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CORRESPONDENCE

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 coinfected 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800 ng/mL) would be withdrawn from the study and switched to EFV600.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 (±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-coinfected 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-coinfected 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-coinfected patients and adds further support for the coadministration of EFV400 with RH in HIV/TB-coinfected patients.

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

PK Parameter	C_{max} (ng/mL)	C_{24h} (ng/mL)	AUC (ng × 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.

Acknowledgments

We are grateful to the study participants and to the study team at Infectious Diseases Institute for their dedicated work. We also thank the following: David Back (University of Liverpool, Liverpool, UK), Laura Waters (University College London, London, UK), and Freya Chapman (St. Stephen's AIDS Trust (SSAT), Chelsea and Westminster Hospital, London, UK) for advice on study design and being part of the protocol steering committee; Melynda Watkins and Paul Domanico from Clinton Health Access Initiative for support on study design and completion; and the research teams at St Stephen's Clinical Research for their hard work. We are grateful to the National Institute for Health Research, Biomedical Research Centre at Imperial College for its support of this study.

Disclaimer. The views expressed do not necessarily reflect the views of the US President's Emergency Plan for AIDS Relief (PEPFAR), US Agency for International Development (USAID), or the United States Government.

Financial support. This work was funded by a research grant from Mylan N. V. through the OPTIMIZE project. The USAID invests in OPTIMIZE through its support of a global consortium, led by WITS RHI, that includes ICAP at Columbia University, Mylan Laboratories, the University of Liverpool, and the Medicines Patent Pool. The USAID is a key implementing agency of the PEPFAR and is responsible for over half of all PEPFAR programs with activities focused in 35 priority countries and regions, mainly in sub-Saharan Africa and Asia. For more information, please visit www.usaid.gov.

Potential conflicts of interest. A. O. has received research funding from Merck, AstraZeneca, Pfizer, ViiV Healthcare, and Janssen and consultancy for Merck and ViiV Healthcare. He is also coinventor of patents relating to nanotechnology-based drug delivery systems. M. L. reports grants and personal fees from Mylan, grants from Janssen, and grants and nonfinancial support from ViiV. M. B. has received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, and Teva. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Julian P. Kaboggoza,[1] Xinxhu Wang,[2] Megan Neary,[3] Pedro Ayuso,[3] Christine Sekaggya-Wiltshire,[1] Shadia Nakalema,[1] Andrew Owen,[3] Myra McClure,[2] Mohammed Lamorde,[1] and Marta Boffito[2,4]

[1]Infectious Diseases Institute, Makerere University College of Health Sciences, Mulago Hospital Complex, Kampala, Uganda; [2]Jeffriess Research Trust Laboratories, Department of Medicine, Imperial College, London, United Kingdom; [3]Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, United Kingdom; [4]St Stephen's Clinical Research, Chelsea and Westminster Hospital, London, United Kingdom

Keywords. HIV; isoniazid/rifampicin; low-dose efavirenz; pharmacokinetics; tuberculosis.

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Received 15 November 2018; editorial decision 15 January 2019; accepted 15 January 2019.

Correspondence: J. Kaboggoza, BPharm, Infectious Diseases Institute, Makerere University College of Health Sciences, P.O. Box 22418, Kampala, Uganda (jkaboggoza@idi.co.ug).

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DOI: 10.1093/ofid/ofz035