

## Case report

# Efavirenz in an obese HIV-infected patient – a report and an *in vitro–in vivo* extrapolation model indicate risk of underdosing

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Here, we report suboptimal efavirenz exposure in an obese patient treated with the standard 600 mg dose. Tripling the dose allowed attainment of therapeutic efavirenz concentrations. We developed an *in vitro–in vivo*

extrapolation model to quantify dose requirements in obese individuals. Obesity represents a risk factor for antiretroviral therapy underdosing.

## Introduction

With successful combined antiretroviral therapy (cART), HIV-infected individuals are increasingly overweight or obese at a rate similar to the general population [1]. Obesity is an additional challenge in the treatment of HIV infection as the recommended drug doses issued from clinical trials may not be sufficient.

Here, we describe a suboptimal therapeutic response in an obese (body mass index [BMI] 66 kg/m<sup>2</sup>) HIV-infected patient treated with the standard efavirenz (EFV) dose of 600 mg once daily and the subsequent clinical course after dose adjustment guided by therapeutic drug monitoring. We developed an *in vitro–in vivo* extrapolation model to quantify EFV dose requirements in individuals with various degrees of obesity.

## Methods

### *In vitro–in vivo* extrapolation

EFV pharmacokinetics (PK) was simulated using the physiologically-based pharmacokinetic (PBPK) model implemented in the Simcyp<sup>®</sup> population-based simulator (version 10.11; Simcyp<sup>®</sup> Limited, Sheffield, UK). *In vitro* data describing the physiochemical properties, the absorption and metabolism of EFV and the effect of genetic variants on protein expression were either obtained from published literature or quantified using

standard methods. Absorption was investigated *in vitro* using Caco-2 monolayers as previously described [2]. The distribution of EFV into tissues, the simulated volume of distribution and full PBPK option were obtained using the Poulin and Theil prediction method [3]. The intrinsic hepatic clearance (Cl<sub>int</sub>) values for cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes were obtained from available *in vitro* data on EFV metabolism [4–6]. The extrapolation of Cl<sub>int</sub> (derived from recombinant enzymes) to the population of interest characterized by parameters, such as abundance of CYP and liver weight, was based on the covariates described in Simcyp<sup>®</sup>. Three different metabolic pathways were considered: hydroxylation to 7-hydroxy EFV mediated by CYP2A6, hydroxylation to 8-hydroxy EFV mediated by CYP2B6, CYP2A6, CYP1A2, CYP3A4 and CYP3A5, and glucuronidation mediated by UGT2B7. The effect of 516 T allele on CYP2B6 expression was based on published literature [7] and its allele frequency was obtained from a publicly available SNPs database [8]. Modelling was based on the assumption of equal allelic distribution in obese and non-obese populations.

These parameters were used to simulate EFV PK in populations of 500 virtual Caucasians selected according to weight criteria: obese (BMI > 30 kg/m<sup>2</sup>) and non-obese (BMI < 25 kg/m<sup>2</sup>). The proportion of individuals with EFV

mid-dose concentrations (12 h post-dose [ $C_{12h}$ ]) above 1,000 ng/ml and below 4,000 ng/ml were calculated for different doses. These values were selected as they represent the commonly accepted EFV target concentrations for reduced risk of treatment failure and toxicity [9].

EFV drug levels were quantified by liquid chromatography coupled to tandem mass spectrometry (LC-MS) in accordance with previously validated methods [10,11].

## Results

### Case report

A 45-year-old morbidly obese (197 kg, 173 cm and BMI 66 kg/m<sup>2</sup>) Caucasian male tested positive for HIV infection in May 2007. At the time of the diagnosis, the CD4<sup>+</sup> T-cell count was 582 cells/mm<sup>3</sup> allowing deferral of cART. A highly active steatohepatitis with severe fibrosis due to fatty liver disease was diagnosed by liver biopsy in May 2010. In the same period, the CD4<sup>+</sup> T-cell count decreased to 202 cells/mm<sup>3</sup> and the HIV viral load was 72,000 copies/ml, which prompted the initiation of cART with tenofovir (300 mg), emtricitabine (200 mg) and efavirenz (600 mg) once daily.

Two weeks after cART initiation, the EFV plasma concentration (determined by validated LC-MS) was 806 ng/ml 18 h after dosing. Despite an early virological response (HIV RNA load decreased to 1,900 copies/ml), the EFV level was below the minimum target concentration of 1,000 ng/ml [9]. The patient reported good adherence and did not receive any comedication interacting with cART. Based on published data showing a negative correlation between body weight and EFV plasma concentrations [12], we concluded that the low observed EFV level may have resulted from inadequate dosing in this patient who weighed 203 kg at that time. Therefore, we increased EFV dose to 1,200 mg once daily at the beginning of June 2010. The plasma concentration of EFV 2 and 4 weeks after the dose increase was 1,855 ng/ml and 1,513 ng/ml 12 h after dosing, respectively. The patient reported good tolerance to EFV and was maintained at 1,200 mg once daily. Because the HIV RNA load was not fully suppressed (58 copies/ml), EFV concentration was measured again in October 2010. At that time, the patient weighed 210 kg and the EFV level was 1,422 ng/ml 12 h after dosing. Due to the progressive decrease in EFV concentrations and given the suboptimal viral suppression, EFV dose was further increased to 1,800 mg once daily at the end of October 2010. EFV concentration and viral load were measured 1 month after increasing EFV and the results indicated a concentration of 2,030 ng/ml 11 h after dosing and 40 copies/ml, respectively.

In February 2011, the patient presented a severe pneumonia that evolved into acute respiratory distress syndrome and renal failure requiring mechanical ventilation and hemofiltration. The transient renal failure prompted

the replacement of tenofovir and emtricitabine with abacavir plus lamivudine to avoid additional tenofovir-related nephrotoxicity. The patient's weight dropped to 180 kg during the 3 months of hospitalization. Abacavir 600 mg and lamivudine 300 mg once daily were maintained after discharge from the hospital together with EFV 1,800 mg once daily, which resulted in mid-dose EFV concentrations repetitively above 2,000 ng/ml (2,071 ng/ml in April 2011 and 2,300 ng/ml in June 2011). The HIV RNA load was undetectable (<20 copies/ml) when measured in March, July and December 2011.

### Pharmacokinetic simulations

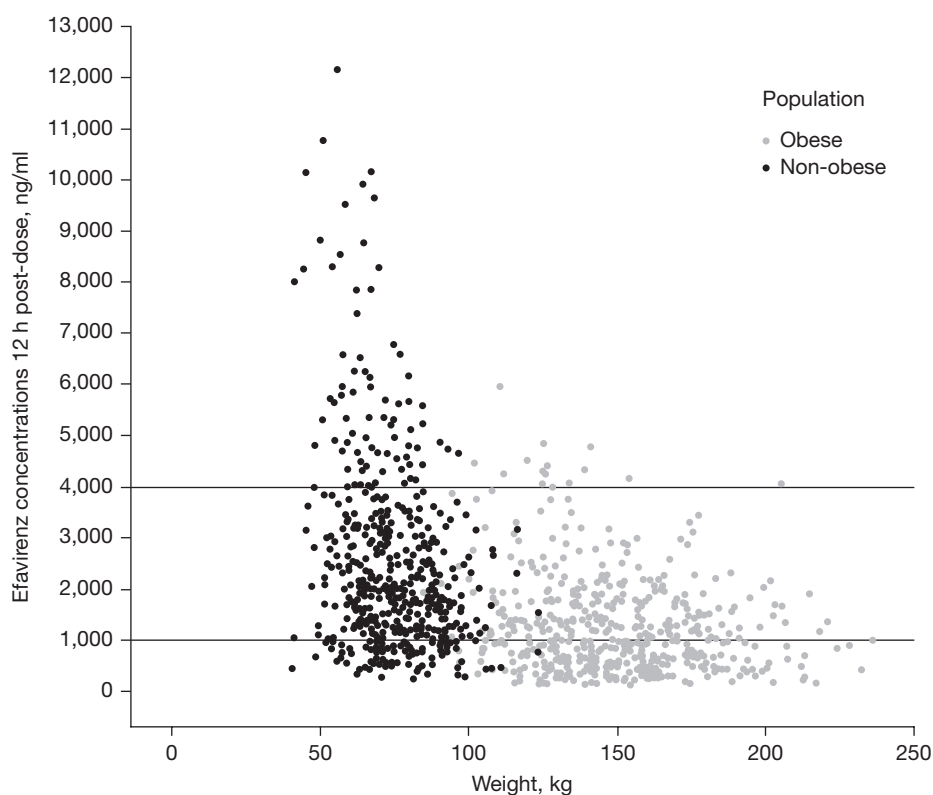
Simulated EFV PK variables at steady-state (600 mg once daily) for a cohort of 500 virtual non-obese individuals (mean  $\pm$ SD weight 74  $\pm$ 14 kg) were comparable with reference values [13]: the mean  $\pm$ SD simulated concentration at the end of the dosing interval ( $C_{trough}$ ) was 2,219  $\pm$ 1,784 versus 1,764  $\pm$ 1,011 ng/ml, the mean  $\pm$ SD maximum concentration ( $C_{max}$ ) was 3,457  $\pm$ 1,964 versus 4,064  $\pm$ 1,169 ng/ml and the mean  $\pm$ SD area under the curve (AUC) was 67,010  $\pm$ 47,204 versus 57,960 ng/ml•h. In 500 virtual obese individuals (mean  $\pm$ SD weight 148  $\pm$ 21 kg), simulated mean  $\pm$ SD  $C_{trough}$  was 1,080  $\pm$ 841 ng/ml, mean  $\pm$ SD  $C_{max}$  was 1,908  $\pm$ 1,022 ng/ml and mean  $\pm$ SD AUC was 36,668  $\pm$ 25,173 ng/ml•h. Simulated mean  $\pm$ SD  $C_{12h}$  was 2,534  $\pm$ 1,872 ng/ml and 1,313  $\pm$ 957 ng/ml in non-obese and obese individuals, respectively. A negative correlation between weight and  $C_{trough}$  was observed in both cohorts:  $r=-0.28$  ( $P=0.0001$ ) for non-obese and  $r=-0.221$  ( $P=0.0001$ ) for obese individuals.

At a dose of 600 mg once daily, 82% of non-obese versus 54% of obese individuals (all categories of obesity) had  $C_{12h}$  above 1,000 ng/ml. Furthermore, 84% of non-obese versus 95% of obese individuals had  $C_{12h}$  below 4,000 ng/ml (Figure 1). The proportion of individuals characterized by various degrees of obesity with  $C_{12h}$  above 1,000 ng/ml and below 4,000 ng/ml are summarized in Table 1.

## Discussion

Although it is well-documented that obesity translates into physiological changes that may alter drug disposition, there is a paucity of information on how to best adjust dose medication and, in particular, antiretroviral agents.

This report describes, for the first time, decreased EFV exposure in a morbidly obese patient. The consequent increase in the EFV maintenance dose observed in this patient is likely attributable to an increased metabolic clearance resulting from obesity-related changes in cardiac output, organ size and metabolic capacity. Because these changes are not proportional to an individual's body weight, simple dose adjustment based on body

**Figure 1.** Prediction of efavirenz mid-dose concentration in populations of non-obese<sup>a</sup> and obese<sup>b</sup> Caucasians

The area within the lines represents the efavirenz target concentrations (1,000–4,000 ng/ml). Predictions were performed using Simcyp<sup>®</sup> (version 10.11; Simcyp<sup>®</sup> Limited, Sheffield, UK). <sup>a</sup>Mean  $\pm$ SD weight of 74  $\pm$ 14 kg. <sup>b</sup>Mean  $\pm$ SD of 148  $\pm$ 21 kg.

**Table 1.** Proportion of non-obese and obese individuals<sup>a</sup> with efavirenz mid-dose concentrations >1,000 ng/ml and <4,000 ng/ml

| Weight                | Efavirenz dose once daily |                 |                 |                 |                 |                 |                 |                 |                 |                 |
|-----------------------|---------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                       | 600 mg                    |                 | 900 mg          |                 | 1,200 mg        |                 | 1,500 mg        |                 | 1,800 mg        |                 |
|                       | >1,000<br>ng/ml           | <4,000<br>ng/ml | >1,000<br>ng/ml | <4,000<br>ng/ml | >1,000<br>ng/ml | <4,000<br>ng/ml | >1,000<br>ng/ml | <4,000<br>ng/ml | >1,000<br>ng/ml | <4,000<br>ng/ml |
| Non-obese individuals | <b>82</b>                 | <b>84</b>       | –               | –               | –               | –               | –               | –               | –               | –               |
| 100–120 kg<br>(n=63)  | 67                        | 95              | <b>81</b>       | <b>84</b>       | 84              | 78              | 92              | 64              | 95              | 54              |
| 120–140 kg<br>(n=130) | 61                        | 94              | <b>76</b>       | <b>86</b>       | 85              | 76              | 88              | 63              | 92              | 52              |
| 140–160 kg<br>(n=135) | 48                        | 99              | 68              | 93              | <b>78</b>       | <b>84</b>       | 85              | 70              | 90              | 64              |
| 160–180 kg<br>(n=100) | 53                        | 100             | 69              | 95              | <b>79</b>       | <b>87</b>       | 85              | 74              | 87              | 65              |
| 180–200 kg<br>(n=41)  | 42                        | 100             | 56              | 100             | 63              | 93              | <b>83</b>       | <b>85</b>       | 88              | 81              |
| >200 kg<br>(n=23)     | 39                        | 96              | 61              | 96              | 69              | 91              | <b>83</b>       | <b>78</b>       | <b>83</b>       | <b>75</b>       |

The data in bold and italics indicate the efavirenz dose for a given degree of obesity that allows attainment of the target concentration range in a comparable proportion to non-obese individuals. <sup>a</sup>Classified by increasing degrees of obesity.

weight may not be optimal. Therefore, we used a PBPK approach that combines drug parameters with demographic, genetic and physiological factors describing the population of interest to predict the PK of EFV in obese subjects. Our simulations showed decreased EFV plasma concentrations in obese compared with non-obese individuals (Figure 1) and quantified dose requirements to reach therapeutic concentrations for various degrees of obesity (Table 1). Our predictions are in agreement with the clinical case because a tripling of EFV dose was required in the patient weighing >200 kg.

Besides changes in the metabolic clearance, obesity can increase the glomerular filtration rate [14]. The modification of the renal clearance may particularly impact drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), which are primarily cleared by the kidneys. The adjustment of renally cleared drugs is challenging as the estimation of glomerular filtration rate using conventional equations (Cockcroft–Gault; modification of diet in renal disease [MDRD]) has been shown to be inaccurate in obese patients [14]. Based on this consideration and the fact that active nucleoside triphosphates poorly correlate with plasma concentrations of the parent compound, we decided not to adjust the NRTI backbone. The retrospective evaluation of this case suggests that the persisting low replication of the virus, even after the increase of EFV dose, could reflect a suboptimal dosage of the NRTI backbone. Published data have indicated that tenofovir exposure was markedly decreased when the body weight/serum creatinine ratio increased, although no definitive dose adjustment is recommended in absence of clinical validation [15]. A 24 h urine collection would have been appropriate to measure the creatinine clearance and adjust the NRTI dose accordingly. Finally, it is important to emphasize that obesity constitutes a risk factor for lactic acidosis; thus, the use of NRTI warrants caution and careful clinical monitoring [14].

The improved health and the related increased prevalence of overweight/obese HIV-infected individuals should prompt research on antiretroviral dose requirements in obesity. Meanwhile, the use of therapeutic drug monitoring when appropriate and careful clinical judgement are imperative when treating obese individuals.

## Disclosure statement

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