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Clinical study of 400mg efavirenz treatment in newly diagnosed patients with HIV/AIDS

Tongtong Yang[1], Ruifeng Zhou[1], Yuanhong He[1], Huanxia Liu[1], Zhihui Guo[1], Xia Zhao[1], Taisheng Li[2] and Shenghua He[1]*

[1]Department of Infection, Chengdu Public Health Clinical Medical Center, Chengdu, Sichuan, China
[2]Department of Infection, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Abstract: The efficacy of 400mg efavirenz (EFV) once daily is reported to be similar to that of 600mg EFV. However, EFV-related toxic and side effects of 400mg EFV are significantly reduced. Here, the feasibility of reducing EFV to 400mg once a day in HIV-infected/AIDS patients was evaluated. Fifty patients were included. Patients were given 3TC+TDF+400mg EFV (n=25) or 3TC+TDF+600mg EFV (n=25). The proportion of patients with HIV RNA < 40 copies/mL and the adverse events served as the primary and secondary outcomes, respectively. HIV inhibition rates of the 3TC+TDF+400mg EFV group and 3TC+TDF+600mg EFV group were both 56.52% at week 24 and respectively 100%, 91.3% at week 48. During 48 weeks, 27 cases of adverse events were reported in the 3TC+TDF+400mg EFV group, lower than those in the 3TC+TDF+600mg EFV group, which had 39 cases. Compared with the 3TC+TDF+400mg EFV group, the incidence of transaminase, dizziness, hyperlipidemia and rashes all increased in the 3TC+TDF+600mg EFV group (P>0.05). No serious adverse events of the central nervous system occurred. The incidence of depression, sleep disturbance, and vertigo were similar (P>0.05). The efficacy of 400mg EFV is comparable to 600mg EFV. However, patients receiving 400mg EFV have fewer adverse events.

Keywords: HIV, AIDS, antiviral therapy, efavirenz.

INTRODUCTION

Combinational antiretroviral therapy (cART) is currently the only effective treatment for HIV infection / AIDS (World Health Organization, 2019, The European AIDS Clinical Society Panel, 2019, Department of Health and Human Services (DHHS), 2019). The cART strategy combining one core drug and two nucleoside-reverse-transcriptase inhibitors is widely recommended. Efavirenz (EFV) is the first-line cART drug recommended by Chinese guidelines. However, its side effects have always been an important issue in the clinic. The common adverse effects include skin rash (8.9-12.28%), liver injury (13.8-16.14%), and central nervous system symptoms (38.71-84.21%) (AIDS Hepatitis C Section of the Infectious Diseases Branch of the Chinese Medical Association, Chinese Center for Disease Control and Prevention, 2018, Fang, 2018, Zou *et al*., 2015, Liu *et al*., 2018). These side effects will affect the safety of cART, and thereby reduce the compliance of patients, which is one of the main causes of treatment failure (Yang *et al*., 2018, Shubber *et al*., 2016, Sidebottom *et al*., 2018).

There is a close relationship between blood drug concentration, drug efficacy and adverse effects. At present, the recognized optimal therapeutic concentration of EFV is 1-4 mg/L. Conversely, the blood concentration of EFV varies among different populations, which may be related to the distribution of CYP2B6 genotypes among different ethnic groups (Peng *et al*., 2018). Studies have shown that the blood drug concentration of EFV in Chinese AIDS patients is relatively high (Li, 2018, Guo *et al*., 2018, Zhao *et al*., 2019). In addition, there is a significant correlation between body weight ≤60kg and body mass index ≤22Kg/m^2 with EFV blood concentration higher than 4mg/L (Zhao *et al*., 2019). In recent years, a growing body of research has demonstrated that low-dose EFV is as effective as the standard dosage of 600 mg in the treatment of viral infections (Kaboggoza *et al*., 2019, Sinxadi *et al*., 2016, Li *et al*., 2019, Amariles *et al*., 2019, Rojas *et al*., 2016, Huang *et al*., 2020). Moreover, the adverse effects of low-dose EFV are also significantly reduced (Kaboggoza *et al*., 2019, Sinxadi *et al*., 2016, Li *et al*., 2019, Amariles *et al*., 2019, Rojas *et al*., 2016, Huang *et al*., 2020). In China, the latest guidelines have recommended the use of 400mg low-dose EFV for patients weighing <60kg ((DHHS)). However, these latest guidelines have not been issued at the beginning of this study and low-dose EFV in Chinese adults with HIV/AIDS has been rarely used till 2020.

Here, we conducted a prospective study to assess the safety and efficacy of low-dose (400mg) EFV in Chinese patients. We analyzed the viral suppression rate and adverse events of patients with newly dragonized HIV infection / AIDS who were treated with different doses of EFV for cART. The study findings could serve as a reference for optimizing the cART.

**Corresponding author:* e-mail: 13198552429@163.com

MATERIALS AND METHODS

Patients and experimental design

This prospective study was part of a national multi-center clinical trial conducted from November 01, 2018 to April 30, 2019. This trial was registered on ClinicalTrials.gov (NCT04463784). Chengdu Public Health Clinical Medical Center was one of the sub-centers of the trial and had undertaken the enrollment and follow-up of 50 subjects. Thus, these 50 subjects, who were adult HIV-infected/ AIDS patients receiving cART treatment from November 2018 to April 2019, were enrolled. The inclusion criteria were: 1) male or female patients aged 18-65 years old, 2) HIV-1 antibody positive by ELISA and confirmed by Western Blot, 3) patients signed the informed consent and could be followed up, 4) patients had not previously undergone cART treatment. The exclusion criteria were: 1) HIV patients with acute infection, 2) patients with opportunistic infection of HIV or AIDS-related malignancies, 3) patients with obvious abnormalities in blood routine results, or liver and kidney function (grade 2 and above), 4) creatinine clearance < 60 mL/min, 5) pregnancy or lactation, 6) drug users, 7) severe mental and neurological diseases, 8) history of alcoholism, and 9) Severe peptic ulcer. The 50 included patients were randomly allocated into the 3TC+TDF+ 400mgEFV group (n=25) (given EFV 400 mg in combination with tenofovir (TDF) and lamivudine (3TC)) and 3TC+TDF+600mgEFV group (n=25) (given EFV 600 mg in combination with tenofovir (TDF) and lamivudine (3TC)). In the 3TC+TDF+400mgEFV group, 18 subjects had body weights below 60 kg.

Follow-up

The follow-up was conducted at 24 and 48 weeks after treatment, respectively. At each follow-up, a clinical evaluation was performed, including the evaluation of skin rash, jaundice, nausea, diarrhea, dizziness, dreaminess, mood disorders and whether there are new infections or other abnormal manifestations, etc. All the scale evaluations were conducted by trained clinical researchers. The scales included dizziness handicap inventory (DHI), Pittsburgh sleep quality index (PAQI), and Hamilton Depression Scale (HAMD). During the follow-up, if the patient changed the treatment plan due to drug resistance or other problems, the patient was considered a withdrawal case.

Data collection

The data of patients on the day of drug delivery were considered as the baseline data. Basic clinical data included demographic data, vital signs, symptoms and signs, other diseases, history of opportunistic infections, combined medication, medication status, etc. The drug-related adverse effects included: 1) Skin rash, central nervous system adverse effects, and digestive system adverse effects, 2) Depression, which was determined by HAMD (≥8 points), 3) Sleep disorders determined by the PAQI (≥11 points), 4) Abnormal laboratory indicators were evaluated by the "Severity Rating table for AIDS-Related Adverse Reaction Time Severity Version 2.0 (2014)".

Outcome measurement

The proportion of patients with HIV RNA <40 copies/mL at 4/12/24/48 weeks was the primary outcome. The secondary outcome measurement was the incidence of adverse events and serious adverse events.

Ethical approval

All patients provided written informed consent. The Ethics Committee of Chengdu Public Health Clinical Medical Center approved this study (No.JS-1431).

STATISTICAL ANALYSIS

All data were statistically analyzed using SPSS 26.0. Normally distributed measurement data were presented as mean ± SD and compared using Student's t-test. Non-normally distributed data were described by median (M) and interquartile range (IQR) and analyzed by rank sum test. The χ^2 test or Fisher's exact test analyzed the count data, which was presented as frequency and rate. Statistical significance was indicated when $P<0.05$.

RESULTS

Baseline data of patients

Table 1 displays the baseline data of patients. The average age of the enrolled fifty patients was (29.74±7.97) years. Among them, there were 48 males (96%). The body mass index was (21.62±2.64) kg/m^2. Among them, 36 patients (72%) were infected by homosexual contact. The median time of patients from the diagnosis of HIV infection to the start of ART was 38 days. Among them, 46% of patients received ART within 30 days after detection of HIV infection, but 30% of patients did not receive ART within 90 days after detection of HIV infection. The baseline $CD4^+$ T lymphocyte was 260cells/μL, and the baseline HIV RNA was 3.6×10^4 copies/mL. Specifically, the randomization and follow-up of 50 patients are shown in fig. 1. At the time of grouping, it is worth noting that the demographic characteristics, laboratory test results (except WBC and BUN), and scale rating scores (except depression scores) were similar between the two groups (table 1) ($P > 0.05$).

Primary outcome measurement

Of the 50 patients, 46 patients were followed up for 4/12/24 weeks and received HIV RNA detection, and 45 patients were followed up for 48 weeks and received HIV RNA detection (table 2). The results showed that in different EFV treatment groups, the HIV inhibition rates were all 56.52% at week 24 and 100% (3TC+TDF+ 400mgEFV) and 91.3% (3TC+TDF+600mgEFV) at week 48, respectively (fig. 2). The above results suggest a similar antiviral efficacy of low-dose (400mg) EFV to that of the standard dose (600mg).

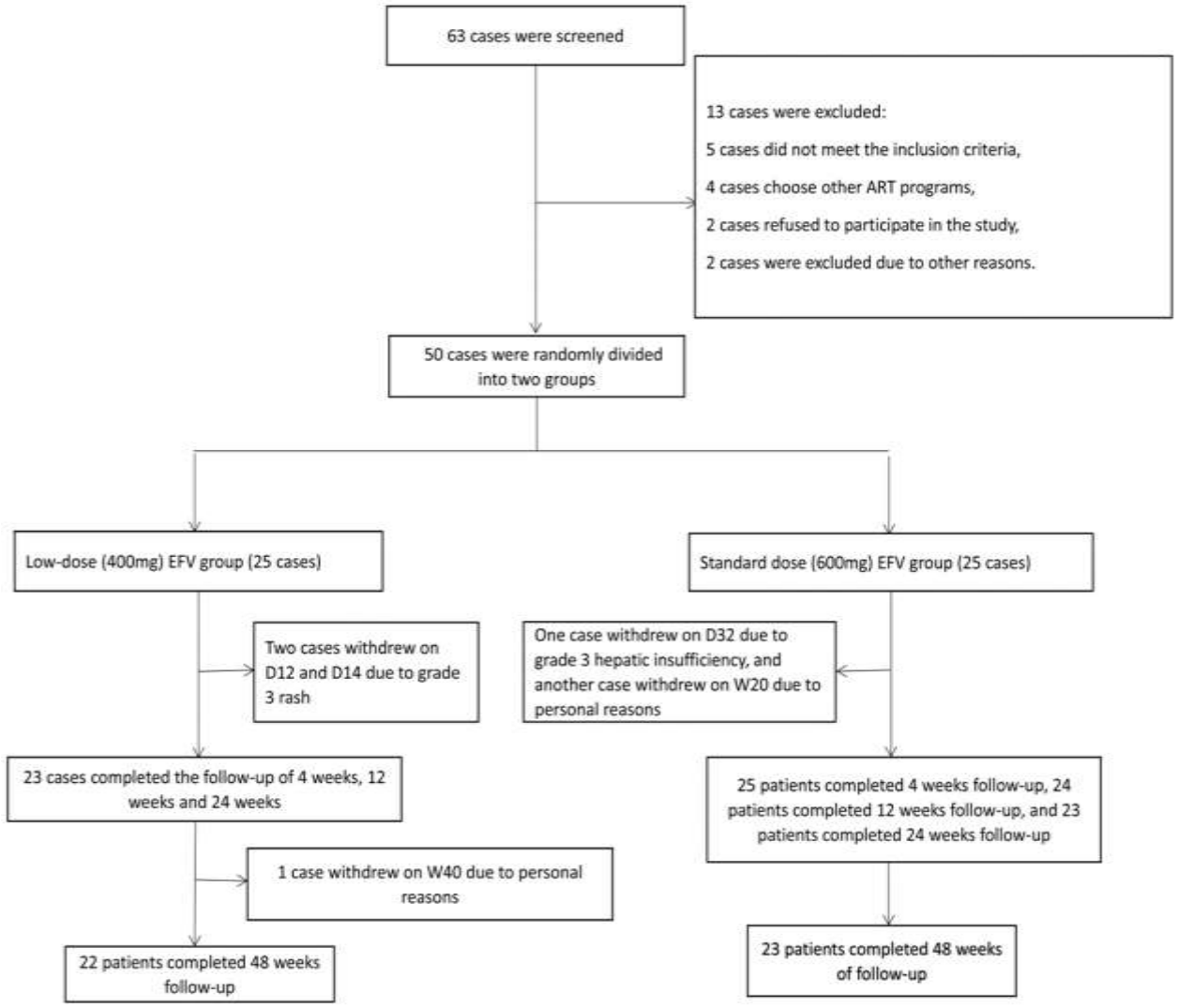

Fig. 1: Flow chart of the randomized grouping and follow-up in fifty patients.

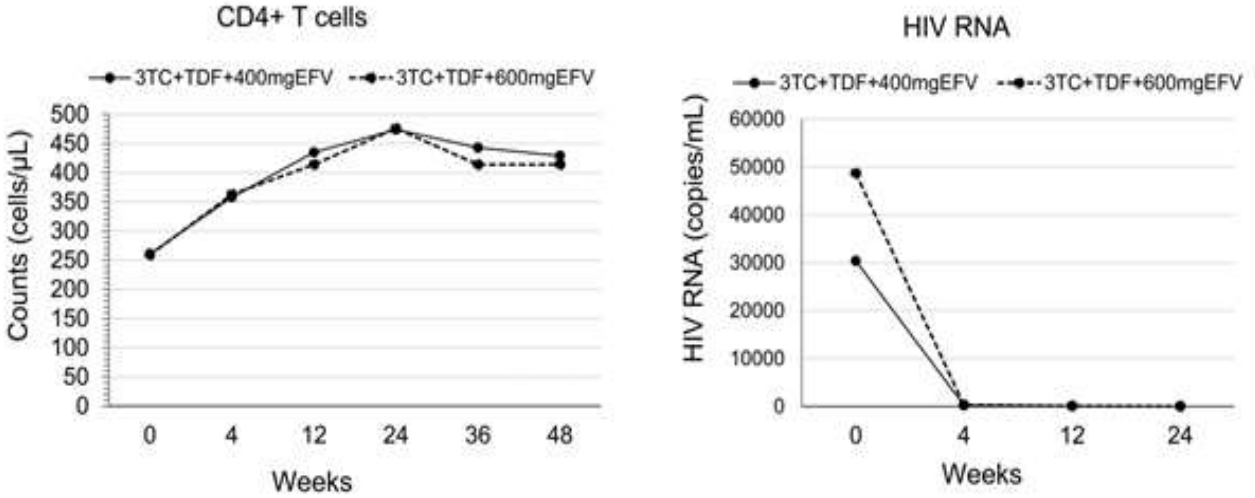

Fig. 2: Changes in $CD4^+$ T lymphocytes and HIV RNA levels at different follow-up times after treatment in the two groups.

Table 1: Demographic and clinical characteristics of the study cohort.

	N=50	3TC+TDF+400mgEFV (N=25)	3TC+TDF+600mgEFV (N=25)	P value
Male NO. (%)	48 (96)	24 (96)	24 (96)	
Age (year)	29.74±7.97	28.16±7.23	31.32±8.51	0.199
BMI (kg/m^2)	21.62±2.64	21.16±2.36	22.07±2.87	0.287
HIV-1 antibody positive-ART time (d)		38 (16, 145)		
< 30 days -- no.(%)		23 (46)		
30-90 days -- no.(%)		12 (24)		
> 90 days -- no.(%)		15 (30)		
WBC (×10^9/L)	5.65±1.06	6.02±1.11	5.28±0.88	0.028
RBC (×10^{12}/L)	5.15±0.41	5.23±0.44	5.07±0.38	0.176
Hgb (g/L)	155.2 (145, 164)	155 (148.5, 165.5)	154 (144.5,163.5)	0.297
PLT (×10^9/L)	193 (156.75, 219.50)	193 (156.5, 213.5)	193 (154.5,227)	0.989
ALT (U/L)	31.66±16.82	27.33±12.13	36.0±19.78	0.089
AST (U/L)	28.0±8.95	26.41±6.71	29.6±10.64	0.167
GGT (U/L)	16.0 (13.0, 25.0)	15(12, 20.5)	17 (14,25)	0.332
TBIL (umol/L)	12.91±4.81	13.19±5.40	12.64±4.24	0.689
Cr (umol/L)	68.80±9.65	68.92±10.52	68.68±8.91	0.933
BUN (mmol/L)	4.33±1.20	4.02±1.14	4.64±1.19	0.035
TG (mmol/L)	1.39±0.69	1.28±0.64	1.50±0.75	0.264
LDL (mmol/L)	2.82±0.73	2.78±0.71	2.86±0.77	0.662
HDL (mmol/L)	1.17 (1.05, 1.32)	1.17 (1.03, 1.31)	1.24 (1.07,1.32)	0.788
CHOL (mmol/L)	4.23±0.68	4.13±0.59	4.33±0.76	0.336
CD4$^+$ T cells (/uL)	260 (205, 350)	261 (206, 372)	259 (202,340)	0.946
HIV RNA (×10^4 copies/mL)	3.6(1.9, 6.4)	3.04 (1.32, 5.26)	4.87 (2.46,7.60)	0.109
Dizziness handicap inventory				0.055
Grade 1 (0-30 points)	46	21	25	
Grade 2 (31-60 points)	4	4	0	
Hamilton Depression Scale				0.011*
Grade 1 (<8 points)	25	8	17	
Grade 2 (8-20 points)	21	13	8	
Grade 3 (20-35 points)	4	4	0	
Pittsburgh Sleep Quality Index Scale				0.305 $^\#$
Grade 1 (0-5 points)	24	12	12	
Grade 2 (6-10 points)	22	10	12	
Grade 3 (11-15 points)	4	3	1	

Note: * Grade 1 *vs* grade l (2+3), $^\#$ grade (1+2) *vs* grade 3. BMI: body mass index, WBC: white blood cell count, RBC: red blood cell count, Hgb: hemoglobin, PLT: platelet count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: transglutaminase, TBIL: total bilirubin, Cr: creatinine, BUN: urea nitrogen, TG: triglycerides, LDL: low density lipoprotein, HDL: high density lipoprotein, CHOL: cholesterol.

Safety (secondary outcome measurement)

The adverse effects were thoroughly recorded during the follow-ups. The results showed that the 3TC+TDF+ 600mgEFV group had significantly elevated ALT and AST compared to the 3TC+TDF+400mgEFV group at week 12 ($P < 0.05$). However, the liver function and blood lipids at the remaining follow-up time points were not significantly different (table 2). During the 48 weeks of follow-up, the incidence of adverse events in the 3TC+TDF+600mgEFV group was higher than that in the 3TC+TDF+400mgEFV (table 3). Moreover, the incidence of elevated transaminases, dizziness, elevated blood lipids, and skin rash was all higher in the 3TC+TDF+ 600mgEFV group than in 3TC+TDF+ 400mgEFV, but there were no statistically significant differences (P values were 0.064, 0.500, 0.377, 0.500, respectively) (table 3). A total of 10% of patients developed allergic dermatitis. In summary, the 3TC+TDF+400mgEFV group had decreased adverse effects than the 3TC+TDF+600mgEFV group, especially in the elevated transaminase, suggesting that the low-dose EFV (400mg) had better safety.

To assess the occurrence of EFV-related neurological side effects, depression, sleep and dizziness were evaluated by corresponding scales (table 4). The depression incidence in the two groups was not statistically different at baseline, ART 4 weeks, ART 8 weeks, ART 12 weeks, ART 24 weeks, ART 36 weeks, and ART 48 weeks (respectively 68.0% vs. 32%, P=0.011; 39.1% vs. 12%, P=0.032; 47.8% vs. 16.7%, P=0.023; 26.1% vs. 26.1%; 21.7% vs. 13.0%, P=0.350; 27.3% vs. 13.0%, P= 0.252). The incidence of sleep disturbance was also not statistically different at each follow-up point (respectively, 52% vs. 52%; 52% vs. 24%, P=0.043; 39.1% vs. 37.5%, P=0.573;

Table 2: Laboratory results of each follow-up after ART treatment.

	3TC+TDF+400mgEFV	3TC+TDF+600mgEFV	P value
ART 4 weeks (N=50)			
ALT(U/L) -- M(IQR)	29.46±17.66	29(23,39.5)	0.158
AST(U/L) -- M(IQR)	27.08±10.5	26(24,30.5)	0.590
GGT(U/L) -- M(IQR)	27 (20.75,39)	30(23.5,39)	0.250
TG(mmol/L) -- M(IQR)	1.19 (0.91,2.31)	1.64±0.88	0.704
HDL(mmol/L) -- M(IQR)	1.11±0.25	1.11±0.25	0.980
LDL(mmol/L) -- M(IQR)	2.38±0.56	2.56±0.55	0.530
CHOL(mmol/L) -- M(IQR)	4.14±0.69	4.24±0.60	0.091
$CD4^+$ T cells (cells/μL)	357.93±128.93	363 (289,428)	0.763
HIV RNA (copies/mL)	197 (99,345)	273 (75,753)	0.901
ART 12 weeks(N=46)			
ALT(U/L) -- M(IQR)	27(18,47)	36.5±19.61	0.002
AST(U/L) -- M(IQR)	25(22,35)	28.79±7.24	0.003
GGT(U/L) -- M(IQR)	31(20,61)	35(27.25,50.75)	0.149
TG(mmol/L) -- M(IQR)	1.29(0.75,1.90)	1.55±0.76	0.468
HDL(mmol/L) -- M(IQR)	1.12±0.30	1.12±0.25	0.828
LDL(mmol/L) -- M(IQR)	2.44±0.49	2.59±0.69	0.104
CHOL(mmol/L) -- M(IQR)	4.22±0.63	4.34±0.73	0.084
$CD4^+$ T cells (cells/μL)	435.18±150.03	413.54±115.87	0.699
HIV RNA (copies/mL)	69(0,154)	77(25,143.25)	0.404
ART 24 weeks(N=46)			
ALT(U/L) -- M(IQR)	29(20,52)	37.35±14.85	0.934
AST(U/L) -- M(IQR)	35.3±16.85	30.39±5.48	0.604
GGT(U/L) -- M(IQR)	46(27,70)	41(34,56)	0.963
TG(mmol/L) -- M(IQR)	1.28(1.05,2.0)	1.74±0.91	0.843
HDL(mmol/L) -- M(IQR)	1.16±0.38	1.11±0.21	0.150
LDL(mmol/L) -- M(IQR)	2.45±0.46	2.53±0.51	0.182
CHOL(mmol/L) -- M(IQR)	4.34±0.64	4.48±0.73	0.814
$CD4^+$ T cells (cells/μL)	473.96±163.69	476.23±124.07	0.137
HIV RNA < 40copies/mL (NO. (%))	13(56.52)	13(56.52)	
ART 48 weeks(N=45)			
ALT(U/L) -- M(IQR)	30(18,62)	34.55±14.47	0.177
AST(U/L) -- M(IQR)	25(21,30)	28.32±4.97	0.231
GGT(U/L) -- M(IQR)	40(30,66)	40.5±13.38	0.344
TG(mmol/L) -- M(IQR)	1.36±0.52	1.56±0.66	0.570
HDL(mmol/L) -- M(IQR)	1.10±0.24	1.15±0.19	0.606
LDL(mmol/L) -- M(IQR)	2.70±0.59	2.63±0.59	0.251
CHOL(mmol/L) -- M(IQR)	4.41±0.77	4.52±0.73	0.197
$CD4^+$ T cells (cells/μL)	429(316.5,553)	413.86±131.03	0.388
HIV RNA < 40copies/mL (NO. (%))	22(100)	21(91.30)	0.256

Note: ALT: alanine amino transferase, AST: aspartate aminotransferase, GGT: transglutaminase, TBIL: total bilirubin, Cr: creatinine, BUN: urea nitrogen, TG: triglycerides, LDL: low density lipoprotein, HDL: High-density lipoprotein, CHOL: Cholesterol.

30.4 % vs. 30.4%; 52.2% vs. 26.1%, P=0.065; 40.9% vs. 13.0%, P=0.054). In addition, the vertigo incidence (respectively, 16% vs. 0%, P=0.055; 8.7% vs. 0%, P=0.224; 4.3% vs. 8.3%, P=0.516; 8.7% vs. 8.7%, P=0.662; 0% vs. 0%; 9.1% vs. 4.3%, P=0.483) was not significantly different.

During the process, a total of 3 patients in 50 patients had serious adverse events (2 in the 3TC+TDF+400mgEFV and 1 in the 3TC+TDF+600mgEFV group). The incidence of serious adverse events was not significantly different (8% vs. 4%, P=0.500) (table 3). Within 48 weeks of follow-up, 2 patients in the 3TC+TDF+ 400mgEFV group were censored due to grade 3 rash and another patient was censored because of personal reasons. Correspondingly, one patient in the 3TC+TDF+ 600mgEFV group withdrew due to grade 3 hepatic insufficiency and one patient withdrew was censored because of personal reasons. However, no patient withdrew due to EFV-related central nervous system adverse events.

DISCUSSION

Here, we included 50 patients with an average age of 29.74 years, including 48 males. All these 50 patients were infected with HIV through sexual contact, and most of them were infected with HIV through homosexual

contact. Thus, the above results suggest that the newly infected population of HIV in Chengdu may be dominated by young and middle-aged gay men. Chengdu is one of the areas where MSM (men who have sex with men) gathers and the incidence of high-risk sexual behavior is high (Zhang *et al*., 2016). In addition, the HIV infection rate and the new infection rate are relatively high in the MSM population (Duan *et al*., 2017). These above reasons make the MSM population currently the main target of AIDS prevention and control in Chengdu. In this study, the median time of patients from the diagnosis of HIV infection to the start of ART was 38 days. The patients who received ART within 1 month after detection of HIV infection accounted for 46%, and those who did not receive ART within 90 days after detection of HIV infection accounted for 30%. Laboratory results showed that the patient's baseline $CD4^+$ T lymphocyte was 260 cells/μL, and the baseline HIV RNA was 3.6×10^4 copies/mL. These results indicated that most patients failed to receive ART treatment in time, resulting in a low $CD4^+$ T lymphocyte count and high HIV RNA in most patients. Thus, it is recommended to further increase the detection range and treat patients as early as possible (Zhao *et al*., 2018) to further decrease the rate of new HIV infections in the MSM population.

Here, the $CD4^+$ T lymphocyte and the HIV suppression rate was similar between 400 mg EFV and 600 mg EFV groups, which was consistent with previous findings (Kaboggoza *et al*., 2019, Sinxadi *et al*., 2016, Huang *et al*., 2020, Rojas *et al*., 2016, Wei-Chieh Huang, 2021, Chen *et al*., 2020). The above results demonstrate that the short-term and long-term efficacy of EFV 400mg and EFV 600mg in the cART regimen was similar.

In this study, patients within 48 weeks of antiviral treatment had common adverse reactions such as rash, abnormal liver function, and headache. The patients in the 3TC+TDF+400mgEFV group reported 27 adverse events, and those in the 3TC+TDF+600mgEFV group reported 39 adverse events. The 3TC+TDF+600mgEFV group had an increased incidence of adverse events than the 3TC+TDF+400mgEFV group. A total of 10% of patients developed allergic dermatitis, which is consistent with related reports (Fang, 2018, Liu *et al*., 2018, Zou *et al*., 2015). It is shown that, except for dizziness, other adverse effects of EFV have no significant correlation with whether the blood concentration of EFV is higher than 4 mg/L (Zhao *et al*., 2019). However, a previous history of drug allergy and young age are independent risk factors for allergic dermatitis caused by EFV treatment in HIV-infected patients (Zou *et al*., 2015). In this study, a total of 5 patients developed rashes (including 2 in the 400mg EFV group and 3 in the 600mg EFV group). After anti-allergic treatment, the rash in 3 patients in the 600mg EFV group was effectively relieved, while the treatment for the rash in 2 patients in the 400mg EFV group was not effective, suggesting that the severity of the rash may not be related to the dose of EFV.

In addition, 5 patients in the 400mg EFV group and 11 patients in the 600mg EFV group had increased transaminase after treatment, without significant difference. It is possible that this finding may be attributed to the limited sample size. Moreover, in this study, 6 patients in the 400mg EFV group and 8 patients in the 600mg EFV group developed elevated blood lipids after treatment. It is reported that co-infection with HBV/HCV and elevated baseline ALT are independent risk factors for hepatotoxicity (Wei-Chieh Huang *et al*., 2022). However, whether EFV dose is another independent risk factor for hepatotoxicity and whether EFV dose is a risk factor for elevated blood lipids need to be confirmed by further large sample studies.

It is worth noting that no serious adverse events of the central nervous system occurred, and the incidence of depression, sleep disorders, and vertigo at each follow-up point was without significant differences, suggesting that the short-term adverse effects of the central nervous system are similar between 400mg EFV and 600mg EFV. The adverse effects on the central nervous system caused by EFV mostly occur within 2 weeks of medication. However, in this study, the first follow-up was at 4 weeks after treatment. As the vertigo scale only reflected the situation within 1 week before the administration, it may fail to reflect the severity of adverse reactions in the central nervous system. Therefore, our research results are inconsistent with related one previous study (Zhao *et al*., 2019).

However, this study acknowledges some limitations. First, the sample size is small. Second, the enrolled subjects were mainly young and middle-aged males, which may cause gender and age bias. It is necessary to include female patients and elderly patients in the future and expand the sample size of the research. Third, the longest follow-up in this study was 48 weeks, which is relatively short. We will continue to follow up with the cohort to get more data and more comprehensive results.

CONCLUSION

In conclusion, there is no significant difference in antiviral efficacy between 400mg EFV and 600mg EFV, which supports the adjustment of the EFV dose to 400mg for ART in HIV-infected patients. Besides, 400 mg EFV causes fewer side effects than 600 mg EFV, including elevated transaminase, dizziness, elevated blood lipids, and skin rashes, suggesting that 400mg EFV may have a lower incidence of adverse reactions and better safety in HIV patients. In summary, our study confirmed the therapeutic properties of 400 mg EFV in HIV-infected patients.

Table 3: Statistics of adverse events and serious adverse events in HIV infected/AIDS patients.

Groups	Transaminase elevation (n, %)	Hyperlipidemia (n, %)	Dizziness (n, %)	Rash (n, %)	Fatty liver (n, %)	Nausea (n, %)	Headache (n, %)	Serious adverse events	Total
3TC+TDF+400mgEFV (n=25)	5 (20)	6 (24)	10 (40)	2# (8)	3(12)	0	1 (4)	3	30
3TC+TDF+600mgEFV (n=25)	11* (44)	8 (32)	11 (44)	3(12)	4(16)	1(4)	1 (4)	1	40
P	0.064	0.377	0.500	0.500	0.166	1.020	-	0.500	-
Total	16 (32)	14 (28)	22 (44)	5 (10)	7 (14)	1 (2)	2 (4)	4 (8)	70

Note: Both adverse events and serious adverse events are expressed in number of cases (n) and percentage (%). #2 patients had serious adverse events, and *1 patient had serious adverse events. TDF: Tenofovir fumarate, 3TC: Lamivudine, EFV: Efavirenz.

Table 4: Scale scores in follow-ups at baseline and after ART treatment.

Groups	Baseline (n1=25, n2=25)			ART 4 weeks (n1=23, n2=25)			ART 12 weeks (n1=23, n2=24)			ART 24 weeks (n1=23, n2=23)			ART 36 weeks (n1=23, n2=23)			ART 48 weeks (n1=22, n2=23)		
Score grade	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Hamilton depression scale score																		
3TC+TDF+400mgEFV (n=25)	8	13	4	14	7	2	12	10	1	17	6	0	18	5	0	17	6	0
3TC+TDF+600mgEFV (n=25)	17	8	0	22	3	0	20	3	1	17	3	3	20	2	1	19	1	2
Pittsburgh sleep quality index scale score																		
3TC+TDF+400mgEFV (n=25)	12	10	3	11	12	0	14	7	2	16	7	0	11	10	2	14	9	0
3TC+TDF+600mgEFV (n=25)	12	12	1	19	6	0	15	9	0	16	7	0	17	6	0	19	2	1
Dizziness handicap inventory score																		
3TC+TDF+400mgEFV (n=25)	21	4	0	21	2	0	22	1	0	20	2	0	23	0	0	20	2	0
3TC+TDF+600mgEFV (n=25)	25	0	0	25	0	0	22	2	0	22	2	0	23	0	0	22	1	0

Note: n1: cases in 3TC+TDF+400mgEFV, n2: cases in 3TC+TDF+600mgEFV. Depression score: < 8: grade 1 (normal), 8-20 points: grade 2 (may have depression), 20-35 points: grade 3 (must have depression). Incidance of depression = [grade 2, grade 3] cases / total cases. Sleep quality score: 0-5 points: grade 1 (good sleep quality), 6-10 points: grade (sleep quality is OK), 11-15 points: grade 3 (moderate sleep quality). Incidence of sleep disorders = [grade 3] cases / total cases. Dizziness disorder score: 0-30 points: grade 1 (mild disorder), 31-60 points: grade 2 (moderate disorder), 61-100 points: grade 3 (severe disorder), incidence of vertigo disorder= [grade 2, grade 3] cases / total cases.

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