Neuropsychiatric Adverse Events During 12 Months of Treatment with Efavirenz in a Treatment-Naïve HIV-Infected Population in China: A Prospective Cohort Study

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Abstract

**Background:** Efavirenz (EFV) is a widely used antiretroviral therapy (ART), but side effect risks of neuropsychiatric adverse events (NPAEs) have not been investigated in Chinese populations receiving rapid ART.

**Methods:** This prospective cohort study assessed HIV-infected patients initiating antiretroviral treatment with EFV to determine prevalence of and factors associated with NPAEs over a 12-month follow-up period using the Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI).

**Results:** A total of 546 patients were enrolled. Prevalence of anxiety, depression, and sleep disturbances at baseline were 30.4%, 22.7%, and 68.1%, respectively. Six patients discontinued treatment due to drug related NPAEs. Treatment was associated with improvements in HADS-A, HADS-D, and PSQI scores over the 12-month follow-up, and the frequencies of patients with anxiety, depression, and sleep disturbances significantly decreased after 12 months. Abnormal baseline HADS-A, HADS-D, and PSQI scores and other factors, including high school education or lower, unemployment, divorce, and WHO III/IV stages, were associated with severe neuropsychiatric disorders over the 12 months.

**Conclusions:** These findings suggested EFV-based first-line antiretroviral therapy was well-tolerated and associated with improvements in HADS-A, HADS-D, and PSQI scores. Certain risk factors associated with neuropsychiatric disorders may be useful in identifying HIV-infected patients at higher NPAE risk.

Background

Efavirenz (EFV) is a non-nucleoside reverse-transcriptase inhibitor (NNRTI), which is widely used for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral therapy (ART)-naïve patients. The clinical use of EFV was first approved in 1998, and the 2016 World Health Organization (WHO) treatment guidelines recommended EFV be used in combination with tenofovir and lamivudine or emtricitabine as the preferred first-line ART regimen in low- and middle-income countries [1]. The clinical efficacy of EFV has been proven by several studies, supporting the idea that starting therapy with EFV induces a better virologic response, and is less frequently associated with severe adverse events than starting therapies with other regimens containing NNRTIs or protease inhibitors (PI) [2–5]. Once-daily dosing and its relatively low cost also support the use of EFV as the preferred option for initiating ART, particularly in low-income settings.

Although EFV is highly efficacious in reducing HIV viral loads, its clinical use is frequently associated with neuropsychiatric adverse events (NPAEs), including confusion, dizziness, nightmares, sleep disturbances, anxiety, and depression, as well as more severe symptoms including suicidal ideation and psychosis [6, 7]. The incidence of NPAEs upon initiation of treatment with EFV-containing regimens has been reported in 25%-40% of HIV patients [8–10]. EFV-related NPAEs occur, most commonly, within the first few days of treatment, but the incidence tends to decrease after the first month of treatment [10]. In some cases, however, these adverse events can persist for months or may not resolve at all [11]. The cellular and
molecular mechanisms responsible for EFV-induced neurotoxicity are not entirely known, though EFV induces autophagy and mitochondrial inhibition in neurons, which may lead to the central nervous system (CNS) toxicity associated with NPAEs [12, 13]. Although there are concerns about the risk of EFV-related NPAEs, a systematic review found the relative risk of discontinuation due to adverse events was higher for EFV compared to other first-line options, but the absolute differences were less than 5%, with no reported suicides [14].

Despite some risks, EFV remains one of the most widely used ART drugs in China, and its use has been recommended and supported under the “Four Frees, One Care” policy. The EFV-related NPAEs and their impact on drug adherence and quality of life still require further study; to the best of our knowledge, there is no relevant literature reporting on these NPAEs in Chinese populations. Recently, a study reported that a once-daily, reduced dose of EFV (400 mg) was associated with a lower risk of NPAEs and fewer patients stopping treatment, with no negative impact on the drug's treatment efficacy [15, 16]. Whether the use of a reduced dose is necessary in Chinese populations is unknown. Additionally, since the recommendations for rapid ART were proposed by the WHO, which supported the initiation of ART as soon as possible after confirming HIV infection, the time interval from diagnosis to the initiation of ART has been significantly shortened. It is unknown, however, what impact early treatment with EFV has on the risk of associated NPAEs.

To address these knowledge gaps, the aims of this study were to evaluate EFV-related NPAEs including anxiety, depression, and sleep disturbances over a 12 month follow-up period in Chinese patients with HIV initiating a first-line regimen containing EFV (600 mg, once daily), and to prospectively identify risk factors associated with severe NPAEs during EFV treatment. The results of this study could help clinicians gain better experience in managing NPAEs of EFV treatment.

**Methods**

**Study design**

In this prospective observational study, we recruited HIV-positive patients who received care at Youan Hospital in Beijing from July 2014 to April 2015 and were followed up for 12 months after the initiation of treatment. HIV center of Youan Hospital is one of the most important HIV/AIDS health care centers in China, where more than 8,000 HIV-infected patients on ART are followed regularly. The inclusion criteria included: 1) ART treatment-naive Chinese patients diagnosed with HIV infection; 2) at least 18 years of age; 3) had not been pregnant within the prior three months; and 4) initiated treatment with EFV (600 mg/day) + lamivudine (3TC) + tenofovir (TDF) or zidovudine (AZT) + lamivudine (3TC). Exclusion criteria included the presence of any condition that could affect the ability to complete the study questionnaires. Patients diagnosed with an ongoing psychiatric illness and those receiving pharmacological treatment for psychiatric problems were also excluded. The prescription of EFV was determined solely by the patients’ physicians according to established guidelines, with treatment administered to the patients during routine clinical practice at the hospital after enrolment.
The study was approved by the Clinical Research Ethics Committee of the Beijing Youan Hospital (LL-2019-038-K) in accordance with the tenets of the Declaration of Helsinki. All subjects provided written informed consent.

**Data collection**

The primary data were collected at baseline (M0), at two weeks (M0.5), and one (M1), three (M3), six (M6), nine (M9), and twelve months (M12) after initiation of treatment. At each time point, depression, anxiety, and sleep quality were assessed using standardized, validated self-reported measures. Sleep disturbance was evaluated using the Pittsburgh Sleep Quality Index (PSQI), and symptoms of anxiety/depression were assessed using the Hospital Anxiety and Depression Scale (HADS).

Basic demographic characteristics and clinical data were collected systematically at each timepoint by reviewing the medical records. These factors included age, sex, race, date of HIV diagnosis, stage of HIV infection based on WHO classifications, viral load, cluster of differentiation 4 (CD4) counts, and psychiatric history.

**Evaluation of sleep quality**

Sleep quality and disturbances were assessed using the Chinese version of the PSQI, a self-rated 19-item questionnaire that scores seven sleep components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the scores of each of these seven components yields one global score ranging from 0-21, with higher scores indicating poorer sleep quality; a score between five and ten indicates mild sleep disturbance, and scores over ten indicate severe sleep disturbance [17, 18]. The PSQI has been validated in the Chinese population [19].

**Evaluation of anxiety and depression**

Anxiety and depression were assessed using the Hospital Anxiety and Depression scale (HADS) developed by Zigmond and Snaith in 1983 [20]. It comprises 14 items, seven of which relate to symptoms of anxiety (HADS-A) and seven to symptoms of depression (HADS-D). Each item is scored from zero to three, with a maximum score of 21 for each scale. Frequencies of anxiety and depressive disorders were calculated using the patients’ responses to the HADS items; the total score ranges from 0-21 points for each subscale. For HADS-A and HADS-D, the score ranges represent the severity of anxiety or depression: 0–7, no anxiety or depression; 8–10, mild anxiety or depression; 11–14, moderate anxiety or depression; 15–21, severe anxiety or depression [21]. The HADS has been validated in Chinese population [22, 23].

**Statistics**

Data were expressed as means ± standard deviations, medians (quantile: 1/4–3/4), or frequencies (percentages). All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS Statistics 19.0, SPSS Inc. Chicago, USA). Parametric tests were used for continuous variables and
nonparametric tests for ordinal, categorical or nonparametric variables. Differences between two groups of data were evaluated by paired t-tests or Wilcoxon matched-pairs signed-rank tests, when appropriate. Changes in normally-distributed variables over time were evaluated by one-way analysis of variance (ANOVA) with a repeated measures design, followed by Bonferroni’s correction. The Chi-square test (or Fisher’s exact test where appropriate) was used to analyse contingency tables and to compare proportions and/or frequency distributions. Multivariate logistic regression analysis was conducted to examine associations between demographic, clinical, physiological factors, and psychological symptoms, independently. All demographic and clinical factors were included in the multivariate analyses. P < 0.05 indicated statistically significant differences. All comparisons were two-tailed.

Results

Baseline characteristics

At baseline (M0), 543 patients with HIV infection were enrolled (Fig. 1). The mean age was 35 years (SD: 11), 98.4% were male, and 91.9% were Han. The mean body mass index (BMI) was 22.5 kg/m² (SD: 4.8), and 26.8% were obese. In terms of education levels, 356 (65.6%) patients had attained a college degree or higher, 125 (23.0%) were married, 40 (7.4%) were students, and 91 (16.8%) were unemployed. Ninety-seven (17.9%) patients began treatment within a week from HIV diagnosis, and 284 (52.3%) received treatment one to four weeks after HIV diagnosis. The mean CD4+ cell count at enrolment was 335 cells/mm³ (SD: 233), and 317 (58.4%) patients had CD4+ cell counts ranging from 200 to 499 cells/mm³. The mean HIV-1 ribonucleic acid (RNA) level was 19,175 [15]copies/mL. The other clinical characteristics, complications, and laboratory indices of all HIV patients are shown in Table 1.
Table 1  
Demographic, clinical, and psychosocial characteristics of HIV patients.

| Characteristics                        | Category                      | N = 543 | %    |
|----------------------------------------|-------------------------------|---------|------|
| Sex                                    | Male                          | 532     | 97.97|
|                                        | Female                        | 11      | 2.03 |
| Age, years                             | < 30                          | 215     | 39.59|
|                                        | 30–50                         | 264     | 48.62|
|                                        | > 50                          | 64      | 11.79|
| Ethnicity                              | Han                           | 492     | 90.61|
|                                        | Others                        | 51      | 9.39 |
| Education                              | High school or lower          | 187     | 34.44|
|                                        | College or higher             | 356     | 65.56|
| Marital status                         | Married                       | 125     | 23.02|
|                                        | Divorced/separated             | 39      | 7.18 |
|                                        | Single                        | 379     | 69.80|
| Employment type                        | White-collar                  | 223     | 41.07|
|                                        | Blue-collar                   | 189     | 34.81|
|                                        | Student                       | 40      | 7.37 |
|                                        | Unemployed                    | 91      | 16.76|
| BMI                                    | < 18.5                        | 53      | 9.76 |
|                                        | 18.5–24                       | 345     | 63.54|
|                                        | 24–28                         | 108     | 19.89|
|                                        | > 28                          | 37      | 6.81 |
| Alcohol use in the past three months   | No                            | 398     | 73.30|
|                                        | Yes                           | 145     | 26.70|
| Cigarette use in the past three months | No                            | 403     | 74.22|

HIV, human immunodeficiency virus; BMI, body mass index; TB, tuberculosis; RNA, ribonucleic acid; CD4+, cluster of differentiation 4-positive; WHO, World Health Organization; cART, combination antiretroviral therapy; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine
|                               | Total participants |
|-------------------------------|--------------------|
| **Other chronic diseases**    |                    |
| Hepatitis C coinfection       | 8                  | 1.47               |
| Hepatitis B coinfection       | 33                 | 6.08               |
| TB                            | 4                  | 0.74               |
| Diabetes                      | 113                | 20.81              |
| Hypertension                  | 98                 | 18.05              |
| **Time since HIV diagnosis**  |                    |
| < 1 week                      | 97                 | 17.86              |
| 1 week- 1 month               | 284                | 52.30              |
| > 1 month                     | 162                | 29.83              |
| **Sexual transmission route** |                    |
| Homosexual/bisexual           | 494                | 90.98              |
| Heterosexual                  | 27                 | 4.97               |
| Unknown                       | 22                 | 4.05               |
| **HIV-1 RNA (copies/mL)**     |                    |
| < 100 000                     | 201                | 37.02              |
| 10000–50000                   | 169                | 31.12              |
| > 500 000                     | 173                | 31.86              |
| **CD4 + cell count, cells/ul**|                    |
| < 50                          | 37                 | 6.81               |
| 50–199                        | 90                 | 16.57              |
| 200–499                       | 317                | 58.38              |
| > 500                         | 99                 | 18.23              |
| **WHO Stage**                 |                    |
| I                             | 391                | 72.01              |
| II                            | 112                | 20.63              |
| III/IV                        | 40                 | 7.37               |
| **cART initiated**            |                    |
| TDF + 3TC + EFV               | 497                | 91.53              |
| AZT + 3TC + EFV               | 46                 | 8.47               |

HIV, human immunodeficiency virus; BMI, body mass index; TB, tuberculosis; RNA, ribonucleic acid; CD4+, cluster of differentiation 4-positive; WHO, World Health Organization; cART, combination antiretroviral therapy; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine

**Incidence of drug discontinuation**
In this study, 444 patients (81.8%) completed all assessments during the 12-month follow-up and were included in the final analysis (Fig. 1), while 99 were excluded due to lack of data throughout the whole 12-month follow-up period. A total of 51 (9.4%) patients discontinued treatment, 20 (3.7%) of which were due to EFV-related side effects, five (0.9%) were due to EFV resistance, and 26 (4.8%) were due to other causes. Of the 20 patients who discontinued treatment due to EFV-related adverse event, six (1.1%) discontinued due to NPAEs, 12 (2.2%) due to rash, one (0.2%) due to abnormal liver function, and one (0.2%) due to dyslipidaemia. In those with NPAEs, two discontinued within the first two weeks, one at one to two months, two at three to six months, and one at nine to twelve months after starting EFV treatment.

**Anxiety, depression and sleep disturbance at baseline (M0)**

The mean HADS-A and HADS-D scores of the 543 enrolled patients at M0 were 5.83 ± 4.13 and 4.94 ± 3.87, respectively. Of these, 165 (30.4%) patients had anxiety and 123 (22.7%) had depression at M0 based on the HADS-A and HADS-D scores. The mean PSQI score at M0 was 7.09 ± 3.08, and 370 (68.1%) patients were suffering from sleep disturbances.

Baseline anxiety, depression, and sleep quality scores for all 543 patients enrolled at the start of the study, the 444 patients who completed the 12-month follow-up, and the 51 patients with drug discontinuation are listed in Table 2. There were no significant differences in any M0 scores between any two of these three groups.
Table 2
Classification of the patients’ anxiety, depression and sleep quality at baseline.

| Parameter | Score          | Participants enrolled at baseline (n = 543) | Participants completing the 12-month follow-up (n = 444) | Participants with drug discontinuation (n = 51) |
|-----------|----------------|---------------------------------------------|---------------------------------------------------------|-----------------------------------------------|
|           |                | Frequency (%) | Frequency (%) | Frequency (%) |                                             |
| Anxiety   | Normal (0–7)   | 380 (70.0)   | 314 (70.7)   | 33 (64.7)     |
| Anxiety   | Mild (8–10)    | 94 (17.3)    | 73 (16.4)    | 10 (19.6)     |
| Anxiety   | Moderate       | 47 (8.7)     | 40 (9.0)     | 5 (9.8)       |
| Anxiety   | Severe (15–21) | 22 (4.1)     | 17 (3.8)     | 2 (3.9)       |
| Depression| Normal (0.7)   | 420 (77.4)   | 346 (77.9)   | 40 (78.4)     |
| Depression| Mild (8–10)    | 69 (12.7)    | 58 (13.1)    | 6 (11.8)      |
| Depression| Moderate       | 38 (7.0)     | 29 (6.5)     | 4 (7.8)       |
| Depression| Severe (15–21) | 16 (2.9)     | 11 (2.5)     | 1 (2.0)       |
| Sleep quality| Normal (0–5)  | 173 (31.9)   | 138 (31.1)   | 13 (25.5)     |
| Sleep quality| Poor sleep    | 299 (55.1)   | 253 (56.9)   | 31 (60.8)     |
| Sleep quality| Severely poor sleep | 71 (13.1) | 53 (11.9) | 7 (13.7) |

Anxiety, depression and sleep quality were assessed and categorized based on the Hospital Anxiety and Depression Scale (HADS-A, HADS-D) and the Pittsburgh Sleep Quality Index (PSQI), respectively.

HADS-D and HADS-A scores decreased over the 12-month follow-up

HADS-A and HADS-D scores steadily and significantly decreased at M0.5, M1, M3, M6, M9, and M12 compared to M0 baseline levels (Table 3, all p-values < 0.001). Based on HADS-A and HADS-D scores at M0, patients were stratified into normal M0-HADS-A (n = 314) and normal M0-HADS-D (n = 346) groups, and abnormal M0-HADS-A (n = 130) and abnormal M0-HADS-D (n = 98) groups. In both abnormal groups, the HADS-A and HADS-D scores significantly decreased at M0.5 compared to M0 (p < 0.001); scores continued to decrease until M12 (Fig. 2). In the normal group, the HADS-A and HADS-D scores were
significantly lower compared to M0 from M3 (p < 0.01) and M9 (p < 0.001) onward, respectively, reaching their lowest values by M12 (Fig. 2a,b).

Table 3
Mean differences (95% CI) and the significance of changes in HADS-A, HADS-D, and PSQI scores between each time point of follow-up versus baseline (using paired t-test with missing values excluded pairwise).

|        | HADS-A |        | HADS-D |        | PSQI |
|--------|--------|--------|--------|--------|------|
|        | mean   | 95% CI | p-value| mean   | 95% CI| p-value| mean   | 95% CI | p-value |
| M0 vs. M0.5 | 1.03 | 0.53 to 1.53 | < 0.0001 | 0.79 | 0.30 to 1.27 | < 0.0001 | 0.17 | -0.24 to 0.59 | 0.9061 |
| M0 vs. M1 | 1.46 | 0.92 to 1.99 | < 0.0001 | 0.89 | 0.39 to 1.39 | < 0.0001 | 0.64 | 0.22 to 1.06 | 0.0002 |
| M0 vs. M3 | 1.78 | 1.21 to 2.34 | < 0.0001 | 1.20 | 0.69 to 1.71 | < 0.0001 | 1.16 | 0.74 to 1.59 | < 0.0001 |
| M0 vs. M6 | 2.19 | 1.61 to 2.76 | < 0.0001 | 1.54 | 0.98 to 2.10 | < 0.0001 | 1.32 | 0.84 to 1.79 | < 0.0001 |
| M0 vs. M9 | 2.37 | 1.82 to 2.92 | < 0.0001 | 1.73 | 1.18 to 2.29 | < 0.0001 | 1.62 | 1.16 to 2.09 | < 0.0001 |
| M0 vs. M12 | 2.69 | 2.08 to 3.29 | < 0.0001 | 2.03 | 1.49 to 2.56 | < 0.0001 | 1.64 | 1.17 to 2.10 | < 0.0001 |

HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; PSQI, Pittsburgh Sleep Quality Index; CI, confidence interval; M, month.

Based on the HADS-A and HADS-D scores, the frequencies of mild anxiety and depression at M0.5 were slightly higher compared to M0 (14.2% vs. 13.1% for HADS-D, and 18.0% vs. 16.4% for HADS-A, respectively), but the differences were not statistically significant. These frequencies decreased from M1 onward, reaching their lowest values at M12 (7.9% for HADS-D and 8.6% for HADS-A). For moderate and severe anxiety, the frequencies decreased significantly at M0.5, M1, M3, M6, M9, and M12 compared to M0 (Fig. 3a, all p-values < 0.01). For moderate and severe depression, the frequencies significantly decreased at M6 and M9, respectively, compared to M0 (p < 0.01). No severe anxiety or depression scores were observed at M9 or M12 (Fig. 3a,b).

Sleep quality over the 12-month follow-up
For all 444 patients, PSQI scores significantly decreased at M1, M3, M6, M9, and M12 compared to M0 (all p-values < 0.001, Table 3). Patients were stratified into two groups based on PSQI scores at M0 into a normal M0-PSQI (n = 138) and an abnormal M0-PSQI (n = 306) group. In the abnormal M0-PSQI group, the PSQI scores decreased significantly from M0.5 onward, reaching the lowest values at M12 (Fig. 2c). However, in the normal M0-PSQI group, PSQI scores increased significantly at M0.5 compared to M0 (p < 0.0001, Fig. 2c), then continually decreased from M1 to M12, although the PSQI score at M12 was still significantly higher than baseline M0 values (p < 0.05).

The frequency of mild sleep disturbance significantly decreased from M3 onward, reaching the lowest values at M12 (p < 0.0001). The rate of severe sleep disturbance significantly decreased at M1, M3, M6, M9 and M12 compared to M0 (Fig. 3c).

**Risk factors for severe anxiety, depression, and sleep disturbances**

To overcome the negative impact of NPAEs during EFV treatment, it is necessary to identify risk factors associated with severe anxiety, depression, and sleep disturbance. In our study, 89 (20.0%), 51 (11.5%), and 54 (12.2%) patients experienced at least one episode of severe anxiety, depression, and sleep disturbance at some point during the 12-month period. In order to assess predictive factors for these severe NPAEs, univariate logistic regression was performed (Table 4). High school education or lower (p = 0.04), being a student (p = 0.003) or unemployed (p = 0.001), and WHO stages of III/IV (p = 0.004) were associated with higher probability of severe anxiety. High school education or lower (p = 0.001), being a blue-collar worker (p = 0.02), unemployed (p < 0.001), or divorced/separated (p = 0.007) were associated with severe depression. A high school education or lower (p = 0.047), being unemployed (0.008), and having a viral load > 50,000 copies/mL (p = 0.035) were associated with severely poor sleep. In addition, abnormal HADS-A, HADS-D, and PSQI scores at M0 were all associated with high probabilities of severe anxiety, depression, and sleep disturbance over the 12-month follow-up (Table 4).
Table 4
Univariate and multivariate logistic regression analyses to identify associations between demographic characteristics and severe anxiety, depression, and sleep disturbance over the 12-month follow-up period.

| Variable                  | Univariate          |         |         | Multivariate |         |         |
|---------------------------|---------------------|---------|---------|--------------|---------|---------|
|                           | OR (95% CI)         | p value | OR (95% CI) | p value      |         |         |
| **Factors for severe anxiety** |                     |         |         |              |         |         |
| Level of Education        |                     |         |         |              |         |         |
| College or higher (reference) | 1                   | 1       | 1       | 1            |         |         |
| High school or lower      | 2.07(1.03–4.15)     | 0.040   | 1.68(0.69–4.07) | 0.254     |         |         |
| Employment type           |                     |         |         |              |         |         |
| White-collar (reference)  | 1                   | 1       | 1       | 1            |         |         |
| Blue-collar               | 1.98(0.93–4.22)     | 0.076   | 2.13(0.88–5.20) | 0.095     |         |         |
| Student                   | 4.83(1.71–13.62)    | 0.003   | 6.26(1.93–20.31) | 0.002     |         |         |
| Unemployed                | 4.14(1.85–9.28)     | 0.001   | 3.4(1.29–8.92) | 0.013     |         |         |
| WHO stage                 |                     |         |         |              |         |         |
| I (reference)             | 1                   | 1       | 1       | 1            |         |         |
| II                        | 1.53(0.77–3.07)     | 0.227   | 1.58(0.73–3.45) | 0.247     |         |         |
| III/IV                    | 3.73(1.52–9.17)     | 0.004   | 4.39(0.77–6.84) | 0.007     |         |         |
| Baseline HADS-A > 7       | 5.72(3.13–10.47)    | <0.001  | 3.53(1.69–7.39) | 0.001     |         |         |
| Baseline HADS-D > 7       | 5.4(2.98–9.78)      | <0.001  | 2.71(1.28–5.71) | 0.009     |         |         |
| Baseline PSQI > 5         | 2.47(1.17–5.21)     | 0.017   | 1.43(0.62–3.31) | 0.400     |         |         |
| **Factors for severe depression** |                 |         |         |              |         |         |
| Level of Education        |                     |         |         |              |         |         |
| College or higher (reference) | 1                   | 1       | 1       | 1            |         |         |
| High school or lower      | 3.13(1.57–6.28)     | 0.001   | 1.94(0.80–4.73) | 0.144     |         |         |
| Employment                |                     |         |         |              |         |         |
| White-collar (reference)  | 1                   | 1       | 1       | 1            |         |         |
| Blue-collar               | 2.55(1.16–5.63)     | 0.020   | 2.5(0.94–6.63) | 0.065     |         |         |

OR, odds ratio; CI, confidence interval; M12, month twelve; WHO, World Health Organization; HADS-A, Hospital Anxiety and Depression Scale- Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale- Depression subscale; PSQI, Pittsburgh Sleep Quality Index.
|                          | Univariate |          | Multivariate |          |
|--------------------------|------------|----------|--------------|----------|
|                          |            | 0.280    | 0.224        |          |
| Student                  | 2.11(0.54–8.20) |        | 2.58(0.56–11.93) | 0.224    |
| Unemployed               | 5.87(2.56–13.47) | < 0.001 | 5.14(1.85–14.29) | 0.002    |
| Marital status           |            |          |              |          |
| Single (reference)       | 1          | 1        |              |          |
| Married                  | 1.87(0.97–3.63) | 0.062 | 1.28(0.57–2.91) | 0.552    |
| Divorced/separated       | 3.71(1.44–9.59) | 0.007 | 3.89(1.18–12.85) | 0.026    |
| Baseline HADS-A > 7      | 5.59(3.01–10.38) | < 0.001 | 2.45(1.13–5.30) | 0.023    |
| Baseline HADS-D > 7      | 9.25(4.91–17.42) | < 0.001 | 5.08(2.33–11.08) | < 0.001 |
| Baseline PSQI > 5        | 3.14(1.38–7.17) | 0.006 | 1.68(0.66–4.27) | 0.279    |
| Factors for severe sleep disturbance |              |          |              |          |
| Level of Education       |            |          |              |          |
| College or higher (reference) | 1          | 1        |              |          |
| High school or lower     | 1.78(0.98–3.24) | 0.047 | 1.55(0.78–3.08) | 0.211    |
| Employment               |            |          |              |          |
| White-collar (reference) | 1          | 1        |              |          |
| Blue-collar              | 1.37(0.79–2.39) | 0.260 | 1.18(0.61–2.26) | 0.626    |
| Student                  | 1.48(0.55–3.96) | 0.438 | 1.69(0.59–4.84) | 0.328    |
| Unemployed               | 2.38(1.26–4.51) | 0.008 | 1.73(0.83–3.58) | 0.143    |
| Viral load (copies/ml)   |            |          |              |          |
| ≤100,000 (reference)     | 1          | 1        |              |          |
| 10,000–50,000            | 0.95(0.52–1.75) | 0.881 | 0.99(0.52–1.89) | 0.985    |
| >50,000                  | 1.81(1.04–3.14) | 0.035 | 1.72(0.96–3.09) | 0.071    |
| Baseline HADS-A > 7      | 2.4(1.49–3.89) | < 0.001 | 1.2(0.67–2.14) | 0.543    |
| Baseline HADS-D > 7      | 3.66(2.21–6.06) | < 0.001 | 2.69(1.48–4.91) | 0.001    |
| Baseline PSQI > 5        | 4.45(2.23–8.90) | < 0.001 | 3.49(1.70–7.15) | 0.001    |

OR, odds ratio; CI, confidence interval; M12, month twelve; WHO, World Health Organization; HADS-A, Hospital Anxiety and Depression Scale- Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale- Depression subscale; PSQI, Pittsburgh Sleep Quality Index.
All factors were included in the multivariate logistic regression analysis using the forward stepwise (conditional) method, which revealed that HADS-A (M0 > 7 (p < 0.001), HADS-D (M0) > 7 (p < 0.001), being a student (p = 0.002) or unemployed (p = 0.013), and WHO stages of III/IV (p = 0.007) were independent predictive factors for severe anxiety. Being unemployed (p = 0.002), divorced/separated (p = 0.026), and scores of HADS-A (M0) > 7 and HADS-D (M0) > 7 (p < 0.001) were predictive factors associated with severe depression. HADS-D (M0) > 7 (p = 0.001) and PSQI (M0) > 5 (p = 0.001) were independent predictive factors for severe sleep disturbances (Table 4).

Risk factors for anxiety, depression and sleep disturbance 12 months after EFV treatment

As shown in Table 5, univariate and multivariate logistic regression analyses were performed to assess the risk factors associated with neuropsychiatric disorders at M12. Abnormal HADS-A, HADS-D, and PSQI scores at M0 were significant factors associated with anxiety, depression, and sleep disturbance at M12 based on univariate logistic analyses (Table 5). High school education or lower (p = 0.032), viral loads > 50,000 copies/mL (p = 0.039), and WHO stages III/IV (p = 0.031) were associated with anxiety at M12. WHO stage III/IV (p = 0.018) was associated with depression and a high school education or lower (p = 0.036) was associated with sleep disturbances at M12. Multivariate analyses revealed that HADS-A (M0) > 7 (p = 0.036), HADS-D(M0) > 7 (p = 0.040), and PSQI (M0) > 5 (p = 0.024) were independent factors associated with higher probability of anxiety, HADS-A (M0) > 7 (p = 0.021) and HADS-D(M0) > 7 (p = 0.001) were associated with depression, and HADS-A (M0) > 7 (p < 0.001) was associated with higher risk of sleep disturbance at M12.
Table 5
Logistic regression analysis to identify associations between demographic characteristics and anxiety, depression, and sleep disturbance at M12.

| Variable                          | Univariate OR (95% CI) | p value | Multivariate OR (95% CI) | p value |
|-----------------------------------|------------------------|---------|--------------------------|---------|
| **Factors for anxiety at M12**    |                        |         |                          |         |
| Level of Education                |                        |         |                          |         |
| College or above (reference)      | 1                      |         | 1                        |         |
| High school or less               | 1.246 (0.583–2.662)    | 0.040   | 1.212 (0.522–2.815)      | 0.654   |
| Viral load (copies/ml)            |                        |         |                          |         |
| ≤100,000 (reference)              | 1                      |         | 1                        |         |
| 10,000–50,000                     | 0.594 (0.256–1.378)    | 0.225   | 0.783 (0.365–1.678)      | 0.529   |
| ≥50,000                           | 1.358 (0.676–4.727)    | 0.039   | 0.451 (0.180–1.127)      | 0.088   |
| WHO stage                         |                        |         |                          |         |
| I (reference)                     | 1                      |         | 1                        |         |
| II                                | 0.628 (0.254–1.552)    | 0.313   | 0.772 (0.291–2.047)      | 0.603   |
| III/IV                            | 1.957 (0.696–5.501)    | 0.031   | 0.801 (0.248–2.590)      | 0.711   |
| Baseline HADS-A > 7               | 4.311 (2.279–8.152)    | < 0.001 | 2.267 (1.055–4.871)      | 0.036   |
| Baseline HADS-D > 7               | 3.292 (1.740–6.231)    | < 0.001 | 2.273 (1.036–4.987)      | 0.040   |
| Baseline PSQI > 5                 | 5.183 (1.818–14.774)   | 0.002   | 3.562 (1.182–10.737)     | 0.024   |

**Factors for depression at M12**

| WHO stage                         |         |         |                          |         |
| I (reference)                     | 1        |         | 1                        |         |

OR, odds ratio; CI, confidence interval; M12, month twelve; WHO, World Health Organization; HADS-A, Hospital Anxiety and Depression Scale- Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale- Depression subscale; PSQI, Pittsburgh Sleep Quality Index.
## Discussion

To our knowledge, this is the first prospective cohort study to evaluate the neuropsychiatric impact of initiating ART regimen containing EFV in HIV-infected patients in China. Our results demonstrated that:

1. In treatment-naive HIV-infected patients, the EFV-containing regimen was well-tolerated, with low risk of discontinuation due to NPAEs.
2. Statistically significant improvements in HADS-A, HADS-D, and PSQI scores of neuropsychiatric symptoms were observed over the 12-month follow-up period. The proportion of patients with abnormal HADS-A, HADS-D, and PSQI scores significantly decreased after 12 months of treatment.
3. Patients' baseline mental states and sociological factors including educational level and marital status were associated with severe neuropsychiatric disorders during the treatment period, and

### Factors for sleep disturbance at M12

| Level of Education            | Univariate       | Multivariate  |
|-------------------------------|------------------|---------------|
| College or above (reference)  | 1                | 1             |
| High school or less           | 1.578 (0.938−2.653) | 0.036  | 1.594 (0.925−2.745) | 0.093 |
| Baseline HADS-A > 7           | 2.864 (1.865−4.397) | < 0.001 | 2.635 (1.603−4.333) | < 0.001 |
| Baseline HADS-D > 7           | 1.800 (1.140−2.841) | 0.012 | 1.056 (0.615−1.813) | 0.843 |
| Baseline PSQI > 5             | 1.935 (1.283−2.920) | 0.002 | 1.497 (0.965−2.322) | 0.072 |

OR, odds ratio; CI, confidence interval; M12, month twelve; WHO, World Health Organization; HADS-A, Hospital Anxiety and Depression Scale- Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale- Depression subscale; PSQI, Pittsburgh Sleep Quality Index.
abnormal baseline HADS-A, HADS-D, and PSQI scores were risk factors for anxiety, depression, and sleep disturbance after 12 months of treatment.

HIV infection is a traumatic and stressful experience, and patients are more likely to exhibit mental health problems than the general population [24–26]. Chronic HIV infection can adversely affect CNS function, leading to HIV-associated neurocognitive disorders [27]. Among the enrolled patients in our study, there was a high rate of anxiety, depression, and sleep disturbance at baseline (30.4%, 22.7% and 68.1%, respectively), consistent with the results of other studies in China [19, 28, 29]. A systematic review in China revealed a relatively high prevalence of depression (greater than 60%) and anxiety (greater than 40%) in patients with HIV infection [30]. This high rate of neuropsychiatric problems may be related to the psychological and social circumstances associated with HIV infection in China, including the psychological burden of HIV diagnosis, the aversive symptons experienced by patients, the stigma and guilt of infection, the general prejudice and misconceptions about this disease [31], as well as the direct biological effects of viral infection [19, 32]. Therefore, although we could screen for patients presenting with a history of confirmed neuropsychiatric disease, the underlying rates of neuropsychiatric disturbances before treatment still require further study.

We found no evidence that EFV-containing regimens resulted in increased frequency of anxiety, depression, and sleep disturbance after 12-months of treatment, consistent with several studies that demonstrated no significant differences in neuropsychiatric disorders in HIV patients receiving EFV compared to other ART regimens [8, 33–35]. Although no apparent impact of EFV on neuropsychiatric symptoms was identified, we found that some patients could develop severe mental disorders during the 12-month treatment period. The subgroup with normal baseline HADS and PSQI scores showed an increased rate of anxiety, depression, and sleep disturbance at M0.5 (11%, 12%, and 13%, respectively), which may be related to the initiation of EFV treatment. These rates gradually decreased after M0.5, and there was almost no severe anxiety, depression, or sleep disorders at M12, confirming that the mental impact of EFV treatment is temporary and transient [6]. Several studies have also demonstrated that the EFV-associated NPAEs do not increase the likelihood of discontinuation, as few patients need to stop treatment [8, 35]. This is consistent with our study, as only six patients discontinued treatment due to NPAEs.

For patients who initiated ART with an EFV-containing regimen, there was a clinically meaningful improvement in neuropsychiatric symptoms based on HADS and PSQI scores over the 12-month follow-up period, possibly due to timely and effective ART. Improvement in neurological performance after effective ART has been observed in previous studies [36–38]. Successful treatments that reduced viral loads were associated with improvements in psychological distress levels [8, 34]. Another possibility could be that the patients in our study were enrolled within a relatively short time interval following HIV diagnosis, with 70.0% of patients initiating ART less than one month after diagnosis. Although these patients may suffer from the psychological burden arising from the acute trauma of the diagnosis [30] as treatment is initiated, this problem is unavoidable, as the WHO recommends early and sustained HIV treatment regardless of CD4 count. Therefore, for these patients, effective ART use and healthy support
systems may outweigh the increased probability of neuropsychiatric disorders caused by EFV-containing regimens.

Several studies have highlighted the role of underlying neuropsychiatric disorders in predicting side effects of EFV [39–41]. In our study, we found that baseline anxiety, depression, and sleep disorders were the most important predictors associated with NPAEs in patients treated with EFV. In addition, sociological factors such as education level, marital status, and employment status were also associated with severe psychological abnormalities during treatment, consistent with previous studies [42, 43]. Since HIV/AIDS has become a chronic, manageable disease with the advent of highly effective ART, mental health management is required as an integral component effective of HIV/AIDS care [44]. For patients in China, this kind of mental health education and support is often lacking; therefore, our findings suggest that in addition to assessing clinical characteristics, education and psychological support of HIV patients are also important and should be recognised by everyone.

There were several limitations to this study. The patients were only recruited from a single metropolitan city (Beijing); therefore, the findings may not be generalizable to patients from all areas of China. Further studies recruiting more representative samples are needed to validate our results in Chinese populations. The population was predominantly male, which might result in selection bias, and the psychiatric symptoms were evaluated based on patients’ self-reported scores, so the severity of these symptoms may not be accurate, which could lead to reporting bias. However, based on the widely proved HADS and PSQI scale, the limit had been minimized and the results could strictly reflect the clinical relevance.

Conclusions

EFV-based first-line antiretroviral therapy was well-tolerated, with a low risk of drug discontinuation in treatment-naïve HIV-infected patients. The prevalence of anxiety, depression, and sleep disturbances significantly decreased after EFV treatment. Some key risk factors were identified that were associated with high probability of severe NPAEs over the 12-month treatment period. These factors could be useful for identifying patients with high-risk psychiatric disorders requiring a more in-depth evaluation and access to psychiatric health services along with HIV care and support.

Declarations

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Contributions

L. S., Z. L., S. W., and L. D. conceived and designed the experiments; Y. S., Y. W., J. Y., B. S., and T. J. collected the sample information and contributed to reagents and materials; S. W., L. D., and A. L. performed the experiments; W. S., L. D., T. Z., H. W., S. M., and S. S. analyzed the data; and S. W., L. D., and S. S. wrote the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The data used in the current study are available from the corresponding author on reasonable request.

Ethics declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Clinical Research Ethics Committee of the Beijing Youan Hospital (LL-2019-038-K).

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest relevant to this article.

References

1. WHO Guidelines Approved by the Guidelines Review Committee. In: Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. edn. Edited by nd. Geneva: World Health Organization 2016.; 2016.
2. Pillay P, Ford N, Shubber Z, Ferrand RA: Outcomes for efavirenz versus nevirapine-containing regimens for treatment of HIV-1 infection: a systematic review and meta-analysis. PloS one 2013, 8(7):e68995.
3. Albrecht MA, Bosch RJ, Hammer SM, Liou SH, Kessler H, Para MF, Eron J, Valdez H, Dehlinger M, Katzenstein DA: Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. The New England journal of medicine 2001, 345(6):398-407.
4. Yeni P, Cooper DA, Aboulker JP, Babiker AG, Carey D, Darbyshire JH, Floridia M, Girard PM, Goodall RL, Hooker MH et al: Virological and immunological outcomes at 3 years after starting antiretroviral
therapy with regimens containing non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or both in INITIO: open-label randomised trial. *Lancet (London, England)* 2006, **368**(9532):287-298.

5. Ford N, Mofenson L, Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Shaffer N, Renaud F: Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS (London, England)* 2014, **28 Suppl 2**:S123-131.

6. Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV: Efavirenz and the CNS: what we already know and questions that need to be answered. *The Journal of antimicrobial chemotherapy* 2015, **70**(10):2693-2708.

7. Dalwadi DA, Ozuna L, Harvey BH, Viljoen M, Schetz JA: Adverse Neuropsychiatric Events and Recreational Use of Efavirenz and Other HIV-1 Antiretroviral Drugs. *Pharmacological reviews* 2018, **70**(3):684-711.

8. Blanch J, Martinez E, Rousaud A, Blanco JL, Garcia-Viejo MA, Peri JM, Mallolas J, De Lazzari E, De Pablo J, Gatell JM: Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. *Journal of acquired immune deficiency syndromes (1999)* 2001, **27**(4):336-343.

9. Gutierrez F, Navarro A, Padilla S, Anton R, Masia M, Borras J, Martin-Hidalgo A: Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2005, **41**(11):1648-1653.

10. Gutierrez-Valencia A, Viciana P, Palacios R, Ruiz-Valderas R, Lozano F, Terron A, Rivero A, Lopez-Cortes LF: Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. *Annals of internal medicine* 2009, **151**(3):149-156.

11. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, Gonzalez-Garcia M, Molto J, Negredo E, Clotet B: Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review. *AIDS reviews* 2009, **11**(2):103-109.

12. Funes HA, Apostolova N, Alegre F, Blas-Garcia A, Alvarez A, Marti-Cabrera M, Esplugues JV: Neuronal bioenergetics and acute mitochondrial dysfunction: a clue to understanding the central nervous system side effects of efavirenz. *The Journal of infectious diseases* 2014, **210**(9):1385-1395.

13. Purnell PR, Fox HS: Efavirenz induces neuronal autophagy and mitochondrial alterations. *The Journal of pharmacology and experimental therapeutics* 2014, **351**(2):250-258.

14. Ford N, Shubber Z, Pozniak A, Vitoria M, Doherty M, Kirby C, Calmy A: Comparative Safety and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials. *Journal of acquired immune deficiency syndromes (1999)* 2015, **69**(4):422-429.

15. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet (London, England)* 2014, **383**(9927):1474-1482.
16. Carey D, Puls R, Amin J, Losso M, Phanupak P, Foulkes S, Mohapi L, Crabtree-Ramirez B, Jessen H, Kumar S et al: Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *The Lancet Infectious diseases* 2015, **15**(7):793-802.

17. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research* 1989, **28**(2):193-213.

18. Macey PM, Woo MA, Kumar R, Cross RL, Harper RM: Relationship between obstructive sleep apnea severity and sleep, depression and anxiety symptoms in newly-diagnosed patients. *PloS one* 2010, **5**(4):e10211.

19. Huang X, Li H, Meyers K, Xia W, Meng Z, Li C, Bai J, He S, Cai W, Huang C et al: Burden of sleep disturbances and associated risk factors: A cross-sectional survey among HIV-infected persons on antiretroviral therapy across China. *Scientific reports* 2017, **7**(1):3657.

20. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta psychiatraca Scandinavica* 1983, **67**(6):361-370.

21. Christodoulou C, Michopoulos J, Tournikioti K, Douzenis A, Bouras G, Seretis D, Kontaxakis V, Lykouras L: Hospital anxiety and depression scale. A quantitative analysis in medical outpatients, psychiatric outpatients and normal subjects. *Psychiatrike = Psychiatriki* 2010, **21**(4):279-286.

22. Li Q, Lin Y, Hu C, Xu Y, Zhou H, Yang L, Xu Y: The Chinese version of hospital anxiety and depression scale: Psychometric properties in Chinese cancer patients and their family caregivers. *European journal of oncology nursing : the official journal of European Oncology Nursing Society* 2016, **25**:16-23.

23. Yang Z, Huang X, Liu X, Hou J, Wu W, Song A, Meyers K, Zhang T, Chen H, Wu H: Psychometric Properties and Factor Structure of the Chinese Version of the Hospital Anxiety and Depression Scale in People Living With HIV. *Frontiers in psychiatry* 2019, **10**:346.

24. Brandt R: The mental health of people living with HIV/AIDS in Africa: a systematic review. *African journal of AIDS research : AJAR* 2009, **8**(2):123-133.

25. Clucas C, Sibley E, Harding R, Liu L, Catalan J, Sherr L: A systematic review of interventions for anxiety in people with HIV. *Psychology, health & medicine* 2011, **16**(5):528-547.

26. Sherr L, Clucas C, Harding R, Sibley E, Catalan J: HIV and depression—a systematic review of interventions. *Psychology, health & medicine* 2011, **16**(5):493-527.

27. Lowther K, Selman L, Harding R, Higginson IJ: Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): a systematic review. *International journal of nursing studies* 2014, **51**(8):1171-1189.

28. Wang YY, Zhao J, Zhang Q, Zhang Y, Bai B, Ng CH, Ungvari GS, Jia FJ, Xiang YT: Prevalence of depressive syndrome and their association with demographic and clinical characteristics in Chinese HIV patients. *AIDS care* 2018, **30**(11):1388-1392.

29. Tao J, Vermund SH, Lu H, Ruan Y, Shepherd BE, Kipp AM, Amico KR, Zhang X, Shao Y, Qian HZ: Impact of Depression and Anxiety on Initiation of Antiretroviral Therapy Among Men Who Have Sex
with Men with Newly Diagnosed HIV Infections in China. *AIDS patient care and STDs* 2017, 31(2):96-104.

30. Niu L, Luo D, Liu Y, Silenzio VM, Xiao S: *The Mental Health of People Living with HIV in China, 1998-2014: A Systematic Review.* *PloS one* 2016, 11(4):e0153489.

31. Zhou YR: "If you get AIDS... you have to endure it alone": understanding the social constructions of HIV/AIDS in China. *Social science & medicine (1982)* 2007, 65(2):284-295.

32. Dube B, Benton T, Cruess DG, Evans DL: *Neuropsychiatric manifestations of HIV infection and AIDS.* *Journal of psychiatry & neuroscience* : *JPN* 2005, 30(4):237-246.

33. von Giesen HJ, Koller H, de Nocker D, Haslinger BA, Arendt G: *Long-term safety and efficacy of NNRTI within the central nervous system.* *HIV clinical trials* 2003, 4(6):382-390.

34. Fumaz CR, Tuldra A, Ferrer MJ, Paredes R, Bonjoch A, Jou T, Negredo E, Romeu J, Sirera G, Tural C *et al.* Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. *Journal of acquired immune deficiency syndromes (1999)* 2002, 29(3):244-253.

35. Perez-Molina JA: *Safety and tolerance of efavirenz in different antiretroviral regimens: results from a national multicenter prospective study in 1,033 HIV-infected patients.* *HIV clinical trials* 2002, 3(4):279-286.

36. Schmitt FA, Bigley JW, McKinnis R, Logue PE, Evans RW, Drucker JL: *Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex.* *The New England journal of medicine* 1988, 319(24):1573-1578.

37. Ferrando S, van Gorp W, McElhiney M, Goggin K, Sewell M, Rabkin J: *Highly active antiretroviral treatment in HIV infection: benefits for neuropsychological function.* *AIDS (London, England)* 1998, 12(8):F65-70.

38. von Giesen HJ, Koller H, Theisen A, Arendt G: *Therapeutic effects of nonnucleoside reverse transcriptase inhibitors on the central nervous system in HIV-1-infected patients.* *Journal of acquired immune deficiency syndromes (1999)* 2002, 29(4):363-367.

39. Boly L, Cafaro V, Dyner T: *Depressive symptoms predict increased incidence of neuropsychiatric side effects in patients treated with efavirenz.* *Journal of acquired immune deficiency syndromes (1999)* 2006, 42(4):514-515.

40. Journot V, Chene G, De Castro N, Rancinan C, Cassuto JP, Allard C, Vilde JL, Sobel A, Garre M, Molina JM: *Use of efavirenz is not associated with a higher risk of depressive disorders: a substudy of the randomized clinical trial ALIZE-ANRS 099.* *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2006, 42(12):1790-1799.

41. Drury A, Gleadow-Ware S, Gilfillan S, Ahrens J: *HIV and mental illness in Malawi and the neuropsychiatric sequelae of efavirenz.* *Malawi medical journal : the journal of Medical Association of Malawi* 2018, 30(1):40-45.

42. Huang X, Meyers K, Liu X, Li X, Zhang T, Xia W, Hou J, Song A, He H, Li C *et al.* The Double Burdens of Mental Health Among AIDS Patients With Fully Successful Immune Restoration: A Cross-Sectional
43. Spire B, Carrieri P, Garzot MA, L'Henaff M, Obadia Y: Factors associated with efavirenz discontinuation in a large community-based sample of patients. *AIDS care* 2004, 16(5):558-564.

44. Moskowitz JT, Carrico AW, Duncan LG, Cohn MA, Cheung EO, Batchelder A, Martinez L, Segawa E, Acree M, Folkman S: Randomized controlled trial of a positive affect intervention for people newly diagnosed with HIV. *Journal of consulting and clinical psychology* 2017, 85(5):409-423.