High efavirenz serum concentrations in TB/HIV-coinfected Ugandan adults with a CYP2B6 516 TT genotype on anti-TB treatment

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Received 27 April 2018; returned 26 June 2018; revised 5 August 2018; accepted 24 August 2018

Objectives: To report the efavirenz serum concentrations in TB/HIV-coinfected Ugandan adults on concomitant anti-TB treatment and analyse factors associated with elevated concentrations in this specific population.

Methods: Serum efavirenz concentrations in TB/HIV-coinfected Ugandan adults on efavirenz-based ART (600 mg daily) were measured onsite at 2, 8, 12 and 24 weeks of concomitant anti-TB treatment, including rifampicin. Genetic analysis was done retrospectively through real-time PCR by allelic discrimination (CYP2B6 516G>T, rs3745274). Univariable and multivariable logistic regression analyses were done to assess factors potentially associated with elevated efavirenz serum concentrations.

Results: A total of 166 patients were included in the analysis. The median age was 34 (IQR 30–40) years, 99 (59.6%) were male, the median CD4 cell count was 195 (IQR 71–334) cells/mm3 and the median BMI was 19 (IQR 17.6–21.5) kg/m2. Almost half of all patients (82, 49.4%) had at least one efavirenz serum concentration above the reference range of 4 mg/L. The serum efavirenz concentrations of patients with genotype CYP2B6 516 TT were consistently above 4 mg/L and significantly higher than those of patients with GG/GT genotypes: CYP2B6 516 TT 9.6 mg/L (IQR 7.3–13.3) versus CYP2B6 516 GT 3.4 mg/L (IQR 2.1–5.1) and CYP2B6 516 GG 2.6 mg/L (IQR 1.3–4.0) (Wilcoxon rank-sum test: P = 0.0001).

Conclusions: A large proportion of our study participants had at least one efavirenz serum concentration >4 mg/L. The CYP2B6 516 TT genotype was the strongest predictor of high concentration. Physicians should be vigilant that efavirenz serum concentrations may be elevated in patients on concomitant anti-TB treatment and that individualized care is warranted whenever possible.

Introduction

In 2016, the WHO reported 44 816 new cases of TB in Uganda, of which 51% were coinfected with HIV, ranking the country among the top 20 high-burden countries for TB/HIV coinfection.1

HIV-infected patients diagnosed with TB are preferably treated with efavirenz-based ART at a dose of 600 mg daily despite complex drug–drug interactions with rifampicin-based anti-TB treatment.2 Efavirenz is known for its neuropsychological side effects,3 predominantly occurring in patients with serum drug levels above the reference range.4,5 High efavirenz serum concentrations are associated with slow metabolism due to SNPs at positions 516 and 983 of the cytochrome P450 (CYP) 2B6 gene, which occur more frequently in the African population [frequency of 18% according to HapMap-YRI (sub-Saharan African)].6

As a potent inducer of CYP2B6, the additional influence of rifampicin on efavirenz concentrations is complex. Previous studies reported a decrease in efavirenz concentrations,7 while others found no evidence of reduced efavirenz exposure in the presence of rifampicin,8 resulting in an ongoing discussion on efavirenz dose reduction. Furthermore, as standard first-line anti-TB treatment includes isoniazid as well, it should be mentioned that the potential inducing effect of rifampicin may be counterbalanced by the concentration-dependent inhibitory effect of isoniazid on efavirenz clearance.9

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A randomized clinical trial demonstrated non-inferiority of an efavirenz dose of 400 versus 600 mg. However, patients coinfected with TB were not included in the study. A previous study from Uganda that enrolled 158 TB/HIV-coinfected patients showed that simulated AUCs for a 600 mg efavirenz dose were 1.2 and 2.4 times greater than the product label for study participants in general and CYP2B6 genotypes, respectively. According to the authors, efavirenz daily doses of 450 and 250 mg for HIV-infected Ugandans in general and individuals homozygous for CYP2B6*6 genotypes receiving rifampicin co-treatment, respectively, yielded simulated exposures comparable to the product label.

Further research on treatment optimization in TB/HIV-coinfected patients is needed. We report here the pharmacokinetic and pharmacogenetic data from a clinical cohort study on TB/HIV-coinfected Ugandan adults and assess factors associated with elevated serum efavirenz concentrations in this specific population.

Methods

Between June 2013 and November 2015, pharmacokinetic data of TB/HIV-coinfected patients on rifampicin-based anti-TB therapy and ART including 600 mg of efavirenz was prospectively collected at the integrated TB/HIV clinic of the Infectious Diseases Institute in Kampala, Uganda. All patients were above the age of 18 years and participants in a clinical trial, with signed informed consent. Serum efavirenz concentrations were measured onsite using a validated UV-HPLC method after 2, 8 and 24 weeks of anti-TB therapy. For patients requiring an extended intensive TB treatment phase of 12 weeks, serum efavirenz concentrations were additionally measured at week 12. Genetic analysis was done onsite retrospectively through real-time PCR by allelic discrimination (CYP2B6 516G>T, rs3745274).

Characteristics of study participants (age, gender, weight, BMI, CD4 cell count, haemoglobin, creatinine and ALT) with at least one efavirenz serum concentration above the upper limit of 4 mg/L were compared with those with concentrations within the reference range (1–4 mg/L) using the Wilcoxon rank-sum test. To assess factors potentially associated with elevated efavirenz serum concentrations, covariates were further investigated by univariable and multivariable logistic regression analyses using generalized estimating equations to account for multiple measurements per patient. These analyses were restricted to patients with available CYP2B6 genotype and included age (per 10 years older), gender and weight (per 10 kg higher). Haemoglobin was strongly correlated with weight and therefore omitted.

This study was reviewed and approved by the Makerere University School of Medicine Research and Ethics Committee (Approval number: 120-2009) and the Uganda National Council for Science and Technology (HS 683).

Results

A total of 166 TB/HIV-coinfected patients on efavirenz-based ART and concomitant anti-TB treatment with at least one efavirenz serum measurement during anti-TB treatment and available CYP2B6 genotype were included in this analysis. The median age was 34 (IQR = 30–40) years, 99 (59.6%) were male, the median CD4 cell count was 195 (IQR = 71–334) cells/mm³ and the median BMI was 19 (IQR = 17.6–21.5) kg/m². Most patients (134, 80.7%) were ART naive at TB diagnosis and started on an efavirenz-based regimen 2 weeks after initiation of anti-TB therapy. Twenty-nine patients (17.5%) were already on efavirenz when anti-TB treatment was initiated, while three (1.8%) patients were switched from nevirapine to efavirenz upon diagnosis of TB. The results of CYP2B6 516G>T genotyping for all 166 patients included in this analysis were as follows: 60 (36.1%) had genotype CYP2B6 516 GG, 81 (48.8%) had genotype CYP2B6 516 GT and 25 (15.1%) had genotype CYP2B6 516 TT.

A total of 333 efavirenz serum concentration measurements from 166 study participants were available for analysis, of which 176 (52.9%) were above the upper limit of 4 mg/L. The median time between last efavirenz dose and blood draw was 11.75 (IQR = 10.75–13.17) h. A total of 82 (49.4%) patients had at least one efavirenz concentration of >4 mg/L. The median efavirenz concentration among these patients was 7.1 (IQR = 5–12.5) mg/L, while those within the reference range had a median concentration of 2.1 (IQR = 1.2–3.0) mg/L. Thirty (18.1%) patients had at least one value below the lower limit of 1 mg/L, of which 24 patients had a single value <1 mg/L, 4 patients had two values <1 mg/L and 2 patients had three or more values below the reference range.

Patients with elevated efavirenz concentrations had a significantly lower median body weight (49 (IQR = 45–55.5) versus 53 (IQR = 48–58) kg, P = 0.007) and median haemoglobin concentration (10.4 (IQR = 9.7–11.4) versus 11 g/dL (IQR = 9.4–12.8), P = 0.01) compared with patients with efavirenz concentrations within the reference range. There was no significant difference in gender (male gender: 63.5% versus 59.8%, Pearson χ² = 0.366), median age (34 versus 33 years, P = 0.098), median CD4 cell count (195 versus 134 cells/mm³, P = 0.073), median creatinine (0.65 versus 0.63 mg/dL, P = 0.244) and median ALT (20 versus 19.5 U/L, P = 0.809) between the groups.

In patients with a CYP2B6 516 TT genotype the median efavirenz serum concentration was consistently above the upper limit of 4 mg/L and significantly higher compared with GG/GT genotypes: CYP2B6 516 TT 9.6 mg/L (IQR = 7.3–13.3) versus CYP2B6 516 GT 3.4 mg/L (IQR = 2.1–5.1) and CYP2B6 516 GG 2.6 mg/L (IQR = 1.3–4.0) (Wilcoxon rank-sum test: P < 0.0001) (Figure 1). As shown in

![Figure 1. Efavirenz serum concentrations in TB/HIV-coinfected Ugandan patients grouped according to CYP2B6 516 genotypes (n = 166). Line at 4 mg/L = upper limit of efavirenz reference range. The box extends from the 25th to the 75th percentile with a horizontal line at the 50th percentile (median). Whiskers extend to ±1.5 times the IQR (height of the box) or the maximum/minimum value if there are no values (outliers) beyond these whiskers.](https://academic.oup.com/jac/advance-article-abstract/doi/10.1093/jac/dky379/5101396/19)
Table 1. Univariable and multivariable logistic regression analyses with generalized estimating equations using 333 efavirenz serum concentration measurements from 166 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (per 10 years older)</td>
<td>1.044</td>
<td>0.735–1.483</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.563</td>
<td>0.316–1.001</td>
</tr>
<tr>
<td>Weight (per 10 kg higher)</td>
<td>0.662</td>
<td>0.454–0.963</td>
</tr>
<tr>
<td>CYP2B6 genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>1</td>
<td>(reference)</td>
</tr>
<tr>
<td>GT</td>
<td>1.624</td>
<td>0.856–3.081</td>
</tr>
<tr>
<td>TT</td>
<td>27.89</td>
<td>7.560–102.9</td>
</tr>
</tbody>
</table>

Table 1, CYP2B6 genetic variant was the only factor independently associated with elevated serum efavirenz concentration in the univariable and multivariable analyses (multivariable analysis: OR = 28.944, 95% CI = 7.121–117.64, P<0.0001).

Discussion

For the majority of our study participants, serum efavirenz concentrations were within the reference range. However, almost half of our patients (n = 82, 49.4%) had at least one efavirenz serum concentration above the upper limit of 4 mg/L. The CYP2B6 516 TT genotype was the strongest predictor of efavirenz levels above the reference range, which is in line with previous studies.

Our study has a few limitations. Firstly, we did not systematically collect information on potential neuropsychiatric side effects in our cohort, so no conclusions can be drawn regarding whether the high efavirenz serum concentrations observed led to more side effects in this population. Secondly, the interpretation of the CYP2B6 genotype analysis is partly limited by the scope of testing (516G>T polymorphism only), as other polymorphisms may contribute to the high efavirenz serum concentrations observed in our study.

Genotype-guided dosing is not yet feasible in this setting. However, efavirenz dose reduction from 600 to 400 mg, as previously identified as an efficacious option for patients without TB coinfection,10 is expected to be feasible in TB/HIV-coinfected patients as well.11 Whether this would result in a significantly reduced efavirenz exposure in individuals with the CYP2B6 516 TT genotype is, however, not certain. We conclude that physicians should be vigilant that efavirenz serum concentrations may be elevated in patients, despite concomitant anti-TB treatment including rifampicin, and that individualized care is warranted whenever possible.

Funding

This work was supported by the collaboration between the Infectious Diseases Institute in Kampala, Uganda and the University of Zürich in Switzerland. The collaboration is supported by the pharmaceutical companies AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViV Healthcare, as well as by Lunge Zürich, Shimadzu and the Swiss HIV Cohort Study. The funders had no role in the design, data collection, analysis or reporting of this study.

Transparency declarations

J. F. has received grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Merck, ViV Healthcare and Roche Diagnostics outside the submitted work. All other authors: none to declare.

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Cohort profile of a study on outcomes related to tuberculosis and antiretroviral drug concentrations in Uganda: design, methods and patient characteristics of the SOUTH study. *BMJ Open* 2017; 7: e014679.