain the absence of major dreams changes.

An obvious limitation of our work is the small size and the possibility of a result by chance. This series may be underpowered to detect significant changes in dream pattern. Other reports on sleep abnormalities after efavirenz treatment evaluated by PSG have explored 10 or 18 patients, a number very similar to our study. The withdrawal adds a difficult to the correct interpretation of the data. However, repeated analysis without withdrawals showed similar results.

In conclusion, in spite of the common belief that efavirenz increases dream production, dream recall and length of dreams were lower after efavirenz treatment. The perception of a higher dream production may be due to the lower percentage of dreams with neutral emotional content. Our data suggest that dream changes after efavirenz treatment are more complex than usually considered. Further research may shed light in the complex effects of efavirenz in dreams.

### Conflict of interest

The authors declare that they do not have competing interests. The study was supported by Bristol-Myers Squibb. BMS had no role in the design, analysis, or interpretation of the study.

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### References