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ORIGINAL RESEARCH

Prospective plasma efavirenz concentration assessment in Chinese HIV-infected adults enrolled in a large multicentre study*

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Objectives

Few studies have explored the optimal dosing for efavirenz in individuals from China. We investigated plasma efavirenz concentrations and their association with efficacy and tolerance of efavirenz 600 mg daily in Chinese HIV-infected adults.

Methods

An analysis was performed using plasma samples from 455 patients enrolled in a prospective multicentre trial in China. A total of 1198 plasma samples collected at weeks 4, 24 and 48 following antiretroviral therapy initiation were analysed. The mid-dose interval efavirenz concentrations (C_{12}) were determined using high-performance liquid chromatography.

Results

The median efavirenz concentration (interquartile range) steadily increased over time from 3.02 (2.28–4.23) to 3.71 (2.91–4.91) mg/L from week 4 to 48 ($P < 0.001$). The proportion of patients with $C_{12} > 4.0$ mg/L also rose from 28.0% to 34.2% and 43.8%, measured at 4, 24 and 48 weeks, respectively ($P < 0.001$). Five patients had efavirenz concentrations < 1.0 mg/L at week 4, 24 or 48. In the multivariable regression analysis, lower body weight and non-Han ethnicities were associated with higher efavirenz concentrations over time. At each time-point, patients with a body weight < 60 kg had significantly higher efavirenz C_{12} compared with those with body weight ≥ 60 kg ($P < 0.05$).

Conclusions

Efavirenz concentrations increased steadily over 48 weeks, and a substantial proportion of participants had efavirenz C_{12} above the upper limit of the proposed therapeutic window, especially those with low body weight (< 60 kg). Based upon these findings, a dosage reduction of efavirenz to 400 mg daily may warrant consideration in this population, especially for those with lower body weight.

Keywords: body weight, efavirenz, HIV, plasma concentration

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Introduction

Efavirenz is a nonnucleoside reverse transcriptase inhibitor and is one of the most commonly prescribed antiretroviral agents used in combination with two nucleoside reverse transcriptase inhibitors for the treatment of

HIV infection. Efavirenz was developed by Merck Research Laboratories (Lansdale, PA, USA) in 1995 (later DuPont Pharmaceuticals, Wilmington, DE, USA) following *in vitro* and animal experiments, with a 600 mg daily dosage granted accelerated approval by the US Food and Drug Administration in 1998 [1,2]. The efficacy and safety of efavirenz were subsequently demonstrated in numerous well-powered randomized controlled clinical trials [3,4]. In view of its good tolerance profile and lower cost, the 2016 World Health Organization (WHO) treatment guidelines recommended efavirenz as part of the preferred first-line antiretroviral regimen used in combination with tenofovir and lamivudine or emtricitabine for adults and adolescents with HIV infection in low- and middle-income countries [5].

In 2001, Marzolini and colleagues demonstrated virological failure in 50% of patients with plasma efavirenz concentrations < 1.0 mg/L when measured at an average of 14 h (between 8 and 20 h) post-intake, and central nervous system (CNS) toxicity (i.e. sleep/dream changes and depression) was approximately three times more frequent in patients with efavirenz levels > 4.0 mg/L, suggesting a narrow therapeutic window (1.0–4.0 mg/L) [6]. Several other studies found a high efavirenz concentration to be associated with adverse events such as neuropsychiatric symptoms, abnormal liver function and dyslipidaemia [6–8]. When compared with integrase inhibitors, studies found that efavirenz usage was limited by a higher prevalence of drug discontinuation and neuropsychiatric adverse events [9,10]. As a result, in developed countries, efavirenz is no longer considered as a preferred agent and has been categorized as an alternative treatment option because of its tolerance profile [11].

Based upon these observations, debate has arisen regarding the optimal dose of efavirenz [12]. Some studies have suggested that dose reduction of efavirenz should be undertaken in certain situations, such as in the presence of the cytochrome P450 2B6 (*CYP2B6*) G516T polymorphism, which has been associated with higher plasma efavirenz concentrations [13–15]. However, because of the cost and logistical barriers to widespread genotyping, this is not feasible in clinical practice. Importantly, in a randomized multicentre clinical trial (the Safety and Efficacy of Reduced Dose Efavirenz (EFV) With Standard Dose EFV Plus Two Nucleotide Reverse Transcriptase Inhibitors (N(t) RTI) in Antiretroviral-naïve HIV-infected Individuals (ENCORE1) study), Carey *et al.* [16,17] assessed the efficacy and tolerance of efavirenz 400 mg daily and found it to be noninferior to efavirenz 600 mg daily for viral control at week 48. Furthermore, adverse events related to the study drug were less frequent among the group receiving the 400 mg daily dose. Follow-up pharmacokinetic and pharmacodynamic evaluation in the ENCORE1 study demonstrated that the 400 mg daily dose was associated with lower rates of efavirenz discontinuation, while effectively achieving and maintaining similar viral suppression to the 600 mg daily dose [18,19]. Therefore, efavirenz dosage reduction to 400 mg daily could potentially increase tolerance without compromising viral control.

Approximately one-third of the ENCORE1 study population was enrolled from sites in southern Asia, including Hong Kong and Singapore. However, no prospective multicentre studies have explored the optimal dosing for efavirenz in individuals from mainland China. To address this issue, we evaluated change in plasma efavirenz concentration and its relationship with efficacy and tolerability over a 48-week period in Chinese patients with HIV initiating a first-line regimen containing efavirenz 600 mg daily, and sought to prospectively evaluate whether dosage reduction of efavirenz to 400 mg daily should be considered in the Chinese population.

Methods

Study design and participants

We performed a prospective multicentre clinical trial from July 2012 to July 2014 across seven provinces and municipalities of China, including Beijing, Guangdong, Guangxi, Henan, Hunan, Shanghai and Sichuan Provinces. Eligibility criteria for adult participants included: (1) HIV treatment-naïve, (2) age between 18 and 65 years, and (3) CD4 T-cell count < 500 cells/μL. The main exclusion criteria were pregnancy or breast feeding, anticipated nonadherence, an AIDS-defining illness within 2 weeks of entry, transaminase and alkaline phosphatase levels more than 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 more than 1.5 times the upper limit of the normal range. None of the patients had a history of using injection drugs.

For the purpose of drug concentration analyses, patients with unknown serological status for hepatitis B or hepatitis C were excluded. Samples were also excluded if patients had taken efavirenz outside the recommended time frame for analysis (< 8 h or > 20 h prior to the time of plasma sample collection), or had mid-dose interval efavirenz concentrations (C_{12}) that were undetectable. The protocol was approved by the Research Ethics Committee of Peking Union Medical College Hospital, and the clinical trial was carried out in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to enrolment.

Clinical and laboratory evaluations

Patients were followed for 48 weeks, and study encounters took place at baseline, and at weeks 4, 12, 24, 36 and 48. Patients were treated with tenofovir (300 mg once daily; Gilead Sciences, Inc., Foster City, CA, USA), lamivudine (300 mg once daily; GlaxoSmithKline, Brentford, UK), and efavirenz (600 mg once daily; Merck & Co., Inc. Kenilworth, NJ, USA).

We used a computerized case record form to collect data on demographics, weight and height, ethnicity, smoking, current alcohol use, HIV transmission route, time since HIV diagnosis, and clinical characteristics including hepatitis B virus (HBV) surface antigen (HBsAg), hepatitis C virus (HCV) antibody (HCV-Ab), creatinine clearance, CD4 cell count and plasma HIV viral load (VL) at baseline and during the follow-up, and the date and time of the last efavirenz dose that was usually taken at bedtime. The laboratory techniques used to obtain these measurements have been described previously [20].

The virological efficacy of antiretroviral therapy (ART) was assessed at weeks 4, 12, 24, 36 and 48. It was described as the proportion of patients with plasma HIV RNA < 50 copies/mL.

Clinical adverse events were reported and graded by on-site investigators using the Division of AIDS table for grading the severity of adverse events in adults and paediatric patients [21]. CNS adverse effects, such as dizziness, sleep disorders and depression, were identified by physicians or patients' self-report. Hepatotoxicity was defined as laboratory abnormalities greater than grade 2, including a significant increase in aspartate aminotransferase, alanine aminotransferase or total bilirubin. Dyslipidaemia was defined as laboratory abnormalities greater than grade 2, including total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-c). Adverse events were recorded throughout the 48 weeks of ART.

Plasma efavirenz concentration analyses

Blood samples were collected at weeks 4, 24 and 48 of efavirenz treatment in the morning in Ethylenediaminetetraacetic acid (EDTA) tubes and reflected mid-dose plasma concentrations [22]. After centrifugation, plasma samples were transferred to and stored at −80°C until analysis. Efavirenz was assayed in plasma samples at the Department of Pharmacy and pharmacology at Peking Union Medical College Hospital, using a validated high-performance liquid chromatography method with ultraviolet (UV) detection described in a previous study [23]. The efavirenz concentration was analysed on a Shimpack CLC-ODS column (Shimadzu, Kyoto, Japan) (6 mm internal diameter × 15 cm; 5 μm) with a mobile phase consisting of water:acetonitrile (50:50) at a flow rate of 1.2 mL/min, and the wavelength for detection was set at 260 nm between 0 and 12 min, and 240 nm between 12 and 22 min. Diazepam was used as an internal standard. The calibration curve of efavirenz was linear in the range of 0.1–10.0 mg/L ($r = 0.999$), and the limit of detection was 0.1 mg/L. The relative standard deviations of intra- and inter-run validations were < 6%. The mean recoveries fell in the range of 90–110% for the high, middle and low concentrations.

Adherence was evaluated by efavirenz therapeutic drug monitoring [24]. The therapeutic range for mid-dose efavirenz concentrations is 1.0–4.0 mg/L [6]. The adherence rate was calculated based upon the proportion of patients with efavirenz concentration > 1.0 mg/L.

Statistical analysis

All statistical analyses were performed using the SPSS 19.0 statistical software package (IBM Corporation, Armonk, NY) and GRAPHPAD PRISM version 6 (GraphPad Software, Inc., La Jolla, CA). Descriptive data were tabulated and reported using medians, interquartile ranges (IQRs), and frequencies. The Mann–Whitney test or Wilcoxon signed-rank test for nonparametric continuous variables, the χ^2 test for categorical variables, and Spearman's rank correlation were used. Generalized estimating equations were utilized to analyse the impact of covariates (age, gender, baseline body weight, ethnicity, smoking, current alcohol use, creatinine clearance, HBsAg, HCV-Ab, HIV transmission route, time from diagnosis of HIV infection to treatment, baseline HIV VL and baseline CD4 T cell count) on efavirenz concentration over time. Factors with associations with $P < 0.20$ in univariate analysis were entered into the multivariable model. Two-sided hypotheses and tests were adopted for all analyses, and $P < 0.05$ was considered statistically significant.

Results

Study population

From a total of 570 antiretroviral-naïve patients enrolled in the original study, data for 455 patients were included in this ancillary analysis. Reasons for exclusion are detailed in Figure 1. Patients were excluded for the following reasons: 11 were lost to follow-up before 4 weeks; seven discontinued efavirenz because of drug-related adverse events before 4 weeks; 13 patients had missing blood samples; 71 patients had unknown serological status for hepatitis B or hepatitis C; 11 were excluded for

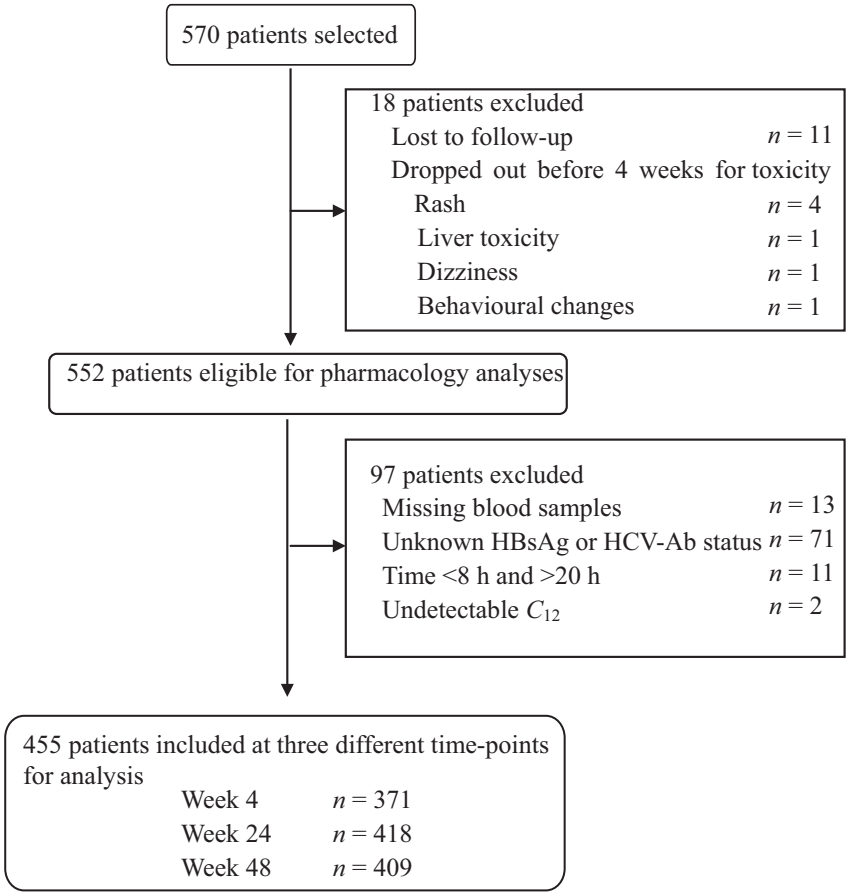

Fig. 1 Flow of patients through the screening process. HBsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody; Time < 8 h and > 20 h, outside the optimal time for drug concentration analysis; C_{12}, mid-dose interval efavirenz concentration.

having taken efavirenz outside the recommended time for analysis (< 8 h or > 20 h prior to the time of plasma sample collection); and lastly, two had an undetectable mid-dose interval efavirenz concentrations.

Table 1 summarizes the demographic characteristics of the study participants. The median age was 33 years, 73.6% of participants were male and 73.6% of participants were Han Chinese. The median (IQR) body weight was 60 (54, 67) kg, and the median body mass index was 21 (20, 24) kg/m^2. The proportions of patients with HBV and HCV coinfection were 10.3% and 2.4% respectively. The median CD4 cell count was 300 cells/μL, and the median HIV VL was 4.76 $\log_{10}$ copies/mL. At baseline, 211 patients (46.4%) had a body weight < 60 kg. Compared with patients with a body weight ≥ 60 kg (Table 1), patients with a body weight < 60 kg were less likely to male or of Han ethnicity, or to report smoking or current alcohol use. Patients with a body weight of < 60 kg were also found to have a lower body mass index and lower creatinine clearance ($P < 0.05$).

Median (IQR) body weight decreased slightly from 60 (54, 67) kg at baseline to 59 (52, 65) kg at week 48 ($P < 0.001$). Among patients with body weight < 60 kg, no significant change in weight was observed between baseline and week 48, while among patients with body weight ≥ 60 kg, the median (IQR) body weight decreased from 66 (62, 71) kg at baseline to 65 (61, 70) kg at week 48 ($P < 0.001$).

Plasma concentrations of efavirenz

The median (IQR) time elapsed between the time of the last dose of efavirenz and the time of plasma sample collection was 12 (11, 13) h. Overall, 1198 samples from 455 patients were included for analysis (Fig. 1). Among the 455 patients, 311 (68.4%) had samples available for all three study time-points.

Median efavirenz concentrations increased by 23% over the 48-week follow-up period. Median (IQR) efavirenz concentrations at weeks 4, 24 and 48 were 3.02

Table 1 Baseline characteristics of study participants

Characteristic	Total (n = 455)	Weight < 60 kg (n = 211)	Weight ≥ 60 kg (n = 244)	P-value
Male	335 (73.6)	114 (54.0)	221 (90.6)	< 0.001
Age (years)	33 (27, 41)	33 (27, 44)	33 (28, 40)	1.00
Han ethnicity	335 (73.6)	132 (62.6)	203 (83.2)	< 0.001
Smoking	110 (24.2)	41 (19.4)	69 (28.3)	0.03
Current alcohol use	156 (34.3)	59 (28.0)	97 (39.8)	0.01
Creatinine clearance (mL/min)	104 (88, 120)	92 (80, 106)	115 (100, 134)	< 0.001
HbsAg positive	47 (10.3)	18 (8.5)	29 (11.9)	0.24
HCV-Ab positive	11 (2.4)	6 (2.8)	5 (2.0)	0.58
Route of HIV transmission				NA
Homosexual	173 (38.0)	58 (27.5)	115 (47.1)	
Heterosexual	253 (55.6)	145 (68.7)	108 (44.3)	
Blood transfusion	2 (0.4)	0	2 (0.8)	
Other/unknown	27 (5.9)	8 (3.8)	19 (7.8)	
Time since HIV diagnosis (years)	0.3 (0.1, 1.2)	0.3 (0.1, 1.3)	0.3 (0.1, 1.2)	0.97
CD4 cell count	300 (209, 379)	297 (205, 375)	306 (213, 384)	0.48
< 200 cells/μL	99 (21.8)	52 (24.6)	47 (19.3)	0.21
200–350 cells/μL	193 (42.4)	81 (38.4)	112 (45.9)	
350–499 cells/μL	163 (35.8)	78 (37.0)	85 (34.8)	
Viral load*	4.76 (4.40, 5.16)	4.75 (4.39, 5.22)	4.77 (4.40, 5.13)	0.74
< 5 $\log_{10}$ copies/mL	269 (59.1)	129 (61.1)	140 (57.4)	0.70
≥ 5 $\log_{10}$ copies/mL	160 (35.2)	70 (33.2)	90 (36.9)	

*26 patients missing data. Values are shown as n (%) or median (interquartile range).
HBsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody; NA, not available.

(2.28, 4.23), 3.44 (2.64, 4.65) and 3.71 (2.91, 4.91) mg/L, respectively (P < 0.001) (Table 2; Fig. 2a).

Only five patients had very low efavirenz concentrations (defined as C_{12} < 1.0 mg/L) at any time-point. Three of them had low efavirenz concentrations at week 4; however, they attained drug concentrations within the proposed therapeutic window of 1.0–4.0 mg/L at weeks 24 and 48. One patient had a low efavirenz concentration measured at week 24; however, the efavirenz concentration remained between 1 and 4 mg/L at weeks 4 and 48, probably reflecting a lapse in adherence at week 24. One patent had plasma efavirenz concentrations < 1.0 mg/L at week 48. The overall adherence rate of the study population was 98.9% (450/455).

The proportions of patients with efavirenz C_{12} levels > 4.0 mg/L at weeks 4, 24 and 48 were 28.0%, 34.2% and 43.8%, respectively (P < 0.001). More specifically, the proportion of patients with efavirenz C_{12} > 4.0 mg/L at week 48 was significantly higher than that at week 4 or week 24 (P < 0.01). A total of 60 patients (13.2%) had concentrations > 4.0 mg/L at all study time-points.

When stratified by baseline body weight, patients with body weight < 60 kg had significantly higher plasma efavirenz concentrations at each study time-point compared with those with body weight ≥ 60 kg (Table 2; Fig. 2b). Steady increases in median efavirenz concentrations were also observed over the 48-week period in both weight-based groups. Among patients with body weight < 60 kg, the proportions of patients with plasma efavirenz concentrations > 4.0 mg/L were significantly higher compared with patients with body weight ≥ 60 kg at each study time-point (33.5% *vs.* 23.5% at week 4, 40.6% *vs.* 28.5% at week 24, and 50.0% *vs.* 38.1% at week 48, respectively; all P < 0.05).

Among patients with HBV or HCV coinfection, median (IQR) efavirenz concentrations at weeks 4, 24 and 48 were 2.63 (2.00, 4.30), 2.67 (2.15, 4.39) and 2.84 (2.25, 4.74) mg/L, respectively. No significant increase of efavirenz concentration among coinfected patients was observed over the 48-week period. No significant differences in the efavirenz concentration were found between HBV- and HCV-coinfected patients at each time-point. Coinfected patients had a significantly lower efavirenz concentration compared with HIV-monoinfected patients at week 24 [2.67 (2.15, 4.39) *vs.* 3.47 (2.71, 4.70), respectively] and week 48 [2.84 (2.25, 4.74) *vs.* 3.78 (3.02, 4.95), respectively] (P < 0.01). The proportions of coinfected

Table 2 Differences in mean and median plasma efavirenz concentrations over the 48-week follow-up period

	n	Mean (mg/L)	Range (mg/L)	Median (mg/L)	IQR (mg/L)	P-value
Week 4	371	3.76	0.34–21.67	3.02	2.28–4.23	
< 60 kg	167	4.25	0.72–21.67	3.40	2.41–4.62	0.002
≥ 60 kg	204	3.35	0.34–13.67	2.80	2.21–3.96	
Week 24	418	4.27	0.93–33.49	3.44	2.64–4.65	
< 60 kg	197	4.81	0.93–33.49	3.60	2.91–5.05	< 0.001
≥ 60 kg	221	3.79	1.27–14.99	3.19	2.43–4.18	
Week 48	409	4.59	0.79–32.19	3.71	2.91–4.91	
< 60 kg	194	5.12	0.79–32.19	4.00	3.16–5.18	< 0.001
≥ 60 kg	215	4.12	1.37–16.59	3.34	2.66–4.59	

IQR, interquartile range.

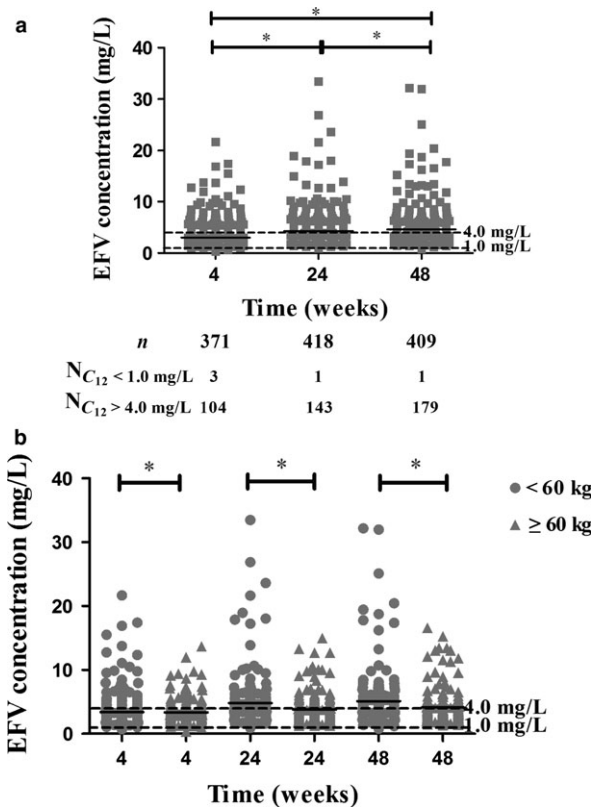

Fig. 2 Change in median mid-dose interval efavirenz plasma concentrations over the 48-week follow-up period. The changes in median efavirenz plasma concentrations for (a) the entire cohort and (b) patients stratified by body weight are shown. The black dashed lines illustrate the recommended therapeutic window for efavirenz of 1.0–4.0 mg/L. Each point represents an individual patient and the solid black lines represent the median efavirenz concentrations. *$P < 0.05$. EFV, efavirenz; *n*, number; C_{12}, mid-dose interval efavirenz concentration.

patients with plasma efavirenz concentrations > 4.0 mg/L at weeks 4, 24 and 48 were 25.0%, 28.0% and 31.5%, respectively, which was not statistically different compared with HIV-monoinfected patients.

Univariate regression analysis demonstrated that body weight, Han ethnicity, current alcohol use and creatinine clearance were significantly associated with efavirenz concentration during the observation period. However, in the multivariable analysis, risk factors significantly associated with the efavirenz concentration over time included body weight [relative risk (RR) (95% confident interval (CI)) 0.94 (0.91, 0.98)] and Han ethnicity [RR (95% CI) 0.40 (0.18, 0.87)].

Efficacy

At weeks 4, 24 and 48, the plasma HIV VL was < 50 copies/mL for 31 (6.8%), 309 (67.9%) and 338 (74.3%) patients, respectively, while the mean CD4 cell counts were 364, 408 and 440 cells/μL, respectively. The five patients who had one efavirenz concentration measurement < 1.0 mg/L all attained virological control at week 48. No correlation between HIV VL or CD4 cell count and efavirenz concentration was observed at week 48. Furthermore, there was no significant difference when the efavirenz concentrations at weeks 24 and 48 were stratified by HIV VL below or above 50 copies/mL (data not shown).

Adverse events

Overall, 74 patients (16.3%) reported experiencing neuropsychiatric symptoms during the observation period. Specifically, the following CNS adverse effects were recorded: dizziness [69 cases (15.2%)], insomnia or abnormal dreaming [14 cases (3.1%)], and depression [one case (0.2%)] (see Table 4). Rash, hepatotoxicity and dyslipidaemia were observed in 31 (6.8%), 62 (13.6%) and 37 (8.1%) patients, respectively. The risk of experiencing neuropsychiatric symptoms, rash, hepatotoxicity and dyslipidaemia was not significantly increased in patients who had efavirenz concentrations that were at least once above, or always above 4.0 mg/L, when compared with patients who never had concentrations > 4.0 mg/L.

Relationships between plasma efavirenz concentration and metabolic parameters at week 48 were analysed. There was a positive correlation of efavirenz concentration with fasting total cholesterol ($r = 0.11$; $P = 0.03$) and high-density lipoprotein cholesterol (HDL-c) ($r = 0.25$; $P < 0.001$), but not with triglycerides, LDL-c or fasting glucose.

Discussion

This is the first multicentre study in China to prospectively assess plasma concentrations of efavirenz over a 48-week period following initiation of ART. Our results showed that median plasma efavirenz concentrations increased gradually over 48 weeks, such that by week 48, 43.8% of patients had efavirenz concentrations > 4.0 mg/L. Efavirenz levels < 1.0 mg/L were rare. Furthermore, we found that lower body weight and non-Han ethnicities were associated with higher efavirenz concentrations over time. When stratified by weight, patients with body weight < 60 kg had higher efavirenz plasma concentrations compared with patients with body weight ≥ 60 kg across all time-points. Efavirenz plasma concentrations were not correlated with efficacy and reported neuropsychiatric symptoms.

Table 3 Generalized estimating equation regression analysis of change in efavirenz concentration over time

	Univariate model		Multivariable model	
Covariate	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Male	0.55 (0.26, 1.13)	0.10	1.63 (0.75, 3.56)	0.22
Age (years)	0.99 (0.96, 1.02)	0.56		
Weight (kg)	**0.93 (0.90, 0.96)**	**< 0.001**	**0.94 (0.91, 0.98)**	**0.001**
Han ethnicity	**0.29 (0.13, 0.65)**	**0.002**	**0.40 (0.18, 0.87)**	**0.02**
Smoking	0.62 (0.37, 1.05)	0.07	0.86 (0.49, 1.51)	0.60
Current alcohol use	**0.51 (0.30, 0.85)**	**0.01**	0.63 (0.38, 1.05)	0.08
Creatinine clearance (mL/min)	**0.98 (0.97, 0.99)**	**0.002**	1.00 (0.99, 1.01)	0.52
HbsAg positive	1.47 (0.41, 5.32)	0.56		
HCV-Ab positive	0.52 (0.12, 2.25)	0.38		
Route of HIV transmission				
Homosexual	Reference			
Heterosexual	1.37 (0.74, 2.51)	0.32		
Blood transfusion	0.92 (0.41, 2.05)	0.84		
Other	0.87 (0.34, 2.22)	0.78		
Time since HIV diagnosis (years)	0.94 (0.81, 1.09)	0.41		
Baseline CD4 count (cells/μL)	1.00 (1.00,1.00)	0.87		
Baseline viral load (log_{10} copies/mL)	1.06 (0.63, 1.81)	0.82		

Significant values are shown in bold. Variables with a *P*-value < 0.20 in the univariate model were included in the multivariable model.
RR, relative risk; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody.

Table 4 Adverse events and efavirenz concentrations at week 48

	Total (*n* = 455)	< 4 mg/L (*n* = 230)	≥ 4 mg/L (*n* = 179)	*P*-value
Neuropsychiatric symptoms	74 (16.3)	34 (14.8)	34 (19.0)	0.256
Dizziness	69 (15.2)	32 (13.9)	31 (17.3)	0.344
Sleep disorders	14 (3.1)	6 (2.6)	7 (3.9)	0.457
Depression	1 (0.2)	0	1 (0.6)	NA
Rash	31 (6.8)	13 (5.7)	15 (8.4)	0.278
Hepatotoxicity	62 (13.6)	30 (13.0)	24 (13.4)	0.914
Dyslipidaemia	37 (8.1)	16 (7.0)	19 (10.6)	0.190

NA, not available.

Previous studies have found a wide range of plasma efavirenz levels among different ethnic groups. In the ENCORE1 study in Asian, African and Caucasian participants, the median efavirenz concentration of a 600 mg daily dosage at week 48 was 2.85 (IQR 2.70–3.00) mg/L [19]. Among 843 European patients participating in the EuroSIDA study [25], a higher proportion of non-Caucasian patients had high efavirenz concentrations (> 4.0 mg/L) when compared with Caucasians (26.9% *vs.* 13.0%, respectively). In studies from largely Caucasian populations, high efavirenz concentrations (> 4.0 mg/L) have been reported in 13.1–18.9% of participants [6,26,27]. By contrast, a study of 80 South African patients, with a median efavirenz concentration of 3.98 mg/L, found that the proportion of patients with high efavirenz concentrations was 40% [28]. Another study with 540 Cambodian patients, with a median (IQR) efavirenz concentration at week 50 of 2.77 (1.94, 3.98) mg/L, found that proportion to be 20–30% [22]. A recent study from Taiwan [29] reported a median efavirenz concentration (IQR) of 2.82 (0.98–10.00) mg/L, and 22.2% of subjects had high efavirenz concentrations after at least 2 weeks of efavirenz treatment.

Over the course of our study, the proportion of patients with plasma efavirenz concentrations > 4.0 mg/L increased from 28.0% to 43.8%. These proportions are higher than previously reported in Caucasians, and closer to proportions reported in South Africa and Asia. This could be explained in part by the higher allelic frequency of CYP2B6 G516T genotype in Chinese HIV-infected patients compared with Caucasians [30,31]. Single nucleotide polymorphisms of *CYP2B6*, especially G516T, have been associated with higher plasma efavirenz concentrations leading to more frequent drug-related events [32]. In recent studies in HIV-infected Chinese patients [29,31,33,34], the allelic frequency of G516T ranged from 16% to 25%, which is higher than the 3–6% reported in Caucasians [30,35]. Efavirenz concentrations were higher in our study compared with patients enrolled in the study in Taiwan; however, the duration of treatment for the patients enrolled in that study was not specified.

In our cohort, the median plasma efavirenz concentration increased from 3.02 to 3.71 mg/L from week 4 to week 48; such findings were not reported in previous studies [22,36], and the mechanism of such an increase over time remains unclear. We speculate that one possibility is improved adherence over time. Another possibility is the inhibition of the activity of human cytochrome P450 by efavirenz during the ART period [37]. Multivariable regression analysis demonstrated that lower baseline

body weight and non-Han ethnicities were associated with higher efavirenz concentration during the observation period. Therefore, other possible explanations are the slight reduction in body weight from baseline to week 48, and the ethnic differences in the present study. One study examining the effect of concurrent rifampin therapy on plasma efavirenz concentrations did not find a change in efavirenz concentrations over time despite concerns that plasma levels would be low as a consequence of rifampin's impact on drug-metabolizing enzymes [22]. This raises the possibility that plasma efavirenz levels increased, offsetting the expected decrease in the setting of rifampin co-administration. More studies are needed to corroborate this finding, to investigate whether the increase continues beyond 1 year of treatment, and to further elucidate the potential mechanisms underlying this observation.

The frequency of suboptimal plasma efavirenz levels (< 1.0 mg/L) was very low in our study, and the adherence rate was 98.9%, demonstrating good adherence in patients. We did not find any correlation between efavirenz concentration and HIV suppression, which further reflects optimal adherence, and is consistent with results from previous studies, including the ENCORE1 trial [18,38].

Patients with HBV or HCV coinfection in our study appeared to have lower plasma efavirenz concentrations compared with monoinfected patients; however, no significant correlation with efavirenz concentration over time was found in the regression analysis and only one patient was found to have plasma efavirenz concentration < 1.0 mg/L at one of three time-points. Prior studies have demonstrated high efavirenz concentrations among coinfected patients with cirrhosis, as a result of the impact of impaired liver function on efavirenz metabolism [27]. No differences in efavirenz concentration have been reported in HBV- or HCV-coinfected patients without cirrhosis when compared with HIV-monoinfected patients [27,39]; however, one report showed a high efavirenz concentration in HCV-monoinfected patients without liver cirrhosis [40]. Patients with HBV or HCV infection in our study did not have cirrhosis. The exact aetiology of lower efavirenz concentrations in HBV- and HCV-coinfected patients in the present study remains unclear, and the small sample size limited our ability to perform more detailed subgroup analyses. However, this finding should be confirmed and explored further in future larger studies.

Body weight was an independent predictor for plasma efavirenz concentration in the present study, similar to the findings of prior studies [41–43]. However, these studies have generally focused on evaluating whether higher body weight leads to lower efavirenz concentrations and therefore lower antiretroviral efficacy. In general, despite the impact observed on plasma efavirenz concentrations, studies have shown that efficacy is not impacted by higher body weight, and therefore weight-based dose adjustment has not been recommended for patients with higher body weight [38,44]. Conversely, our study focused on individuals with lower body weight, and found that 50.0% of patients with body weight < 60 kg had plasma efavirenz concentrations > 4.0 mg/L.

In our study, the prevalence of neuropsychiatric symptoms was 16.3%, significantly lower than those reported in prior studies [45,46]. One review reported that neuropsychiatric adverse events of any grade related to efavirenz affected 29.6% [95% CI 21.9 to 37.3%] of patients, and 6.1% (95% CI 4.3 to 7.9%) of these events were considered to be severe [45]. In the 48-week ENCORE study, up to 50% of patients had CNS syndrome [46]. Possible explanations for the low rates of CNS symptoms in our study include: (1) although HIV-infected Chinese patients had higher efavirenz concentrations, they might have a better tolerance of the CNS adverse effects related to efavirenz; (2) the prevalence of neuropsychiatric adverse events might have been underestimated, because clinicians may not have recorded minor symptoms such as impaired concentration, anxiety or headache; and patients may have neglected to mention mild CNS symptoms. In our study, adverse events were collected based on patient self-report or clinician observation during follow-up examinations. No difference in the proportions of neuropsychiatric adverse events based upon efavirenz concentration was noted in the present study, which was contrary to findings from previous studies showing that CNS toxicity was more frequent in patients with high efavirenz levels, especially > 4.0 mg/L [6,47,48]. However, in the 2NN (NN=non-nucleoside) study, the Swiss HIV Cohort Study [49] and the EuroSIDA study [25], no relationship was observed between CNS events and efavirenz exposure [50], consistent with our results, suggesting that such discrepancies might also be related to differences in ethnicity, genetics, pharmacokinetics, and method of evaluation of CNS side effects.

Although there were no differences in the proportion of patients with dyslipidaemia among efavirenz concentration groups, we found that higher plasma efavirenz concentrations were associated with higher cholesterol and HDL-c. The former finding has been reported in previous studies [8,51], and a long-term and concentration-dependent beneficial effect of efavirenz on HDL-c in HIV-infected patients is also well documented [8,52,53]. It remains uncertain whether efavirenz has a net beneficial or detrimental effect on lipid metabolism in the long term.

The ENCORE1 trial researchers carried out a randomized controlled, double-blind, placebo-controlled, noninferiority trial in 630 patients with HIV infection across 13 countries that randomly assigned participants to receive tenofovir plus emtricitabine with either efavirenz 600 mg daily or a reduced dose of efavirenz 400 mg daily. At 48 weeks, the reduced dose was demonstrated to be noninferior to the standard dose, and fewer adverse effects attributable to the study drug were reported in the reduced dose group [16]. They concluded that the lower dose efavirenz should be considered in clinical practice. Specific groups of patients in which dose adjustment may be prudent to consider include patients from populations where the allelic frequency of the G516T polymorphism is known to be high, and, as suggested by our study, those with a body weight of < 60 kg.

Given what is known from previous studies, including the ENCORE1 trial, we feel that treatment with the 400 mg daily dose of efavirenz should be considered in our population, especially for individuals with low body weight. Our findings also support the most recent WHO guidelines [5], which propose efavirenz 400 mg daily as an alternative regimen for patients with HIV infection in low- and middle-income countries, and provide potential parameters using which the guidelines may be applied. In China, it is estimated that almost 260 000 HIV-infected patients are treated with efavirenz-containing regimens. Therefore, a recommendation for efavirenz dose adjustment would have a large influence in China. As a 200 mg formulation of efavirenz was recently approved for production (Shanghai Desano Pharmaceuticals Co., Ltd, Shanghai, China) by the Chinese food and drug administration, a seamless transition to 400 mg efavirenz dosing in the future is highly feasible [24].

Our study has two notable limitations that warrant mention. First, for the purposes of our study we were unable to perform genetic analysis to measure the frequency of the G516T polymorphism among our study participants. Secondly, we did not evaluate CNS adverse effects using a formal neuropsychological test battery such as the Hamilton Depression Scale, Dizziness Handicap Inventory, or Pittsburgh Sleep Quality Index, and therefore it is possible that the prevalence of CNS adverse effects has been underestimated in our cohort.

Conclusions

In conclusion, our study found that HIV-infected Chinese patients had higher plasma efavirenz concentrations compared with those reported in Caucasian populations, and that levels above 4.0 mg/L were particularly frequent among those with body weight < 60 kg. Based upon these findings, dosage reduction of efavirenz to 400 mg daily may warrant consideration in this population, especially in those with lower body weight, and future studies should evaluate this prospectively.

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Author contribution

FG, XC and TL participated in the conception and design of the study. FG, XC and EH performed the data analysis and drafted the manuscript. XD, QF, WP, YL and XS performed the original data collection (including patient recruitment, laboratory analyses and clinical data collection) and provided direct input into development of the methodology section of the manuscript. J-PR contributed to the writing of the manuscript. TL supervised the study. All authors reviewed and revised the draft, and approved the final version of the manuscript.

References

1 Young SD, Britcher SF, Tran LO *et al.* L-743, 726 (DMP-266): a novel, highly potent nonnucleoside inhibitor of the human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob Agents Chemother* 1995; **39**: 2602–2605.

2 US Food and Drug Administration. Center for Drug Evaluation and Research Medical Review Application number 20-972. Oct 19, 1998. http://accessdata.fda.gov/drugsatfda_docs/nda/98/20972clinical_review.pdf (accessed Sept 10, 2014).

3 Riddler SA, Haubrich R, DiRienzo AG *et al.* Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–2106.

4 van Leth F, Phanuphak P, Ruxrungtham K *et al.* Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN study. *Lancet* 2004; **363**: 1253–1263.

5 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach- Second edition. 2016 revision. World Health Organization. (Accessed June 2016 at http://www.who.int/hiv/pub/arv/chapter4.pdf.

6 Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; **15**: 71–75.

7 Yimer G, Amogne W, Habtewold A *et al.* High plasma efavirenz level and CYP2B6*6 are associated with efavirenz-based HAART-induced liver injury in the treatment of naive HIV patients from Ethiopia: a prospective cohort study. *Pharmacogenomics J* 2012; **12**: 499–506.

8 Sinxadi PZ, McIlleron HM, Dave JA *et al.* Plasma efavirenz concentrations are associated with lipid and glucose concentrations. *Medicine* 2016; **95**: e2385.

9 Rockstroh JK, DeJesus E, Lennox JL *et al.* Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr* 2013; **63**: 77–85.

10 Walmsley SL, Antela A, Clumeck N *et al.* Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369**: 1807–1818.

11 Mollan KR, Smurzynski M, Eron JJ *et al.* Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med* 2014; **161**: 1–10.

12 Lanzafame M, Lattuada E, Cucchetto G, Concia E, Vento S. Efavirenz dose reduction in HIV-infected patients: a long-term follow-up. *AIDS* 2014; **28**: 2789–2790.

13 Hui KH, Lee SS, Lam TN. Dose optimization of efavirenz based on individual CYP2B6 polymorphisms in Chinese patients positive for HIV. *CPT Pharmacometrics Syst Pharmacol* 2016; **5**: 182–191.

14 Gatanaga H, Oka S. Successful genotype-tailored treatment with small-dose efavirenz. *AIDS* 2009; **23**: 433–434.

15 Martín AS, Gómez AI, García-Berrocal B *et al.* Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. *Pharmacogenomics* 2014; **15**: 997–1006.

16 Carey D. Efavirenz 400 mg daily remains non-inferior to 600 mg: 96 week data from the double-blind, placebo-controlled ENCORE1 study. *J Int AIDS Soc* 2014; **17** (Suppl. 3): 19523.

17 ENCORE1 Study Group, Carey D, Puls R *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. *Lancet Infect Dis* 2015; **15**: 793–802.

18 Dickinson L, Amin J, Else L *et al.* Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz 400 and 600 mg in treatment-naive HIV-infected patients at 96 weeks: results of the ENCORE1 study. *Clin Pharmacokinet* 2016; **55**: 861–873.

19 Dickinson L, Amin J, Else L *et al.* Pharmacokinetic and pharmacodynamic comparison of once-daily efavirenz (400 mg vs. 600 mg) in treatment-naive HIV-infected patients: results of the ENCORE1 study. *Clin Pharmacol Ther* 2015; **98**: 406–416.

20 Li T, Guo F, Li Y *et al.* An antiretroviral regimen containing 6 months of stavudine followed by long-term zidovudine for first-line HIV therapy is optimal in resource-limited settings: a prospective, multicenter study in China. *Chin Med J (Engl).* 2014; **127**: 59–65.

21 Division of AIDS Table for grading the severity of the adults and pediatric adverse events version 1.0, December, 2004; Clarification August, 2009.

22 Borand L, Madec Y, Laureillard D *et al.* Plasma concentrations, efficacy and safety of efavirenz in HIV-infected adults treated for tuberculosis in Cambodia (ANRS 1295-CIPRA KH001 CAMELIA trial). *PLoS ONE* 2014; **9**: e90350.

23 Donnerer J, Haas BJ, Kessler HH. Single-measurement therapeutic drug monitoring of the HIV/AIDS drugs abacavir, zidovudine, lamivudine, efavirenz, nevirapine, lopinavir and nelfinavir. *Pharmacology* 2008; **82**: 287–292.

24 Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G. Comparison of six methods to estimate adherence in an ART-naive cohort in a resource-poor setting: which best predicts virological and resistance outcomes? *AIDS Res Ther* 2017; **14**: 20.

25 van Luin M, Bannister WP, Mocroft A *et al.* Absence of a relation between efavirenz plasma concentrations and

toxicity-driven efavirenz discontinuations in the EuroSIDA study. *Antivir Ther* 2009; **14**: 75–83.
26 Burger D, Van Der Heiden I, La Porte C *et al*. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; **61**: 148–154.
27 Meynard JL, Lacombe K, Poirier JM, Legrand J, Morand-Joubert L, Girard PM. Influence of liver fibrosis stage on plasma levels of efavirenz in HIV-infected patients with chronic hepatitis B or C. *J Antimicrob Chemother* 2009; **63**: 579–584.
28 Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G>T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther* 2010; **7**: 32.
29 Lee KY, Lin SW, Sun HY *et al*. Therapeutic drug monitoring and pharmacogenetic study of HIV-infected ethnic Chinese receiving efavirenz-containing antiretroviral therapy with or without rifampicin-based anti-tuberculous therapy. *PLoS ONE* 2014; **9**: e88497.
30 Haas DW, Ribaudo HJ, Kim RB *et al*. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004; **18**: 2391–2400.
31 Naftalin CM, Chan KC, Wong KH, Cheung SW, Chan RC, Lee SS. CYP2B6-G516T genotype influences plasma efavirenz concentration in a Hong Kong population, allowing potential individualization of therapy. *HIV Med* 2014; **15**: 63–64.
32 Wyen C, Hendra H, Siccardi M *et al*. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. *J Antimicrob Chemother* 2011; **66**: 2092–2098.
33 To KW, Liu ST, Cheung SW, Chan DP, Chan RC, Lee SS. Pharmacokinetics of plasma efavirenz and CYP2B6 polymorphism in southern Chinese. *Ther Drug Monit* 2009; **31**: 527–530.
34 Chen J, Sun J, Ma Q *et al*. CYP2B6 polymorphism and nonnucleoside reverse transcriptase inhibitor plasma concentrations in Chinese HIV-infected patients. *Ther Drug Monit* 2010; **32**: 573–578.
35 Powers V, Ward J, Gompels M. CYP2B6 G516T genotyping in a UK cohort of HIV-positive patients: polymorphism frequency and influence on efavirenz discontinuation. *HIV Med* 2009; **10**: 520–523.
36 Mukonzo JK, Okwera A, Nakasujja N *et al*. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study. *BMC Infect Dis* 2013; **13**: 261.
37 von Moltke LL, Greenblatt DJ, Granda BW *et al*. Inhibition of human cytochrome P450 isoforms by nonnucleoside reverse transcriptase inhibitors. *J Clin Pharmacol* 2001; **41**: 85–91.
38 Luetkemeyer AF, Rosenkranz SL, Lu D *et al*. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis* 2013; **57**: 586–593.
39 Pereira SA, Caixas U, Branco T *et al*. Efavirenz concentrations in HIV-infected patients with and without viral hepatitis. *Br J Clin Pharmacol* 2008; **66**: 551–555.
40 Calza L, Danese I, Colangeli V *et al*. Plasma concentrations of efavirenz, darunavir/ritonavir and raltegravir in HIV-HCV-coinfected patients without liver cirrhosis in comparison with HIV-monoinfected patients. *Infect Dis* 2015; **47**: 625–636.
41 Stohr W, Back D, Dunn D *et al*. Factors influencing efavirenz and nevirapine plasma concentration: effect of ethnicity, weight and co-medication. *Antivir Ther* 2008; **13**: 675–685.
42 Poeta J, Linden R, Antunes MV *et al*. Plasma concentrations of efavirenz are associated with body weight in HIV-positive individuals. *J Antimicrob Chemother* 2011; **66**: 2601–2604.
43 Dhoro M, Zvada S, Ngara B *et al*. CYP2B6*6, CYP2B6*18, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe. *BMC Pharmacol Toxicol* 2015; **16**: 4.
44 Marzolini C, Sabin C, Raffi F *et al*. Impact of body weight on virological and immunological responses to efavirenz-containing regimens in HIV-infected, treatment-naive adults. *AIDS* 2015; **29**: 193–200.
45 Ford N, Shubber Z, Pozniak A *et al*. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: a systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr* 2015; **69**: 422–429.
46 ENCORE1 Study Group, Puls R, Amin J *et al*. 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* 2014; **383**: 1474–1482.
47 Nunez M, Gonzalez de Requena D, Gallego L, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Higher efavirenz plasma levels correlate with development of insomnia. *J Acquir Immune Defic Syndr* 2001; **28**: 399–400.
48 Gutiérrez F, Navarro A, Padilla S *et al*. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis* 2005; **41**: 1648–1653.
49 Rotger M, Colombo S, Furrer H *et al*. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics* 2005; **15**: 1–5.

50 Kappelhoff BS, van Leth F, Robinson PA *et al.* Are adverse events of nevirapine and efavirenz related to plasma concentrations? *Antivir Ther* 2005; **10**: 489–498.
51 Gotti D, Cesana BM, Albini L *et al.* Increase in standard cholesterol and large HDL particle subclasses in antiretroviral-naive patients prescribed efavirenz compared to atazanavir/ritonavir. *HIV Clin Trials* 2012; **13**: 245–255.
52 Alonso-Villaverde C, Coll B, Gómez F *et al.* The efavirenz-induced increase in HDL-cholesterol is influenced by the multidrug resistance gene 1 C3435T polymorphism. *AIDS* 2005; **19**: 341–342.
53 Pereira SA, Branco T, Côrte-Real RM *et al.* Long-term and concentration-dependent beneficial effect of efavirenz on HDL-cholesterol in HIV-infected patients. *Br J Clin Pharmacol* 2006; **61**: 601–604.

