Infect Dis Trop Med 2017; 3 (2): e394

Anxiety, depression and sleep disturbances in HIV+ patients chronically treated with an efavirenz-based regimen

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ABSTRACT:

— ***Objective:*** Sleep disturbances have frequently been observed in HIV+ patients. Low sleep quality has also been associated with the use of Efavirenz (EFV). Anxiety and depression have also been associated with HIV infection while the weight of an association among EFV, sleep disturbances and depression is controversial. Aim of this study was to analyze the sleep quality, to describe the prevalence of anxiety and depression and to detect the presence of any association among these symptoms and sleep disturbances in a group of subjects treated with an EFV-based regimen.

— ***Patients and Methods:*** A single-center cross-sectional study was performed on 60 patients anti-HIV+ on stable EFV-based antiretroviral treatment. Self-administered, standardized questionnaires including the Pittsburg Sleep Quality Index - PSQI, the Self Rating Anxiety State SAS 054 and Beck Depression Inventory - BDI SF were administered.

— ***Results:*** 28 subjects (42.9%) reported any sleep disturbance, 13 (21.7%) nightmares, 28 (42.9%) an unrefreshed awakening. 77% of subjects referring nightmares reported to be unrefreshed at wake up (p=0.031) and a pathological score at PSQI (p=0.031) while 82.1% of them referring an unrefreshed awakening reported a pathological score at PSQI (p<0.001). Finally, reporting nightmares and unrefreshed awakening were not associated to total time of EFV exposition. 23 (38%) subjects reported anxiety, 18 (30%) depression; these symptoms don't correlate with time of exposition to EFV. 69% of subjects referring nightmares also reported anxiety (p=0.023). 64.3% and 57.1% of subjects referring unrefreshed awakening reported anxiety (p<0.001) and depression (p<0.001), respectively. The global PSQI score shows a strong correlation with SAS 054 score and BDI SF score.

— ***Conclusions:*** After a median time of five years of exposure to EFV, a high number of subjects maintain any sleep disturbances or nightmares. These symptoms could be considered an expression of persisting CNS side effects in patients treated for a long time with EFV.

— ***Keywords:*** Efavirenz, Sleep disturbances, Anxiety, Depression, HIV treatment.

INTRODUCTION

Sleep disturbances have frequently been observed in patients affected by chronic syndromes as cardiovascular diseases, pulmonary diseases, end stage renal diseases, psychiatric diseases[1-4] and HIV infection[5-11]. Low sleep quality could be detected during different stages of HIV infection although pathogenesis, at all, remains undefined. Some sleep disturbances have been associated with the use of Non-Nucleosidic Reverse Transcriptase Inhibitors (NNRTIs) as Efavirenz[12-15] or, more recently, with Integrase Inhibitors (INSTIs) as Dolutegravir[16-19]. Efavirenz (EFV) is a potent NNRTI and, for more than 15 years, has been the more used

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drug in this class; at the same time EFV has been considered for many years, the gold standard of HIV treatment and, in combination with Tenofovir (TDF) and Emtricitabine (FTC), the first one of a series of Single Tablet Regimen (STR). The more common side effects associated to EFV use are referred to Central Nervous System (CNS) as dizziness, headache, moderate neurocognitive impairment, asthenia at the wake-up, sleep disturbances as insomnia, nightmares and vivid dreams[12-15,20-29]. Generally, these symptoms are more frequent during the first weeks of treatment and show a progressive reduction along the time[21,23,24,28]; however, a variable percentage of patients reported different levels of persistence[13,14]; paradoxically, some patients develop any tolerance during the treatment and recognize the previous persistence of these symptoms just after the drug interruption[15]. Moving from these considerations, many patients, in the last years, mainly in developed country and when possible, stopped EFV switching to a more convenient and tolerated treatment[15,30-32]. Anxiety and depression have frequently been associated with different circumstances of HIV infection (diagnosis and disclosure, the beginning of the first or a new treatment, during a therapeutic failure, at the time of clinic progression)[33-40]; moreover, these conditions could interfere with the treatment, negatively modifying the therapeutic adherence and reducing the chance to obtain and maintain the virologic success[41]. It was a theme of debate if EFV could have played a role in making manifest or exacerbate some psychiatric symptoms[13,15,37,42]; conversely, it is discussed the weight of any association between these drugs and the onset of some depressive symptoms or suicidal attempts[21,22,23,37]. Different studies tried to show these associations, but methods and diagnostic criteria applied to this analysis are not always comparable[13,15,21,22,33,37,42]. Aims of this study were to analyze the sleep quality in a group of subjects in treatment with an EFV based regimen, to describe the prevalence of symptoms associated to anxiety and depression and to detect the presence of any association between these symptoms and sleep disturbances.

PATIENTS AND METHODS

Study Participants

A single-center cross-sectional study was performed on 60 consecutive patients anti-HIV+ on stable antiretroviral treatment (cART), from more than 6 months, with an EFV-based regimen. The study was authorized by local Ethics Committee. All patients gave their written informed consent prior to enrolment. Socio-demographics (age, sex, HIV transmission risk) and clinical parameters (HIV RNA viral load, CD4+ T-cell count, CDC stage, time from infection and length of antiretroviral exposure and EFV exposure) were collected from medical records at the time of test administration. All recruited patients were submitted to a series of three validated self-administered questionnaires.

Pittsburg Sleep Quality Index – PSQI

PSQI is a self-reported questionnaire[43,44] assessing sleep quality over one-month-time interval. It contains 19 self-rated questions and 5 questions rated by the bed partner, when one is available. Only the self-rated questions are included in the scoring. The 19 items are combined to form seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction) with a range score grading from 0 to 3 points. A score of 0 indicated no difficulty while a score of 3 indicated severe difficulties. The seven component score are added to compose a global score ranging from 0 to 21 points, where 0 indicated no difficulty and 21 indicated severe difficulties in all the fields. A global score higher than 5 points was considered diagnostic of sleep disturbance.

Self Rating Anxiety State SAS 054

The Self Rating Anxiety State SAS 054, a self-submitted test[45,46] exploring last week symptoms, consists of:

- 15 items exploring sympathetic symptoms (palpitations, accelerated heart rate, sweating, nausea, shortness of breath, paresthesias) and symptoms of post-traumatic stress disorders (PTSD), such as panic attacks, sleep disorders, nightmares;
- 5 items exploring the well-being status.

A score from 1 to 4 was assigned to each answer (never, sometime, frequently and always). The total raw scores range from 20 to 80. The crude score was then converted into a standard score (n + n/4 = z score). The clinical interpretation of anxiety index score is reported below: 20-44: normal range; 45-59: mild or moderate anxiety levels; 60-74: marked or severe anxiety levels; 75 and over: extreme anxiety levels. According to test procedures, we considered "anxious" all patients with a Z score $\geq$ 45 points.

Beck Depression Inventory - BDI SF

The short form of BDI (BDI-SF), originally developed by Beck et al[47] as a brief self-report rating screening test for depression for outpatient[48], comprises 13 item; each of them was scored on a 4 increasing seriousness points and explores, during the last two weeks, a range of symptoms and attitudes of depression (pessimism, distrust, self-accuse) keeping out that anxiety related. A total score ranging from 0 to 39 was computed by summing all the items values. A total score below 10 was considered normal, within 10 and 19 suggestive of mild clinical depression, within 20 and 29 of moderate depression while a more than 30 points score was associated to a severe depression.

Further symptoms including presence of nightmares and fatigue or restlessness at wake up, relevant to the assessment of CNS side effects of EFV, were extrapolated from SAS 054 and analyzed separately as additional questions. Regarding these two items, only the answers "often" and "always" were considered pathological and included in a quality score for statistical analysis.

Table 1. Epidemiological and clinical data of 60 subjects treated with an EFV-based regimen.

Sex number of cases (%)	Males Females	47 (78.3%) 13 (21.7%)
Median age (IQR) years		46 (41-51)
Risk number of cases (%)	MSM Heterosexuals Others	37 (61.6) 18 (30%) 5 (8.3)
Clinical stage CDC number of cases	CDC A CDC B CDC C	48 (80%) 5 (8.3%) 7 (11.7%)
Median time from diagnosis (IQR) years		9 (7-14)
Median time on cART (IQR) years		8 (5-14)
Median time on EFV (IQR) years		5 (3-8)
Median number of therapeutic (IQR)		2 (2-3)
HIV RNA <20 copie/ml number of cases (%)		60 (100%)
Median CD4 cell count number of cells (IQR) µl		668 (453-796)

Statistical Analysis

Categorical variables are presented as a number of cases (percentage) and were compared by the χ^2 test with Yates correction or Fisher's exact test, when appropriate. Continuous variables are expressed as median (interquartile range, IQR) and were compared by Mann-Whitney test. Correlations were performed by Spearman correlation for unpaired data. Statistical significance was defined as $p<0.05$. The primary endpoint was to evaluate the prevalence of sleep disturbance and symptoms associated to anxiety and depression in a group of subject in treatment with a regimen EFV based. The secondary endpoint was to describe the presence of any association between these symptoms and sleep disturbances.

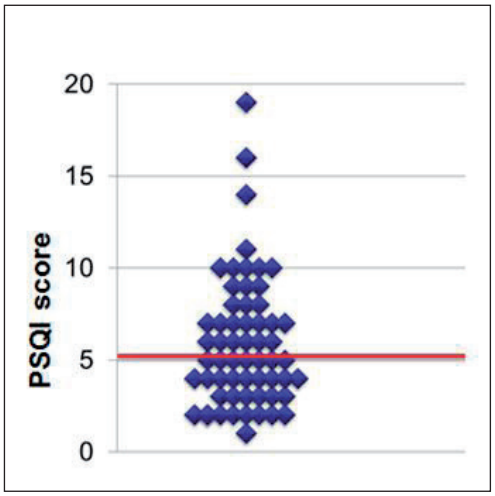

Fig. 1. Distribution of global PSQI score in 60 subjects. A global score higher than 5 points is considered diagnostic of sleep disturbances.

RESULTS

60 subjects were enrolled, 47 of them were male (78%), with a median age of 47 (IQR 42-50) years; 18 (30%) were heterosexuals, 37 (61.6%) males having sex with males (MSM). Most of them were asymptomatic (80%) with a median time from first HIV diagnosis of 97-14 years; the median length of complex antiretroviral treatment (cART) was 85-14 years, while the median time of exposition to an EFV-based treatment was 53-8 years. At enrollment, the median CD4 cell count was 668 (453-796) cells/µl; all of them had HIV RNA below 20 copies/ml. Epidemiological and clinical data of enrolled subjects are summarized in Tab. 1. 28 subjects (42.9%) reported any sleep disturbance (PSQI global score >5); data are summarized in Figure 1; moreover, 13 (21.7%) reported nightmares, while 28 subjects (42.9%) reported an unrefreshed awakening in the morning. Data on frequency of nightmares in all enrolled subjects are summarized in Figure 2. 10 (77%) out of 13 subjects

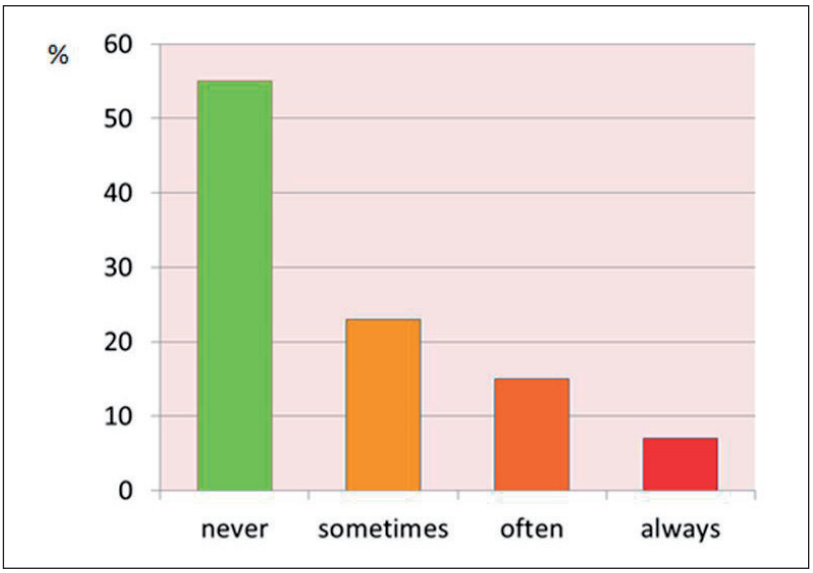

Fig. 2. Frequency of nightmares reported from 60 subjects on treatment with an EFV based regimen.

referring nightmares reported to be unrefreshed at wake up (p=0.031) and a pathological score at PSQI (p=0.031) while 23 out of 28 (82.1%) referring an unrefreshed awakening in the morning reported a pathological score at PSQI (p<0.001); eventually 100% of subjects referring nightmares and an unrefreshed awakening scored more than 5 points at PSQI (p<0.001). Finally, reporting nightmares and unrefreshed awakening wasn't associated to total time of EFV exposition (respectively p=0.6 and p=0.7). 23 (38%) patients reported symptoms associated to anxiety (z-score ≥45); arranged results for symptoms intensity are summarized in Figure 3. 18 (30%) subjects showed a score suggestive for depressive symptoms; data are summarized in Figure 4. Finally 16 (26.7%) subjects showed at the same time scores suggestive of anxiety and depression associated symptoms. Finally anxiety and depression scores do not correlate with time of exposition to EFV. 9 (69%) out of 13 subjects referring nightmares reported anxiety associated symptoms (p=0.023) while none comparable association was showed with depression (7/13, 54%; p=0.07). Respectively 18 (64.3%) and 16 out of 28 (57.1%) referring an unrefreshed awakening in the morning reported anxiety (p<0.001) and depression (p<0.001) associated symptoms. The global PSQI score do not show any correlation with years of exposition to EFV (r=0.176 p=0.18), while a strong correlation was evidenced with SAS 054 score (r= 0.530; p<0.001) and BDI SF score (r=0.499; p<0.001). SAS 054 score and BDI SF scores are mutually strongly correlated (r=0.723; p<0.001).

DISCUSSION

Many studies[22-24] have associated the EFV use with neuropsychological side effects and mood disorders; furthermore, they agree upon observing that neuropsychiatric adverse reactions associated with EFV occurred mainly during the first month of therapy, although often persisting[21-25]. In this study, after a five years median time of exposure to EFV, more than 40% of treated subjects maintain any sleep disturbance, while around 20% of analyzed patients report frequent or persistent nightmares. Most of them were hardly exposed to EFV with 25% of enrolled patients assuming these drugs for more than 7 years. Along the time, some CNS symptoms could begin a sort of habit and patients and clinicians could have underestimated this persistence, mainly when alternative treatments on single tablet regimen were unavailable[30,31]. These data confirm that for a consistent number of subjects the sleep abnormalities did not resolve after the starting weeks of treatment but remained, although in a weakened way, for years and years. The existing conditions associated to persistence or disappearance of sleep disturbances is actually unclear. Analyzing predictive factors of EFV associated neuropsychiatric adverse events, Gutierrez et al[25], after adjusting for body weight and hepatitis C virus co-infection, found that EFV plasma concentrations were the only risk factors associated with CNS toxicity. Other studies[14, 26-29] have reported that patients with high EFV concentrations are more likely to experience side effects with variable extent. We didn't analyze this aspect in our study but agree with the authors of this report moving from some anecdotic cases in our cohort. Different patients report discomfort and slowness that disappear throughout the morning, although most of them are unconscious of experience of nightmares. 77% out of subjects referring nightmares reported to be unrefreshed at wake up (p=0.031) and a pathological score at PSQI (p=0.031), while 100% of subjects reporting nightmares and an unrefreshed awakening referred sleep disturbance (p<0.001). Reported nega-

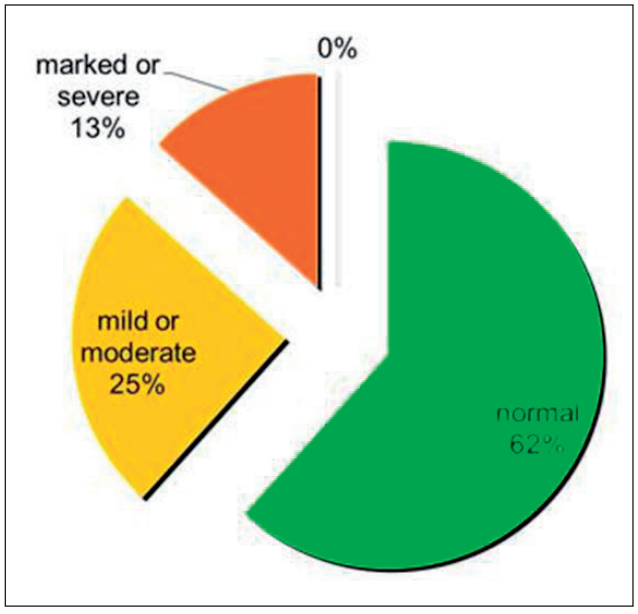

Fig. 3. Frequency of anxiety related symptoms reported from 60 subjects on treatment with an EFV based regimen.

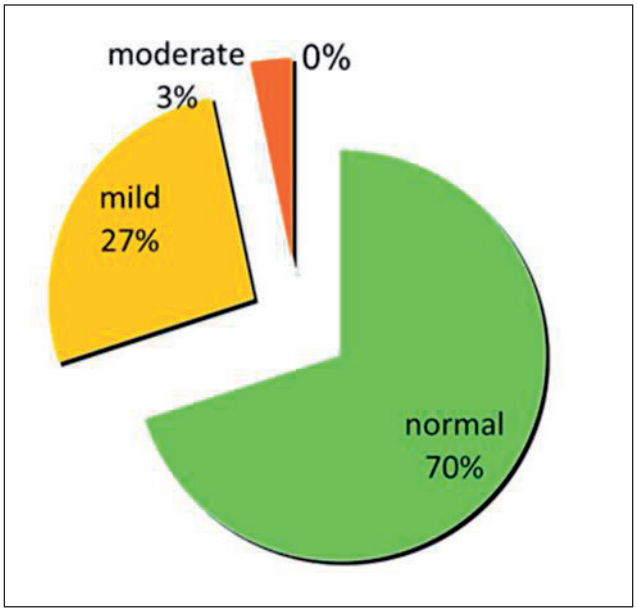

Fig. 4. Frequency of depression related symptoms reported from 60 subjects on treatment with an EFV based regimen.

tive feeling of restless syndrome at wake up and the bad sleep performances could indeed be determined by the persistence, although occasionally ignored, of nightmares. The percentage of subjects reporting anxiety-associated symptoms (38%) is comparable with another cross-sectional study performed in our outpatient unit[34], independently from the type of antiretroviral treatment used. Around a quarter of examined subjects referred the presence, at the same time, of symptoms associated with anxiety and depression. The existing relationships among HIV infection and some neurological conditions as anxiety and depression remain at all a complex issue to resolve. Subjects referring nightmares or restless syndrome showed more frequently pathological score when evaluated for depression, anxiety and sleep quality. At the same time we couldn't show any association with years of exposition to EFV: nightmares and unrefreshed awakening affect the patients independently from the length of time of exposition to the drug. At the same time it is possible that subjects with high level of CNS intolerance to EFV stopped early the treatment while patients at high-risk of neurocognitive impairment were treated with alternative regimens. All of them were naturally not included in this analysis. Therefore, the personal perception of bad quality sleep could be associated mainly to anxiety or depressive symptoms, less to time of exposition to EFV. At the same time anxiety and depression could be a consequence of exposition to EFV, although we were not able to evidence any correlation between intensity of symptoms and time of exposition to the drug. The substitution of EFV with other more tolerated drugs could determine a measurable benefit for all patients in which a therapeutic switch is possible[30-32]. In our experience, most of the patients with a low tolerance to an EFV based regimen were switched, after these evaluations, to a Rilpivirine-based treatment with a substantial advantage. Considering depressive symptoms, some authors have found no association while others found a high prevalence of depression associated with EFV use[21-25]. A Brazilian study[33] didn't show any association with depressive symptoms and EFV use, although a statistically non-significant relative risk reduction of 28% for depressive symptoms was detected among patients not using EFV. The presence of nightmares appear associated with anxiety (p=0.023) and with a pathological score at PSQI (p=0.031); none association was evidenced with depression. The personal perception of an unrefreshed awakening appears to be associated to anxiety (p<0.001) and depression symptoms (p<0.001) and to a pathological score at PSQI (p<0.001). The strict relationship existing among these neurologic symptoms and sleep disturbance is strenuously resolvable. Depression could modify the perception of the personal status, the quality of the sleep, the perception of a satisfactory rest. EFV has been associated to onset or increase of depressive symptoms and an amelioration of these conditions has been registered after the interruption of treatment. EFV has been a cornerstone treatment but perhaps, at this point, it could be time to move on.

CONCLUSIONS

We were able to show that, also after different years of exposure to EFV, a considerable number of treated subjects maintain any sleep disturbance with frequent or persistent nightmares. Moreover the strong relationship among chronic use of an EFV based regimen, anxiety and depression associated symptoms and sleep disturbance symptoms may be an expression of persisting CNS side effects. The principal biases of this study were the limited number of evaluated subjects and the absence of a control group of patients treated with others drugs than EFV. Thereafter we believe that our results, beyond to confirm the persistence for a long time of CNS side effects during an EFV treatment, could give an overview on the complex relationship existing among EFV, sleep disturbances, anxiety and depression.

Acknowledgement:
The authors thank all of the patients who were involved in this study

Funding:
No funding sources

Competing interest:
BMC received grants, travel grant and speaker honoraria from Abbvie, BMS, MSD, Gilead, Janssen-Cilag, ViiV. SAS received travel grant from BMS and Gilead. LV received travel grant from Gilead. MM received grants and speaker honoraria from BMS, MSD. MG received travel grant and speaker honoraria from BMS, MSD, Gilead, ViiV. BC received grants, travel grant and speaker honoraria from Abbvie, BMS, MSD, Gilead. LR reported no potential conflict of interest.

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