Pharmacodynamics of efavirenz 400mg in treatment-naïve Chinese HIV-infected patients in a prospective cohort study

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Research Article

**Keywords:** Chinese HIV-infected patients, EFV 400mg, HIV RNA load, CD4 cell counts, plasma EFV concentration, HAMD, PSQI

**DOI:** https://doi.org/10.21203/rs.3.rs-85398/v1

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Abstract

Background

The plasma concentration of efavirenz (EFV) 600mg dose was found to exceed the upper limit of proposed therapeutic window in most Chinese HIV-infected individuals, thus dosage reduction of EFV to 400mg daily warrant consideration. This study aimed at assessing the pharmacodynamics of EFV 400mg for HIV-infected patients in China.

Method

Twenty cART-naïve individuals were enrolled in this study. EFV 400mg combined with tenofovir (TDF) and lamivudine (3TC) as initial antiretroviral regimens were administered for 48 weeks. EFV concentration and T-cell subsets as well as HIV RNA load were evaluated at baseline, 4, 12, 24, 48 weeks. Moreover, the neuropsychiatric adverse effects were also assessed by Hamilton depression scale (HAMD) and Pittsburgh sleep quality index (PSQI).

Results

Eighteen males and two females whose median age was 26 (interquartile range [IQR]: 23-32) years completed 48 weeks of follow-up. The median EFV concentration was 1.88 (IQR: 1.54-2.42), 1.74 (IQR: 1.36-1.93), 1.93 (IQR: 1.66-2.22), 1.85 (IQR: 1.54-2.14) mg/L at week 4, 12, 24, 48, respectively. The viral load was 4.59 (IQR: 4.10-5.19) lg copies/mL at baseline and it decreased by 4.6 (IQR: 3.98-5.18) lg copies/mL from baseline to weeks 48. 3 of 20 (15%), 10 of 20 (50.0%), 17 of 20 (85%), 18 of 19 (95%) participants had a plasma viral load less than 50 copies/mL at weeks 4, 12, 24, 48 respectively. The median CD4 cell count was 330 (IQR: 237-410) cells/µL at baseline and it increased to 473 (IQR: 344-574) cells/µL at 48 weeks. The score of HAMD was 5 (IQR: 3-9.8), 3 (IQR: 2.25-4) at baseline and 48 weeks. And the score of PSQI was 4 (IQR: 2-5.8), 3 (IQR: 2-4) at baseline and 48 weeks. Dizziness was the most common event, occurring in 70% patients within the first two weeks of treatment.

Conclusion

Patients prescribed with EFV 400mg-containing agents demonstrated favorable virological and immunological responses. And the plasma EFV concentration was within the recommended therapeutic range with less adverse reactions. EFV 400mg was effective and safe in Chinese HIV-infected patients.

Introduction

Efavirenz (EFV) played a key role in suppressing HIV RNA replication as a nonnucleoside reverse transcriptase inhibitor (NNRTI)[1] and was recommended as the first-line treatment combined with two nucleoside reverse transcriptase inhibitors for HIV-1-infected patients by WHO in 2013[2]. However, it was reported that neuropsychiatric adverse events such as dizziness and nightmare occurred frequently in
patients prescribed with EFV, which forced many patients to replace it with other agents\textsuperscript{[3–5]}. Interestingly, plasma EFV concentration which was recommended at the range of 1–4 mg/L, was positively correlated with the occurrence of central nervous system (CNS) toxicity\textsuperscript{[6]}. Patients with EFV concentration > 4 mg/L experienced three times more frequent of CNS adverse events \textsuperscript{[7]}. Moreover, our previous multicenter study showed that median plasma EFV concentration increasing gradually over 48 weeks and 43.8% patients had EFV concentration > 4 mg/L in China\textsuperscript{[8]}. This meant that HIV-infected Chinese adults were more likely to suffer from neuropsychiatric symptoms. Although integrase strand transfer inhibitor (INSTI)-based cART had been recommended as the first-line regimen in developed countries, lamivudine (3TC), tenofovir (TDF), plus EFV were still considered as preferred regimen due to the accessibility and cost-efficiency in China. Therefore it was necessary to choose suitable dosage of EFV for Chinese patients to improve their treatment safety.

A study conducted in Netherlands had revealed that EFV dose reduction was safe in patients with high plasma concentrations and may prevent EFV discontinuations\textsuperscript{[9]}. The results of ENCORE1 study also showed that EFV 400 mg was non-inferior to EFV 600 mg with fewer EFV-related adverse events, supporting the routine use of EFV 400mg\textsuperscript{[10]}. However, it was rarely reported the pharmacodynamics of EFV 400 mg in follow-up time in HIV-1-infected patients. This prospective study recruited 20 HIV-1 infected individuals commenced on EFV 400 mg combined with TDF and 3TC as initial regimens. They were followed up for 48 weeks to assess the dynamics of plasma EFV concentrations as well as the efficacy and safety of the regimens, to optimize current treatment for HIV-1-infected Chinese patients.

**Method**

**Study population**

We performed a prospective trial from June 2017 to December 2018 at the clinics of the Department of Infectious Disease in Peking Union Medical College Hospital (PUMCH). Eligibility criteria for adult participants included: (1) HIV treatment-naïve, (2) age between 18 years or older, (3) be willing to complete the HAMD and PSQI scale and follow-up regularly, (5) not participating in other studies. The exclusion criteria were: (1) acute HIV-1-infected patients, (2) an AIDS-defining illness within 2 weeks of entry, (3) transaminase and alkaline phosphatase levels beyond three times the upper limit of the normal range, bilirubin level more than 2.5 times the upper limit of the normal range, and serum creatinine level excess 1.5 times the upper limit of the normal range, (4) pregnancy or breast feeding

**Procedures**

Participants were assessed at baseline, weeks 4, 12, 24 and 48, including clinical adverse events, physical examination and biochemical analyses. Moreover, they were asked to complete the HAMD and PSQI scale at each visit.

T-cell subsets and HIV-1 RNA determination
CD4+ T lymphocytes and CD8+ T lymphocytes were determined by flow cytometry (FACS Canto, BD Biosciences, NJ, USA) using commercially available monoclonal antibodies and plasma HIV-1 RNA load was measured using the COBAS Ampliprep/TaqMan 48 real-time RT-PCR Test (Roche, CA, USA) according to the manufacturer’s instructions. The detection range was from 20 to 1000000 copies/mL. Viral suppression was defined as plasma HIV-1 viral load below 50 copies/mL. Those who were not capable to achieve a plasma HIV-1 viral load < 200 copies/mL after 48 weeks treatment were considered as virological failure.

Plasma EFV concentrations analyses

Blood samples were collected at weeks 4, 12, 24 and 48 of EFV 400 mg treatment in the morning in Ethylenediamine-tetraacetic acid (EDTA) tubes. After centrifugation, plasma samples were transferred to and stored at -80°C until analysis. EFV was assayed in plasma samples at the Department of Pharmacy and pharmacology at PUMCH, using a validated high-performance liquid chromatography method with ultraviolet (UV) detection described in a previous study[8].

Assessment of depression and the quality of sleep

Trained clinician evaluated depression by asking patients whether had experienced the items that included in the HAMD in the prior week. Patients with score < 8 on HAMD scale were considered to be normal, patients with score 8 to 20 tended to be depressed, patients with score 20 to 35 were thought to be depressed and patients with score > 35 were severely depressed. Participants also self-administered the PSQI to evaluate sleep disturbance during the prior month. The score > 5 on PSQI was defined as sleep disturbance in this study.

Ethics statement

The Institutional Review Board of PUMCH approved this study and each participant provided written informed consent.

Statistical analysis

Analyses were performed using SPSS 23.0 (IBM Corp, Armonk, NY, United States), and statistical significance was defined as a p-values < 0.05. Descriptive statistics were presented as mean with standard deviation (SD) or median (M) with interquartile ranges (IQRs). The Student's t-test was used for parametric data and the Mann-Whitney U test was conducted for comparison of noncategorical variables. Categorical variables were analyzed by Chi-squared test or Fisher exact test. Association between continuous variables was tested using a nonparametric Spearman rank correlation test.

Results

Characteristic of study population
From a total of 169 cART-naïve patients seeking HIV care in PUMCH, 20 were eligible for this study. Reasons for exclusion were detailed in Figure 1. The baseline characteristics of patients were summarized in Table 1. The median age was 26 (IQR: 23-32) years, and median body weight was 57 (IQR: 54-60) kg. Eighteen (90.0%) were male and they were contaminated by homosexual contact. None of these patients had hepatitis B surface antigen or HCV antibody positive.

**Plasma concentrations of EFV**

Plasma sample collection time intervals were in the range of 8-20 hours after last dosage of EFV in this study. Overall, 79 samples from 20 individuals were included for analysis. Median EFV concentrations at weeks 4, 12, 24, and 48 were 1.88 (IQR: 1.54-2.42), 1.74 (IQR: 1.36-1.93), 1.93 (IQR: 1.66-2.22), 1.85 (IQR: 1.54-2.14) mg/L, respectively (Table 2). No significant difference was found in EFV concentration at any time-point ($p>0.05$), indicating there was no drug accumulation in these patients. Moreover, the EFV concentrations of 93.67% (74/79) samples were within the proposed therapeutic window of 1.0-4.0 mg/L. Only 6.33% (5/79) patients had plasma EFV concentrations < 1.0 mg/L, 0.884, 0.814, 0.916, 0.885, 0.79 mg/L, respectively. Nobody was with EFV concentrations > 4.0 mg/L (Figure 2A). When stratified by baseline body weight, patients with body weight < 60 kg had similar EFV concentrations with those with body weight > 60 kg at each study time-point (Figure 2B). Additionally, correlation analysis showed that there was no significant association between weight and EFV concentration at every study time-points (Figure 2C).

**Efficacy**

Of enrolled patients, the median HIV RNA load was 4.59 (IQR: 4.10-5.19) lg copies/mL at the baseline. As expected, the largest decrease in HIV RNA occurred during the first 24 weeks, the median decrease from baseline was 4.24 (IQR: 3.98-5.18) lg copies/mL. At 48 weeks, the median decrease from baseline was 4.6 (IQR: 3.98-5.18) lg copies/mL (Figure 3A). The proportion of participants with a viral load below 50 copies/mL were 15%(3/20), 50% (10/20), 85% (17/20), 95% (18/19) at weeks 4, 12, 24, 48 respectively (Figure 3B). Furthermore, the median CD4 cell counts were 330 (IQR: 237-411) cells/μL at baseline and it had increased by 133 (IQR: 49-223) cell/μL at weeks 48 (Figure 4A). The CD4/CD8 ratio also experienced a rising trend, from 0.37 (IQR: 0.2-0.47) at baseline to 0.68 (IQR: 0.48-0.81) at weeks 48 (Figure 4B). Specifically, three patients achieved normalization of CD4/CD8 ratio (CD4/CD8>1) at the end of follow-up.

**Adverse events**

Overall, the median scores of HAMD were 5 (IQR: 3-9.8), 3 (IQR: 2-6), 3.5 (IQR: 1.0-4.8), 3 (IQR: 2-6.5), 2 (IQR: 1-3.5) at baseline, weeks 4, weeks 12, weeks 24, weeks 48, respectively. 6 patients were likely to be depressed at baseline and the condition did not progress during the follow-up. The median scores of PSQI were 4 (IQR: 2-5.8), 3.5 (IQR: 2-5), 3 (IQR: 2.3-4.8), 3 (IQR: 1.5-6.5), 4 (IQR: 3-6) at baseline, weeks 4, weeks 12, weeks 24, weeks 48, respectively. None of them experienced poor sleep throughout the duration of follow-up (Figure 5A).
Dizziness was the most frequent symptom and one patient stopped taking EFV because of dizziness at weeks 36. Rash, abnormal dreaming, gastrointestinal occurred in 7, 5, 4 patients respectively during the 48 weeks of follow-up (Figure 5B).

White blood cell, lymphocyte, neutrophil, and platelet counts were within normal range from baseline to weeks 48 (Figure 6). Alanine aminotransferase was 88U/L in one patient and total bilirubin was 39.6 mmol/L in another patient at baseline. But both of them recovered at weeks 48.

**Discussion**

Although some literature had shown the efficiency and safety of EFV 400 mg in HIV-infected patients, it was rarely reported the dynamics of EFV 400 mg concentration by longitudinal study. In this prospective, single-arm study, we firstly demonstrated that reduced dose of EFV combined with two NRTIs as initial antiretroviral therapy maintained stable EFV concentration and was effective to suppress viral replication with less neuropsychiatric adverse events over 48 weeks in HIV-infected Chinese adults. These results provided the support for widespread use of EFV 400 mg in China, where the accessibility of INSTI was limited due to its high cost.

Our previous study had indicated that nearly half of Chinese patients who were treated with EFV 600 mg-containing cART had EFV concentrations above the upper limit of the proposed therapeutic window, especially those with body weight less than 60 kg. Nyakutira et al also showed that EFV plasma concentrations were above 4 mg/L in 50% of the patients with EFV 600 mg in Zimbabwe[11]. Based upon these findings, a dosage reduction of EFV to 400 mg seemed reasonable. In our study, we found that EFV concentration of 93.67% samples was in the recommended range. Moreover, the concentration at 48 weeks was not higher than that at 4 weeks, 12 weeks, 24 weeks, suggesting EFV reduced dose would not have drug accumulation. This characteristic was different from the results of EFV 600 mg, which showing that the concentration at 4 weeks was lower than that at 24 weeks and 48 weeks. We suspected that the half life of EFV was up to 40–80 hours[12], thus dose reduction could be beneficial for less of drug accumulation. Additionally, reduced dose concentration was not beyond 4 mg/L. While in patients who took EFV 600 mg, there were 45.28% patients whose concentration was more than 4 mg/L at 48 weeks. Taken together, these results indicted the safety of the dose reduction.

However, the concentration of three patients was less than 1 mg/L during follow-up, they all achieved fully virological suppression in the end. Laura et al proposed that EFV concentration cutoffs between 0.47 and 0.76 mg/L provided acceptable sensitivity and specificity criteria for virological failure[13]. The lowest concentration in our study was 0.79 mg/L, higher than the proposed cutoff range, suggesting that EFV concentration in our study was virologically effective.

Previous literatures also showed that weight > 60 kg was associated with lower EFV concentrations in HIV-infected patients[8,14]. In our study, weight of patients at baseline ranged from 47 to 67 kg. we found that individuals whose weight was more than 60 kg had comparable EFV concentrations to those whose
weight was less than 60 kg. Weight was not linked to the concentrations of reduced dose, suggesting 400 mg EFV dose may be appropriate across a wide weight range. But further studies are needed to confirm this result because we have not included patients with higher weight such as more than 70 kg.

At weeks 48, 96.9% HIV-infected patients treated with EFV 600 mg-containing cART had virological suppression (< 40 copies/mL)\(^{[15]}\). ENCORE1 study had revealed that 94.1% cART-naïve HIV-infected individuals achieved a viral load below 200 copies/mL in the EFV 400 mg group\(^{[10]}\). Encouragingly, in our study, 95% patients had a viral load less than 50 copies/mL and all patients were with a viral load below 200 copies/mL at 48 weeks. These consequences were similar to the above results, indicting the potency of reduced dose. Notably, we found CD4 cell counts increased by 133 (IQR: 49–223) cells/uL at weeks 48, which were higher than the counts that observed in the ENCORE1 study. The difference may be the consequence of higher baseline CD4 cell counts in our study, which was positively associated with the recovery of CD4 cell counts after cART initiation\(^{[16,17]}\). These results suggested the efficacy of EFV 400 mg and provided support for the widespread use of reduced dose in HIV-infected Chinese patients.

The common EFV related CNS adverse events was dizziness, abnormal dreams, insomnia, depression\(^{[18,19]}\). It was reported that 50% patients who were prescribed by EFV 600 mg experienced these events, which usually occurred in the first month treatment and continually existed\(^{[20,21]}\). We found that 70% (14/20), 25%(5/20) patients suffered from dizziness and abnormal dreams in the preliminary two weeks in our study, which was in agreement with previous researches\(^{[20,21]}\). After that, patients self-reported that discomfort happened less often except one patient having drug discontinuation. We assumed that it may be associated with the improved tolerance and less drug accumulation.

PSQI included 19 items questionnaire that evaluating sleep quality, duration, efficiency and so on during the prior month\(^{[22]}\). And HAMD was one of the most widely applied clinical measures of depression in psychiatric studies that had strong psychometric reliability and validity\(^{[23,24]}\). Thus we assessed the sleep quality and depression by PSQI and HAMD in this study, finding the quality of sleep in participants was satisfactory and nobody developed depression. This finding was not consistent with previous literature documenting symptoms of depression existing in 32.9% HIV-infected adults on treatment in China\(^{[25]}\). This discrepancy may be due to following reasons: First, dose reduction contributed to reduce the CNS toxicity and improve patients’ long-term tolerance. Second was associated with the availability of free antiretroviral regimens and considerate medical care in our study whereas earlier study included patients with limited medical resource.

Our study has several limitations that warrant mention. First, this is a pilot study with a limited sample size and thus, limited power. Therefore, a randomized, multicenter study is performing to further investigate the efficacy and safety of EFV 400 mg in HIV-infected individuals from China. Second, we are unable to measure the frequency of the G516T polymorphism\(^{[26–30]}\), which has been associated with higher plasma EFV concentration, among our study participants. Future studies should be conduct to
evaluate the distribution of G516T polymorphism and its effect on EFV 400 mg concentration in HIV-infected adults from China.

**Conclusion**

Our study demonstrated that EFV 400 mg-containing regimens was successful in suppressing HIV RNA replication and rebuilding immunological function in HIV-infected Chinese patients. Importantly, plasma EFV concentration remained within the normal range and CNS toxicity reduced. These results suggested the efficacy and safety of EFV 400 mg in HIV-infected individuals from China, facilitating the optimizing current treatment for these patients.

**Abbreviations**

cART: combined antiretroviral therapy; HIV: Human immunodeficiency virus; EFV: efavirenz; 3TC: lamivudine; TDF: tenofovir; HAMD: Hamilton depression scale; PSQI: Pittsburgh sleep quality index; PUMCH: Peking Union Medical College Hospital; INSTI: integrase strand transfer inhibitor

**Declarations**

**Availability of data and materials**

Datasets used in this analysis are available from the corresponding author upon request.

**Ethics approval and consent to participate**

The Ethic Committee of Peking Union Medical College Hospital approved this study and all the participant provided written informed consent.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by the National Key Technologies R&D Program for the 13th Five-year Plan (2017ZX10202101-001), the National Key Technologies R&D Program for the 12th Five-year Plan
The funding bodies played no role in the design of the study, data collection, data analysis, interpretation of data, or writing of the manuscript.

**Authors’ contributions**

LX acquired, analyzed all the data, interpreted the data and drafted the manuscript; WXP, QF, YH and TZ performed laboratory experiments; XJS, YLL and WC collected patient samples and collected clinical data; TSL designed the study, evaluated and interpreted data, obtained funding; All authors participated in the manuscript review.

**Acknowledgements**

We thank all participants for their contributions to this study and PUMCH team who established the original cohort.

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Tables

Table 1 Characteristic of enrolled patients

| Variables                              | N=20 |
|----------------------------------------|------|
| Age(years)                             | 26(23-32) |
| Men                                    | 18(90.0%) |
| Transmission                           |      |
| Homosexual contact                     | 18(90.0%) |
| Heterosexual contact                   | 2(10.0%) |
| Weight(kg)                             | 57(54-60) |
| Plasma HIV RNA (lg copies/mL)          | 4.59(4.10-5.19) |
| HIV RNA (copies/mL)                    |      |
| <10000                                 | 4(20.0%) |
| 10000-100000                           | 10(50.0%) |
| >100000                                | 6(30.0%) |
| CD4+ T cell count (cells/µL)           | 330(237-411) |
| <200                                   | 3(15.0%) |
| 200-350                                | 10(50.0%) |
| >350                                   | 7(35.0%) |
| CD8+ T cell count (cells/µL)           | 803(678-1167) |
| cART regiments                         |      |
| 3TC+TDF+EFV                            | 19(95.0%) |
| 3TC+ABC+EFV                            | 1(5.0%) |

Table 2 Median plasma EFV concentration over the 48 weeks
| Time     | N  | EFV concentration (mg/L) |
|----------|----|--------------------------|
| 4 weeks  | 20 | 1.88 (1.54-2.42)         |
| 12 weeks | 20 | 1.74 (1.36-1.93)         |
| 24 weeks | 20 | 1.93 (1.66-2.22)         |
| 48 weeks | 19 | 1.85 (1.54-2.14)         |

**Figures**

**Figure 1**

Flow of patients through the screening process

166 HIV-infected patients started cART from June, 2017 to December, 2018.

- Co-infection (N=15)
- CNS-related disease (N=1)
- WBC < 3*10^9/L (N=1)
- Choosing INSTI (N=38)
- Participating in other researches (N=5)
- NNRTI resistance at baseline (N=2)
- Rejecting to complete HAMD and PSQI (N=84)

20 patients included for analysis
**Figure 2**

The plasma EFV concentration in 79 samples (A) and patients stratified by body weight (B) and the correlation between weight and EFV concentration (C) were shown.

**Figure 3**

HIV RNA load (A) and proportion of patients who achieved virological suppression at different time-points (B).
Figure 4

The trajectory of CD4 cell counts (A) and CD4/D8 ratio during follow-up period (B)

Figure 5

The changes of score on HAMD and PSQI (A) and the number of patients with adverse events (B) during follow-up period
Figure 6

The dynamics of biochemical or haematological parameters