

A Lower Dose of Efavirenz Can Be Coadministered With Rifampicin and Isoniazid in Tuberculosis Patients

TO THE EDITOR—The ENCORE-1 study demonstrated noninferiority of efavirenz 400 mg once daily (EFV400) when compared with the standard dose (EFV600) [1]. Based on these data, the World Health Organization (WHO) recommends EFV400 as an alternative first-line antiretroviral drug but restricts its use to nonpregnant patients and patients without tuberculosis (TB) [2]. However, a recently published study in United Kingdom human immunodeficiency virus (HIV)-positive patients without TB found EFV concentrations to be adequate when EFV400 was coadministered with rifampicin and isoniazid (RH) [3]. To confirm these results in a TB-infected population, we conducted an open label, nonrandomized, pharmacokinetic study in HIV/TB coinfecting patients in Uganda.

Ethics approval was obtained from the Joint Clinical Research Committee Institutional Research Board. We enrolled patients who were receiving EFV600 once daily plus lamivudine and tenofovir disoproxil fumarate or zidovudine for at least 3 weeks in addition to the WHO-recommended oral doses of RH. Thereafter, we reduced their EFV dose to 400 mg but maintained doses of the remaining drugs in their HIV and TB regimens.

To ensure prompt identification of subtherapeutic concentrations, we conducted twice-weekly therapeutic drug

monitoring (TDM) of EFV400 mid-dose concentrations. A priori, the protocol stipulated that patients with more than 3 low EFV levels (<800 ng/mL) would be withdrawn from the study and switched to EFV600. A threshold of 800 ng/mL was chosen based on the receiver operating characteristic (ROC) curve analysis performed in the ENCORE-1 study [4].

At 28 (\pm 7) days of EFV400 treatment, intensive pharmacokinetic sampling was performed at 0, 2, 4, 8, 12, and 24 hours postdose. Afterwards, patients had their EFV dose restored to 600 mg. We then measured EFV concentrations using a validated reversed-phase ultraperformance liquid chromatography coupled with UV detection method as described previously [3]. Pharmacokinetic parameters were calculated using noncompartmental techniques (WinNonlin Phoenix, version 7.0; Pharsight Corp, Mountain View, CA). Results were presented as geometric means and 95% confidence intervals. In addition, we performed genotyping of known functional polymorphisms linked with increased EFV concentrations (CYP2B6 516G>T [rs3745274, CYP2B6*6] and 983T>C [rs28399499, CYP2B6*18]) as described previously [3].

We enrolled 10 HIV/TB-coinfecting patients, 5 of whom were female. The median age and weight were 34 (range, 23–45) years and 54 (range, 41–65.5) kg, respectively. All subjects completed day 28 (1 missed the 24-hour pharmacokinetic blood draw). Median baseline and day 28 viral load were 38.5 (range,

10–405 081) and 10 (range, 10–393 886) copies/mL, respectively.

No study subjects had to be withdrawn from the study before day 28 because of EFV TDM results below 800 ng/mL. One subject had EFV concentrations below 800 ng/mL before and on day 28 and had to be discontinued; however, these were all above 470 ng/mL, the lower limit of the ROC curve established by Dickinson et al [4] in the ENCORE-1 pharmacokinetic substudy. Of the 10 subjects, 9 were genotyped. Four subjects were EFV intermediate metabolizers (as carriers of 2 variant alleles at position 516 but none at 983) and showed higher EFV concentrations despite the EFV dose reduction. On the other hand, 5 subjects were extensive metabolizers with no variant allele at position 516 or 983.

Efavirenz 400 mg once daily with RH pharmacokinetic parameters at day 28 are shown in Table 1. Overall, target EFV concentrations were achieved in TB-HIV-coinfecting patients receiving EFV400 once daily when coadministered with RH, with EFV trough concentrations maintained above those measured by Cerrone et al [3] when EFV400 was coadministered with RH in people living with HIV but not TB.

CONCLUSIONS

This study provides the first clinical data on the use of EFV400 in HIV-TB-coinfecting patients and adds further support for the coadministration of EFV400 with RH in HIV/TB-coinfecting patients.

Table 1. EFV PK Parameters During Coadministration With Rifampicin and Isoniazid in People Living With HIV and Coinfecting With Tuberculosis in Uganda (n = 10)

PK Parameter	C_{max} (ng/mL)	C_{24h} (ng/mL)	AUC (ng \times h/mL)
Geometric mean, 95% confidence intervals	2814 (1714–4620)	1806 (982–3321)	50269 (26520–95287)
Coefficient of variation	69%	75%	75%

Abbreviations: AUC, area under the curve; C_{max} , maximum concentration; C_{24h} , 24 hours postdose concentration; EFV, efavirenz; HIV, human immunodeficiency virus; PK, pharmacokinetic.

Results from this study should be validated in a larger cohort.

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