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

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Title: High efavirenz serum concentrations in TB/HIV co-infected Ugandan adults with CYP2B6 516 TT genotype on anti-TB treatment

Short title: Efavirenz in TB/HIV co-infection

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Abstract

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

Methods: Serum efavirenz concentrations in TB/HIV co-infected Ugandan adults on efavirenz-based ART (600mg daily) were measured on-site 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). Uni- 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 (63.5%) were male, the median CD4 cell count was 195 (IQR: 71;334) cells/mm³, and the median BMI was 19 (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 4mg/L and significantly higher compared to patients with GG/GT genotypes: CYP2B6 516 TT 9.6mg/L (IQR: 7.3;13.3) versus CYP2B6 516 GT 3.4mg/L (IQR: 2.1;5.1) and CYP2B6 516 GG 2.6mg/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 >4mg/L. CYP2B6 516 TT genotype was the strongest predictor of high concentrations. 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.
Brief report

Background:
In 2016, the WHO reported 44,816 new cases of TB in Uganda, of which 51% were co-infected with HIV, ranking the country among the top 20 high burden countries for TB/HIV co-infection.\(^1\)

HIV-infected patients diagnosed with TB are preferably treated with efavirenz-based ART at a dose of 600mg daily despite complex drug-drug interactions with rifampicin-based anti-TB treatment.\(^2\)

Efavirenz is known for 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 single nucleotide polymorphisms (SNP) at the positions 516 and 983 of 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.\(^9\)

A randomized clinical trial demonstrated non-inferiority of efavirenz dose 400 mg versus 600 mg.\(^10\) However, patients co-infected with TB were not included in the study. A previous study from Uganda which enrolled 158 TB/HIV co-infected patients showed that simulated area under the curves (AUCs) for 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.\(^11\) 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 co-infected patients is needed. We report here the pharmacokinetic and pharmacogenetic data from a clinical cohort study on TB/HIV co-
infected Ugandan adults, and assessed factors associated with elevated serum efavirenz concentrations in this specific population.
Methods:
Between June 2013 and November 2015, pharmacokinetic data of TB/HIV co-infected patients on rifampicin-based anti-TB therapy and ART including 600mg efavirenz was prospectively collected at the integrated TB/HIV clinic of the Infectious Disease Institute in Kampala, Uganda. All patients were above the age of 18 years and participants of a clinical trial, with signed informed consent. Serum efavirenz concentrations were measured on-site 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 on-site retrospectively through real-time PCR by allelic discrimination (CYP2B6 516G>T, rs3745274).

Characteristics of study participants (age, gender, weight, BMI, CD4 cell count, hemoglobin, creatinine, alanine aminotransferase) with at least one efavirenz serum concentration above the upper limit of 4mg/L were compared to those with concentrations within the reference range (1-4mg/L)^5 using Wilcoxon rank-sum test. To assess factors potentially associated with elevated efavirenz serum concentrations, co-variates were further investigated by uni- 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 10kg higher). Hemoglobin 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 co-infected 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 (63.5%) were male, the median CD4 cell count was 195 (IQR: 71;334) cells/mm$^3$, and the median BMI was 19 (17.6;21.5) kg/m$^2$. Most patients (134, 63.5%) were ART naïve at TB diagnosis and started on an efavirenz-based regimen two 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%) genotype CYP2B6 516 GT, and 25 (15.1%) 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 4mg/L. The median time between last efavirenz dose and blood draw was 11.75 (IQR: 10.75;13.17) hours. A total of 82 (49.4%) patients had at least one efavirenz concentration of >4mg/L. The median efavirenz concentration among these patients was 7.1mg/L (IQR: 5;12.5), while those within the reference range had a median concentration of 2.1mg/L (IQR: 1.2;3.0). Thirty (18.1%) patients ever had values below the lower limit of 1mg/L, of which 24 patients had a single value <1mg/L, four patients had two values < 1mg/L, and two patients had three or more values below the reference range. Patients with elevated efavirenz concentrations had a significantly lower median body weight (49kg (IQR: 45;55.5) versus 53kg (IQR: 48;58), p-value=0.007), and median hemoglobin concentration (10.2 g/dL (IQR: 8.7;11.4) versus 11 g/dL (IQR: 9.4;12.8), p-value=0.01) compared to patients with efavirenz concentrations within the reference range. There was no significant difference in gender (male gender: 63.5% versus 59.8%, Pearson chi2=0.366), median age (34 years versus 33 years, p-value=0.098), CD4 cell count (195 cells/mm$^3$ versus 131 cells/mm$^3$, p-value=0.073), median creatinine (0.65 mg/dL versus 0.63 mg/dL, p-value=0.244), and alanine aminotransferase (20 U/L versus 19.5 U/L, p-value=0.809) between the groups.
In patients with CYP2B6 516 TT genotype the median efavirenz serum concentration was consistently above the upper limit of 4mg/L, and significantly higher compared to GG/GT genotypes: TT 9.6mg/L (IQR: 7.3;13.3) versus GT 3.4mg/L (IQR: 2.1;5.1) and GG 2.6mg/L (IQR: 1.3;4.0) (Wilcoxon rank-sum test: p<0.0001) (Figure 1). As shown in table 1, CYP2B6 genetic variant was the only factor independently associated with elevated serum efavirenz concentration in the uni- and multivariable analysis (aOR: 28.9, 95% CI: 7.12-117.64, p-value=<0.001).
Conclusions:

For the majority of our study participants, serum efavirenz concentrations were within reference range. However, almost half of our patients (n=82, 49.4%) had at least one efavirenz serum concentration above the upper limit of 4mg/L. \textit{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 that no conclusions can be drawn whether the high efavirenz serum concentrations observed lead to more side effects in this population. Secondly, the interpretation of the \textit{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 600mg to 400mg - as previously identified as an efficacious option for patients without TB co-infection - is expected to be feasible in TB/HIV co-infected patients as well. Whether this would result in a significantly reduced efavirenz exposure in individuals with \textit{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

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Transparency declaration

Jan Fehr has received grants from Abbvie, Bristol Myers Squibb, Gilead Sciences, Janssen Merck, ViiV Healthcare and Roche Diagnostics outside the submitted work. The other authors declare that they have no conflict of interests.
References


Table 1: Univariable and multivariable logistic regression analyses with generalized estimating equations using 333 efavirenz serum concentration measurements from 166 patients.

<table>
<thead>
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<th>Variable</th>
<th>Univariable analysis</th>
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<th></th>
<th>Multivariable analysis</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
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<tr>
<td>Age (per 10 years older)</td>
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<td>0.735 – 1.483</td>
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<td>0.050</td>
<td>0.535</td>
<td>0.287 – 0.996</td>
<td>0.048</td>
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<tr>
<td>Weight (per 10kg higher)</td>
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<td>0.454 – 0.963</td>
<td>0.031</td>
<td>0.665</td>
<td>0.454 – 0.974</td>
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<td>(reference)</td>
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<td>28.944</td>
<td>7.121 – 117.6</td>
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</tbody>
</table>

Figure 1: Efavirenz serum concentrations in TB/HIV co-infected Ugandan patients grouped according to CYP2B6 516 genotypes (n=166)

Line at 4mg/L: upper limit of efavirenz reference range