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Is there a need to increase the dose of efavirenz during concomitant rifampicin-based antituberculosis therapy in sub-Saharan Africa? The HIV-TB pharmagene study

Aims: The current HIV treatment guidelines are inconsistent about the need for weight-based efavirenz dose adjustment during rifampicin containing antituberculosis (anti-TB) cotreatment. We investigated effect of rifampicin-based anti-TB cotreatment on plasma efavirenz exposure and treatment outcome, considering effect of *CYP2B6* genotype and bodyweight. **Patients & methods:** HIV-only (arm 1, $n = 285$) or TB-HIV (arm 2, $n = 208$) coinfecting patients were enrolled and received efavirenz-based ART alone or with rifampicin-based anti-TB therapy, respectively. Plasma efavirenz concentrations at 4th and 16th weeks, viral load and CD4 cell count at 24th and 48th weeks were determined. **Results:** The mean plasma efavirenz concentration at weeks 4 ($p = 0.03$) and 16 ($p = 0.08$) was inconsistently higher in arm 2 than arm 1, mainly in *CYP2B6**6 carriers. Effect of bodyweight on efavirenz pharmacokinetics was significant only in arm 1, but not in arm 2. Proportion of patients with nondetectable viral load (≤ 50 copies/ml) at week 24 was higher in arm 1 than arm 2 patients (91.0 vs 76.3%; $p = 0.002$), but no significant difference was observed at week 48 (89.5 vs 87.8%; $p = 0.22$). **Conclusion:** Rifampicin-based anti-TB cotreatment has no significant influence on long-term efavirenz plasma exposure and efficacy. Hence, there is no need to increase the dose of efavirenz during concomitant rifampicin-based anti-TB cotreatment in the sub-Saharan African population.

Keywords: *CYP2B6* • efavirenz • Ethiopia • HIV/AIDS • rifampicin • sub-Saharan Africa • treatment guideline • tuberculosis

Tuberculosis (TB) is the most common opportunistic infection and cause of death in HIV-infected patients. HIV infected individuals with active TB need to be treated with both anti-TB and antiretroviral therapy (ART). However, the high pill burden, significant drug-drug interactions and additive toxicities from concomitant antiretroviral (ARV) and anti-TB drugs use remain challenging [1–3]. Rifampicin (RIF), a cornerstone first-line anti-TB drugs in resource-limited countries, is a potent inducer of drug metabolizing enzymes and transporter proteins, and this may reduce plasma exposure of antiretroviral drugs including protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Despite its long-term auto-induction effect [4–7], efavirenz (EFV) is

the preferred NNRTI to be used with RIF-based anti-TB therapy because of its proved efficacy, simpler dosing schedule, better side-effect profile and reduced impact on its pharmacokinetics compared with nevirapine or protease inhibitors [8–10].

CYP2B6, the major EFV-metabolizing enzyme, is induced by EFV and RIF. Therefore, coadministration of RIF with EFV may result in additive effect to induce *CYP2B6* enzyme and this may further reduce systemic EFV exposure. Earlier studies in white population [11] and in healthy volunteers [12] reported that RIF coadministration decreases plasma exposures of EFV. In a relatively small number of patients, a previous study suggested to increase the EFV dose from 600 to 800 mg/day to compensate for the

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effect of RIF induction, particularly in patients with baseline bodyweight >50 kg [11]. Using pharmacokinetic simulation of nonclinical data to predict human EFV exposure in healthy volunteers, Rekić *et al.* suggested increasing the EFV dose during concomitant RIF treatment mainly in patients weighing >50 kg regardless of *CYP2B6* genotype [13]. However, studies from diverse populations, mainly in black and Asian populations, reported no effect of RIF on EFV plasma concentration or increase in plasma EFV concentration during RIF-based anti-TB treatment [14–20]. The extent of EFV auto-induction over time and EFV plasma exposure varies between populations, partly due to *CYP2B6* pharmacogenetic variations [21]. Therefore findings on EFV-RIF drug interaction study from one population may not be extrapolated to others. Besides, the impact of RIF coadministration on EFV-based ART virologic suppression and immunologic recovery is understudied.

The current TB–HIV treatment guidelines are inconsistent as to whether or not to increase the dose of EFV during concomitant RIF-based anti-TB therapy. The International Antiviral Society-USA panel recommend increasing the dose of EFV from 600 to 800 mg/day when coadministered with RIF in patients with pretreatment bodyweight of >50 kg [22]. Recently, the US FDA approved a revised EFV package label recommending a 800-mg EFV dose for patients receiving RIF-based anti-TB treatment who weigh >50 kg [23]. The British HIV Association guidelines for the treatment of TB–HIV coinfection recommend increasing dose of EFV from 600 to 800 mg/day during RIF-based anti-TB treatment in patients weighing >60 kg [24]. However, the current WHO TB–HIV treatment guideline recommends using the standard EFV dose (600 mg/day) irrespective of bodyweight during concomitant RIF therapy. Consequently, extensive RIF-EFV interaction studies evaluating not only the effect on EFV concentration but also its effect on HIV antiretroviral treatment outcome in diverse populations are urgently needed.

In the present study, we performed a two-arm parallel prospective study to investigate the effect of RIF-based anti-TB treatment on plasma EFV exposure and treatment response considering both the safety (incidence of drug-induced liver toxicity) and efficacy (virologic and immunologic response). Our aim was to identify whether there is a need to increase the dose of EFV during RIF-based anti-TB treatment considering any effect of pretreatment bodyweight and *CYP2B6* genotype. The mean EFV plasma concentrations, incidence of drug-induced liver enzyme abnormality, percentage change in CD4 cell count and proportion of patients with nondetectable HIV RNA viral load mon-

itored during a one year ART were compared between HIV patients receiving EFV-based ART alone versus TB–HIV coinfecting patients receiving concomitant RIF and EFV.

Patients & methods

Study design & participants

The study design was prospective, comparative, observational, open-label, parallel-assignment, two-arm pharmacogenetic and pharmacokinetic drug–drug interaction study between RIF-based anti-TB and EFV-based ART as part of the European and Developing Countries Clinical Trial Partnership (EDCTP)-funded multicenter clinical research project entitled ‘Optimization of TB–HIV cotreatment in Africa.’ The study was conducted between June 2007 and June 2011 at HIV and TB clinics in Addis Ababa, Ethiopia.

Newly diagnosed, ART naive HIV-infected individuals (arm 1, $n = 285$) without active TB were included as a control group and in parallel newly diagnosed treatment naive patients with active TB–HIV coinfection (arm 2, $n = 208$) were enrolled. The eligibility criteria were HIV positive men and nonpregnant women, age >18 years, and CD4 count less than 200 cells per mm^3 at baseline.

The study protocol received approval from Institutional Review Boards (IRBs) of School of Medicine, Addis Ababa University, National Ethics Review Committee and Karolinska Institutet in Stockholm, Sweden. Prior written informed consent was obtained from all study participants. The study was conducted as per guidelines laid in the International Conference of Harmonization, Good Clinical Practice.

Treatment

Treatment was initiated following WHO and Ethiopian national treatment guidelines for the treatment of TB and HIV valid during the study period. Treatment type, duration and dosing schedule were strictly applied following the above mentioned TB and HIV treatment guidelines and no treatment modification or treatment intervention was done for the purposes of the study.

HIV patients without active TB received EFV-based ART (600 mg/day) containing stavudine/lamivudine/EFV or zidovudine/lamivudine/EFV or tenofovir/lamivudine/EFV. Patients with HIV and TB coinfection received RIF-based short course treatment: Intensive phase for two months consisting of RIF/isoniazid/pyrazinamide/ethambutol (600/300/1600/1100 mg for patients weighing ≥ 50 kg and 450/225/1200/825 mg for patients weighing <50 kg) followed by a continuation phase with isoniazid and RIF for four months. Daily 600 mg of EFV-

based ART was initiated on the 4th week of RIF-based anti-TB therapy and continued throughout. Adherence was monitored by self-reported use of medication on scheduled clinic visits.

Clinical & laboratory monitoring

Pretreatment laboratory tests included complete and differential blood counts, hemoglobin, platelet count, CD4 cell count, HIV RNA determination, hepatitis B surface antigen, anti-hepatitis C antibody, serum albumin, renal function tests, liver function tests were carried out by monitoring the change in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and direct and total bilirubin levels. Laboratory investigations were performed following a parallel time schedule in both treatment groups. Follow-up for liver enzymes were performed at baseline and on the 1st, 2nd, 4th, 8th, 12th weeks after initiation of treatment. CD4 cell counts were determined before the initiation of ART and on the 12th, 24th and 48th weeks. Plasma HIV-1 RNA viral load was quantified by real-time polymerase chain reaction at baseline and on the 24th and 48th weeks of ART. The standard protocol (limit of detection, <400 copies/ml) was used to analyze plasma samples collected at baseline and the ultra-sensitive protocol (limit of detection, <50 copies/ml) was used at week 24 and 48 of ART.

Quantification of EFV plasma concentrations

A previous study reported that EFV AUC₀₋₂₄ can accurately be estimated from a single plasma sample obtained at 12 or 16 h post-EFV dosing [25]. Thus for the present study 16 ± 1 h postdose of EFV blood samples were collected in Vacutainer tubes (Becton Dickinson Heidelberg, Germany), at the 4th and/or 16th weeks of initiating EFV-based ART. Plasma samples were sent on dry ice to the Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Germany for determination of EFV using LC-MS/MS as described previously [5,26]. The lower limits of quantification in plasma were 10.0 ng/ml. The EFV calibration range was 10–10,000 ng/ml. The method was validated according to the FDA validation guidelines and fulfilled all criteria concerning accuracy, precision, recovery, linearity and stability.

CYP2B6 genotyping

Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA Maxi Kit (QIAGEN GmbH, Hilden, Germany). Allelic discrimination reactions were performed using TaqMan® (Applied Biosystems®, Foster City, CA, USA) genotyping assays with the following ID number for each

SNP: C__11711730_20 for *CYP2B6**6 (c.516G>T rs3745274) and C__60732328_20 for *CYP2B6**18 (c.983T>C, rs28399499) on Applied Biosystems® 7500 Real-Time PCR Systems (Applied Biosystems). The final volume for each reaction was 10 µl, consisting of 2 × TaqMan Universal PCR Master Mix (Applied Biosystems), 20 × drug metabolizing genotype assay mix and 10 ng genomic DNA. The PCR profile consisted of an initial step at 50°C for 2 min and 50 cycles with 95°C for 10 min and 92°C for 15 s.

Statistical analysis

Plasma EFV concentrations were log₁₀-transformed for statistical analysis. Diagnostic tests for normality ensured normal distribution of log transformed EFV concentration data. Independent group *t*-test was used to compare plasma concentrations of EFV between the two treatment groups stratified by baseline bodyweight group (≤50 kg vs >50 kg). In case where Levene's test for variance was greater than 0.05, equal variance was assumed, otherwise unequal variance was assumed. Percentage change in CD4 cell count from baseline by weeks 12, 24 and 48 of ART was compared between the two treatment groups stratified by pretreatment bodyweight category using a Mann–Whitney test. Univariate followed by multivariate linear regression analyses were used to identify factors influencing immunologic response (defined as % change in CD4 cell count from baseline). Percentage change in CD4 cell count from baseline at 12, 24 and 48 weeks after initiation of EFV therapy was calculated using the following formula:

$$\begin{aligned} &\% \text{ CD4 change at 24 or 48 weeks} \\ &= \left(\frac{\text{CD4 cell count at 24 or 48 weeks} - \text{CD4 at baseline}}{\text{CD4 at baseline}} \right) \end{aligned}$$

Comparison of CD4 cell count at baseline, 12, 24 and 48 weeks between treatment-groups were analyzed using repeated measure ANOVA. Chi-squared test, Fishers exact test and odds ratio with the respective 95% CI were used to estimate differences in the proportion of subjects with virologic success between and within treatments groups stratified by baseline bodyweight. Univariate binary logistic regression followed by multivariate analysis using stepwise backward elimination was performed to identify predictors of viral response. The variables included in the multivariate model were those with either a theoretical importance or ones with a *p*-value <0.10 in the univariate models. Statistical analyses were performed using Statistica, version 12 (StatSoft Inc., OK, USA) and SPSS Statistics (IBM Corporation, Somers, NY, USA) software, version 22. GraphPad Prism version 5 (GraphPad Software, CA, USA) was used for graphi-

cal presentation of the data. $p < 0.05$ was considered statistically significant.

Results

A total of 493 study participants were enrolled prospectively in two treatment groups: HIV patients without active TB infection received EFV-based ART ($n = 285$) and in parallel TB–HIV coinfecting patients received concomitant EFV-based ART with RIF-based anti-TB therapy ($n = 208$). The demographic characteristics and baseline biochemical laboratory parameters of the study populations is presented in Table 1.

Effect of RIF-based anti-TB treatment on EFV plasma exposure

In TB–HIV coinfecting patients, RIF-based anti-TB therapy was initiated 4 weeks prior to starting ART. In both treatment groups, plasma EFV concentration was determined in parallel at the 4th and 16th week of post-ART initiation (which corresponds to the intensive phase and the continuation phase of anti-TB therapy in TB–HIV coinfecting patients, respectively). The observed median (interquartile range) EFV plasma concentrations and proportion of patients with EFV plasma concentration <1000 ng/ml between the two treatment groups at week 4 and week 16 in all patients and stratified by baseline bodyweight group is presented in Table 2. There was no significant difference in the proportion of patient having EFV plasma concentration <1000 ng/ml at week 4 (Chi-square $p = 0.38$) or 16 ($p = 0.32$) between the two treatment groups.

The mean log plasma concentration of EFV at week 4 was significantly higher in patients receiving EFV-based ART together with RIF-based anti-TB therapy (mean $\pm$ SD = 3.22 ± 0.38) than patients receiving EFV based ART alone group (mean $\pm$ SD = 3.11 ± 0.30 ; mean difference = -0.012 ; 95% CI for the mean difference = -0.210 to -0.009 ; $p = 0.03$, using independent two tailed t-test not assuming equal variances Levene's test for equality of variances $p < 0.05$). The mean log plasma concentration of EFV at week 16 was not significantly higher in patients receiving EFV-based ART together with RIF-based anti-TB therapy (mean $\pm$ SD = 3.23 ± 0.39) than patients receiving EFV-based ART alone group (mean $\pm$ SD = 3.13 ± 0.27 ; mean difference = -0.010 ; 95% CI for the mean difference = -0.210 to -0.119 ; $p = 0.08$, using independent two tailed t-test (see Figure 1).

Effect of bodyweight

First, we analyzed the effect of pretreatment bodyweight categorization (≤ 50 kg vs >50 kg) on plasma EFV concentration in each treatment group separately. Within treatment group analysis indicated significant

effect of baseline bodyweight on EFV plasma concentration among patients treated with EFV-based ART alone; the mean EFV plasma concentration was significantly lower in patients who had pretreatment bodyweight >50 kg than those weighing ≤ 50 kg at week 4 ($p = 0.06$) and week 16 ($p = 0.03$). However, among patients cotreated with RIF-based anti-TB therapy, there was no significant differences in EFV plasma concentrations between patients who had pretreatment bodyweight of $>$ or ≤ 50 kg.

Second, we compared EFV plasma concentration across the two treatment groups (presence or absence of RIF-based anti-TB cotreatment) having the same baseline bodyweight category. Between treatment-group analyses indicated that among patients with pretreatment bodyweight ≤ 50 kg, there was no significant difference in the mean plasma EFV concentration between the two treatment groups at both week 4 and 16. However among patients weighing >50 kg, the mean plasma EFV concentration was significantly higher in patients cotreated with RIF based anti-TB therapy than those treated with EFV-based ART only at both week 4 and week 16 (Figure 2).

Effect of CYP2B6 genotype

There was no significant differences in *CYP2B6**6 allele frequency (31.4% in EFV-based ART alone group, 28.1% in EFV-based ART plus RIF-based anti-TB group) or genotype frequency between the two treatment groups. *CYP2B6**18 variant allele was not detected. There was significant effect of *CYP2B6**6 genotype on EFV plasma concentration at week 4 and 16 ($p < 0.0001$) in both treatment groups. Having the same *CYP2B6* genotype, higher EFV plasma concentrations were noted in RIF-cotreatment group than without RIF-based anti-TB therapy at week 4 and a similar trend was seen at week 16 particularly in *CYP2B6**6 carriers. However, in *CYP2B6**1/*1 genotype groups, no difference in plasma EFV concentration was observed between the two treatment groups at both week 4 and 16 (Figure 3).

Factors predicting EFV plasma exposure

Factors predicting log plasma EFV concentrations at week 4 and week 16 separately were analyzed using univariate followed by multivariate regression analysis (Table 3). Variables resulting in a p -value of < 0.1 in the univariate were included in multivariate analysis. *CYP2B6* genotype, hepatitis B surface antigen, baseline white blood cells (WBCs) counts and treatment groups were significant predictors of EFV plasma concentration at week-4. *CYP2B6* genotype, treatment group and hepatitis B surface antigen remained significant predictors of EFV plasma concentration at week 16.

Category	Treatment group		p-value
	EFV-based ART (n = 285)	EFV-based ART + RIF-based anti-TB (n = 208)	
Sex, n (%):			
– Female	207 (73)	99 (47.4)	0.001
– Male	78 (27)	109 (52.6)	
WHO HIV stage, n (%):			
– 1	4 (1.5)	1 (0.5)	0.001
– 2	22 (7.7)	4 (2.0)	
– 3	113 (39.8)	135 (65.0)	
– 4	146 (51.1)	68 (32.5)	
ART, n (%):			
– d4T/3TC/EFV	147 (51.5)	87 (45.5)	0.01
– TDF/3TC/EFV	24 (8.4)	57 (28.3)	
– ZDV/3TC/EFV	114 (40.1)	52 (26.2)	
Hepatitis B surface antigen, n (%):			
– Negative	258 (94.5)	191 (91.8)	0.37
– Positive	15 (5.5)	17 (8.2)	
Hepatitis C antibody, n (%):			
– Negative	278 (97.5)	204 (98.0)	
– Positive	7 (2.5)	4 (2.0)	
Baseline weight group, n (%):			
– ≤50 kg	142 (49.8)	114 (54.8)	0.41
– >50 kg	143 (50.2)	94 (45.2)	
Age, median (IQR); years	34 (28–40)	35 (29–42)	0.50
Bodyweight, median (IQR); kg	50 (46–56)	50 (45–55)	0.47
BMI, median (IQR)	19.4 (17.8–21.6)	18.4 (16.9–19.7)	0.001
Karnofsky score, median (IQR)	100 (90–100)	90 (80–100)	
Aspartate aminotransferase, median (IQR); U/l	33 (27–45)	43 (32–68)	0.001
Alanine aminotransferase, median (IQR); U/l	29 (22–40)	29 (21–41)	0.001
Alkaline phosphatase, median (IQR); U/l	109 (88–129)	121 (95–171)	0.001
Median total bilirubin, median (IQR); μmol/l	0.5 (0.3–0.8)	0.4 (0.3–0.8)	0.06
Median direct bilirubin, median (IQR); μmol/l	0.1 (0.1–0.1)	0.1 (0.1–0.3)	0.05
Median plasma albumin, median (IQR); g/dl	4 (3.5–4.4)	3.5 (3–4.1)	0.004
Median urea, median (IQR); mg/dl	24 (19–30)	26 (21–33)	0.004
Median serum creatinine, median (IQR); μmol/l	0.8 (0.7–1)	0.9 (0.8–1.1)	0.02
Median baseline CD4 cells/μl, median (IQR)	103 (56–154)	80 (46–138)	0.004
Log median baseline HIV RNA/ml, median (IQR)	4.99(5.19–4.59)	5.23 (4.57–5.57)	0.65
3TC: Lamivudine; AZT: Zidovudine; d4T: Stavudine; EFV: Efavirenz; TDF: Tenofovir.			

Immunologic recovery

A comparison of median CD4 cell count at baseline and at week 12, 24 and 48 of ART as well as % change in the median CD4 cell count from baseline during ART between patients treated with EFV-based ART

alone versus TB–HIV coinfecting patients treated with concomitant RIF-based anti-TB therapy, stratified by baseline bodyweight group (≤50 kg vs >50 kg) is presented in (Table 4). Within treatment group analysis indicated no effect of baseline bodyweight categoriza-

Table 2. Comparison of efavirenz plasma concentrations and proportion of patients with plasma efavirenz concentration <1000 ng/ml between patients receiving efavirenz-based antiretroviral therapy alone or with rifampicin-based anti-tuberculosis therapy at week 4 and week 16 stratified by pre-treatment bodyweight.							
Group	Weeks on ART	EFV-based ART alone			EFV-based ART + RIF-based anti-TB		
		n	Median (IQR)	EFV <1000 ng/ml (% of n)	n	Median (IQR)	EFV <1000 ng/ml (% of n)
All	4	210	1215 (841–1857)	33.8	75	1331 (984–2807)	28.2
	16	187	1290 (934–1869)	31.6	60	1515 (856–3039)	38.6
BW >50 kg	4	106	1169 (787–1841)	36.8	37	1512 (1074–2807)	34.2
	16	101	1233 (848–1670)	33.7	26	1515 (962–3019)	43.3
BW ≤50 kg	4	104	1292 (958–2075)	31.3	38	1313 (852–2785)	21.2
	16	86	1410 (1067–2155)	29.7	34	1345 (765–3058)	33.3
No significant differences in the proportion of patients with EFV plasma concentration <1000ng/ml was observed between the two treatment groups (p > 0.05). ART: Antiretroviral therapy; BW: Bodyweight; EFV: Efavirenz; IQR: Interquartile range; RIF: Rifampicin; TB: Tuberculosis.							

tion on CD4 cell recovery. Between treatment group analysis indicated that regardless of baseline body-weight categorization, the% change in the median CD4 cell count from baseline was significantly higher in TB–HIV coinfectd patients treated with concomitant EFV-based ART and RIF-based anti-TB therapy than HIV-only infected patients treated with EFV-based ART. Repeated measure ANOVA indicated a tendency of having higher median CD4 cell count over time in patients treated with concomitant EFV-based ART plus RIF-based anti-TB therapy than those treated with EFV-based ART only (p = 0.06). Having the same *CYP2B6* genotypes, patients cotreated with RIF-based anti-TB therapy displayed higher CD4 cell

gain than those treated with EFV-based ART only. The change in median CD4 cell count from baseline, at 12, 24 and 48 weeks of ART between the two treatment groups and stratified by pretreatment bodyweight group is illustrated in [Figure 4](#).

HIV RNA viral suppression

Viral suppression at week 24 and week 48 of ART between the two treatment groups were assessed using both <50 copies/ml and <200copies/ml thresholds. At week 24, regardless of baseline bodyweight category, the proportion of patients with nondetectable HIV RNA (<50 copies/ml) was significantly higher in HIV-only infected patients treated with EFV-based ART alone (91%) than TB–HIV coinfectd patients treated with concomitant RIF-based anti-TB therapy and EFV-based ART (76.3%). However, no significant differences in the proportion of HIV viral responders were observed at week 48 (89.5% vs 87.8%) irrespective of bodyweight category ([Table 5](#)). In both treatment groups, the proportion of patients with detectable viral load was higher in those with pretreatment bodyweight >50 kg than those ≤50 kg at week 24 of ART but no significant difference was observed at week 48 of ART.

Using HIV-1 RNA viral load >200 copies/ml as a threshold for virological failure given by the US Department of Health and Human Services panel on Antiretroviral Guidelines for Adults and Adolescents [27], the proportion of patients with virological failure at week 24 was significantly higher in the TB–HIV coinfectd cohort receiving concomitant RIF therapy (15.3%) than HIV patients receiving EFV-based ART alone (6.1%; p = 0.006; odds ratio: 2.75; 95% CI: 1.298–5.849). However, no significant difference was observed between TB–HIV coinfectd patients receiving concomitant RIF therapy (10.6%) and HIV patients receiving EFV-based ART alone (8.8%) by week 48 of ART (p = 0.64; odds ratio: 1.22;

Figure 1. Comparison of mean efavirenz plasma concentrations between HIV patients treated with efavirenz-based antiretroviral therapy only (efavirenz) or HIV–tuberculosis coinfectd patients cotreated with rifampicin-based anti-tuberculosis therapy (efavirenz + rifampicin). Efavirenz plasma concentration was measured at the 4th and 16th weeks of antiretroviral therapy.
ART: Antiretroviral therapy; EFV: Efavirenz; RIF: Rifampicin; SE: Standard error.

Figure 2. Comparison of efavirenz plasma concentration (at the 4th and 16th weeks of antiretroviral therapy) between HIV patients treated with efavirenz-based antiretroviral therapy alone (efavirenz) versus those treated with efavirenz-based antiretroviral therapy plus rifampicin-based anti-tuberculosis therapy (efavirenz + rifampicin) stratified by pretreatment bodyweight (≤50 kg vs >50 kg).

ART: Antiretroviral therapy; EFV: Efavirenz; RIF: Rifampicin; SE: Standard error.

95% CI: 0.516–2.888). Binary logistic regression of viral response at week 24 indicated that plasma EFV concentration was significant predictor of virological response only in HIV patients receiving EFV-based ART alone but not in TB–HIV coinfectd patients receiving concomitant EFV-based ART and RIF-based anti-TB therapy. Univariate and Multivariate logistic regression analysis of factors influencing proportion of patients with detectable HIV viral load (>50 copies/ml) at 24 and 48 weeks of EFV-based ART in HIV patients is presented in Table 6. Type of treatment group, baseline bodyweight group and plasma EFV concentration at week 16 were independent predictors of virological success by the 24th week of ART. None of these parameters were significant predictors at week 48.

Incidence of drug-induced liver toxicity

Incidence and predictor of liver toxicity in HIV-only infected patients treated with EFV-based ART only [28] and in TB–HIV coinfectd patients treated with both EFV-based ART and RIF-based anti-TB therapy is reported previously [2]. In brief the incidence of drug-induced liver injury was much higher in TB–HIV coinfectd patients treated with both ART and anti-

TB drugs (30%) compared with HIV patients without active TB treated with ART only (15.7%). Higher EFV plasma concentration and *CYP2B6**6 genotype were predictors of drug-induced liver injury in both treatment groups [2,28]. Furthermore, NAT2 slow-acetylator genotype, as determined by sequencing of the NAT-2 coding region, was significant predictor of drug-induced liver injury in TB–HIV coinfectd patients cotreated with isoniazid containing anti-TB regimen [2].

Discussion

We performed a comparative observational study to examine the effect of RIF-based anti-TB cotreatment on EFV plasma exposure and treatment outcomes considering implications of baseline bodyweight and *CYP2B6* genotype. Our major findings include:

- In consistently higher EFV plasma exposure in patients cotreated with RIF-based anti-TB drugs than those without, particularly in patients with >50 kg baseline bodyweight and *CYP2B6**6 carriers;
- Pretreatment bodyweight influences EFV plasma exposure only in HIV patients treated with EFV-

Figure 3. Comparison of efavirenz plasma concentration at week 4 and 16 of antiretroviral therapy between HIV patients treated with efavirenz-based antiretroviral therapy alone (efavirenz) versus those treated with efavirenz-based antiretroviral therapy plus rifampicin-based anti-tuberculosis therapy (efavirenz + rifampicin) stratified by *CYP2B6* genotype.

ART: Antiretroviral therapy; EFV: Efavirenz; RIF: Rifampicin; SE: Standard error.

based ART alone, but not in TB–HIV patients cotreated with RIF-based anti-TB drugs;

- Irrespective of baseline bodyweight or *CYP2B6* genotype, higher immunological recovery was observed in TB–HIV coinfecting patients treated with both ARV and RIF-based anti-TB drugs;
- At week 24, higher virological response was observed in HIV-only infected patients treated with EFV-based ART compared with TB–HIV coinfecting patients treated with concomitant RIF-based anti-TB therapy. However regardless of pretreatment bodyweight category, no significant difference in viral response was observed between the two treatment groups at week 48;
- Mainly due to overlapping toxicity (from ARV and anti-TB drugs) and disease burden (TB and HIV coinfection), the incidence of drug-induced liver toxicity was much higher in TB–HIV coinfecting patients receiving dual therapy for TB and HIV.

Overall, our results indicate that *CYP2B6* genotype but not RIF-based anti-TB therapy is main predictor of long-term EFV exposure. Furthermore pretreatment bodyweight >50 kg is not a risk factor for having lower EFV plasma exposure, immunologic or virological response in TB–HIV coinfecting patients receiving RIF-based anti-TB treatment.

Both EFV and RIF induce *CYP2B6* enzyme and their concomitant use may have additive effect to lower EFV plasma exposure even more. Earlier study by Lopez-Cortes *et al.*, reported that RIF coadministration for 2 weeks decreased EFV AUC by approximately 25% [11]. Another study in healthy volunteers reported a 1-week RIF cotreatment significantly reduced EFV bioavailability [12]. Accordingly pretreatment weight-based EFV dosage adjustment (800 mg/daily dose) to compensate for the effect of RIF induction is recommended [11–13]. However HIV/AIDS patients display reduced relative bioavailability of EFV and hence findings from healthy volunteers needs to be confirmed in HIV/AIDS patients before direct extrapolation to the target patient population [29]. Indeed a recent study

in Ugandan population reported that prior RIF-based anti-TB therapy significantly reduces EFV plasma exposure during the first two weeks of EFV initiation, but it has no significant effect then after [30]. EFV auto induction is long term, lowering its plasma concentration over time [4–7]. Currently RIF-based anti-TB treatment is provided for 6 months and HIV treatment is lifelong. Therefore drug interaction studies between EFV and RIF need to monitor the short- and long-term effect of RIF-based anti-TB therapy on EFV exposure and treatment outcome for dosing recommendations. Furthermore the current short course anti-TB treatment regimen consists of different combination of drugs in the intensive (RIF/isoniazid/pyrazinamide/ethambutol) and continuation (RIF/isoniazid) phases of anti-TB therapy. In the present study, EFV plasma concentration was determined both during the intensive phase and the continuation phase of TB therapy in TB–HIV patients with a parallel cross matching study time point for determination of EFV exposure, safety

and efficacy parameters in HIV patients who received EFV-based without anti-TB therapy.

Contrary to the anticipated enzyme induction effect, higher mean plasma EFV concentrations was observed in TB–HIV patients treated with concomitant RIF-based anti-TB therapy than HIV patients treated with EFV-based ART only during early therapy, but no significant long-term effect was observed. The increase in EFV concentration by RIF-based anti-TB treatment was significant in patients with pre-treatment bodyweight >50 kg and *CYP2B6**6 carriers. Our finding is consistent with the recent report from Uganda [14,30] and South Africa where, concomitant RIF-containing TB treatment unexpectedly increased EFV plasma exposure with a corresponding reduction in apparent EFV clearance [17]. In a recent report, coadministration of RIF-based anti-TB therapy was associated with a trend toward higher EFV C_{min} compared with EFV alone, which was statistically significant in Black patients [19]. In another study, a higher

Table 3. Univariate and multivariate regression analysis of factors influencing log plasma efavirenz concentrations at 4 and 16 weeks of efavirenz-based antiretroviral therapy in HIV patients.

Variable	Week 4				Week 16			
	Univariate		Multivariate		Univariate		Multivariate	
	t	p-value	t	p-value	t	p-value	t	p-value
Treatment group (arm)	2.09	0.03	3.18	0.002	1.78	0.08	2.48	0.014
Sex	-1.26	0.21			-1.35	0.18		
Age (years)	0.22	0.83			1.03	0.30		
Pretreatment bodyweight	1.28	0.20			0.81	0.42		
Body mass index	-0.33	0.74			-1.78	0.08		
Type of antiretroviral therapy	1.05	0.30			0.20	0.84		
Hemoglobin (g/dl)	0.34	0.74			0.11	0.91		
White blood cell count $\times 10^3$	1.90	0.06	2.05	0.04	1.58	0.12		
Neutrophils (%)	0.99	0.33			0.64	0.53		
Blood platelet count (cells/ μ l)	0.37	0.71			-0.43	0.67		
Aspartate aminotransferase (U/l)	1.27	0.21			0.74	0.46		
Alanine aminotransferase (U/l)	-0.82	0.41			0.28	0.78		
Alkaline phosphatase (U/l)	0.45	0.65			0.40	0.69		
Bilirubin (total μ mol/l)	0.79	0.43			-0.07	0.95		
Bilirubin direct (μ mol/l)	-0.29	0.78			-1.35	0.18		
Serum albumin (g/dl)	-0.10	0.92			0.09	0.93		
Urea (mg/dl)	-0.59	0.56			-1.03	0.31		
Serum creatinine (μ mol/l)	-1.07	0.29			-0.28	0.78		
Hepatitis B surface antigen	2.16	0.03	1.77	0.08	1.95	0.05	2.92	0.004
Hepatitis C antibody	-0.77	0.44			-0.28	0.78		
CD4 cells (cells/ μ l)	-0.38	0.70			-0.23	0.82		
<i>CYP2B6</i> *6 genotype	6.11	<0.001	5.74	<0.0001	6.29	<0.0001	6.71	<0.0001

Table 4. Comparison of CD4 cell count and its percentage change from baseline between patients treated with efavirenz-based antiretroviral therapy alone or with rifampicin-based anti-tuberculosis therapy, stratified by baseline bodyweight using Mann–Whitney Test.

Group	Measure of CD4 cell count	n	EFV-based ART, median (IQR)	n	EFV-based ART + RIF-based anti-TB, median (IQR)	p-value
All	CD4 at baseline	285	103 (56–154)	208	80 (46–138)	0.03
	CD4 at week 12	235	173 (128–234)	160	186 (114–269)	0.35
	CD4 at week 24	217	183 (127–255)	144	200 (146–280)	0.19
	CD4 at week 48	196	200 (139–267)	125	241 (162–337)	0.01
	Percentage change week 12	235	59 (18–143)	160	117 (39–296)	0.001
	Percentage change at week 24	217	71 (31–151)	144	130 (54–337)	0.001
	Percentage change at week 48	196	95 (33–184)	126	143 (76–367)	0.009
BW ≤50 kg	CD4 at baseline	149	104 (59–154)	98	95.5 (54–155)	0.45
	CD4 at week 12	126	184 (128–234)	82	198.5 (114–285)	0.48
	CD4 at week 24	118	195 (127–255)	73	206 (139–304)	0.51
	CD4 at week 48	103	209 (139–267)	61	288 (189–351)	0.01
	Percentage change week 12	123	65 (17–143)	80	113 (34–268)	0.05
	Percentage change at week 24	117	73 (31–151)	73	123 (54–370)	0.02
	Percentage change at week 48	104	86 (33–184)	61	142 (85–336)	0.09
BW >50 kg	CD4 at baseline	125	92 (59–154)	98	66 (39–122)	0.05
	CD4 at week 12	104	155 (137–244)	78	176 (114–258)	0.08
	CD4 at week 24	99	168 (137–266)	71	195 (147–240)	0.13
	CD4 at week 48	92	191 (143–277)	64	208 (151–290)	0.62
	Percentage change week 12	104	54 (24–136)	79	132 (47–311)	0.006
	Percentage change at week 24	99	68 (39–141)	71	135 (54–321)	0.005
	Percentage change at week 48	92	103 (36–184)	65	154 (58–367)	0.19

ART: Antiretroviral therapy; BW: Bodyweight; EFV: Efavirenz; IQR: Interquartile range; RIF: Rifampicin.

mean plasma EFV concentration during RIF-based anti-TB treatment was observed in general and particularly in four individuals where EFV concentration eventually decreased after withdrawal of RIF [31]. Lack of a significant effect or even paradoxically increased plasma EFV concentration during RIF-based anti-TB treatment is reported recently mainly in black populations [14–19,30]. In Tanzanian HIV patients no significant long-term effect of RIF on EFV concentration was observed [6]. RIF-based anti-TB treatment was not associated with reduced EFV concentrations in South African adult and children [20,32]. Studies from Ghana and South India reported no difference in median plasma concentration of EFV regardless of presence of RIF [18,33,34]. A minor impact of rifampin on the plasma EFV concentration was observed in Thai population [35].

Overall, the current available data from black population indicate that RIF-based anti-TB therapy in TB–HIV coinfecting patients; either has no signifi-

cant effect or paradoxically increases efavirenz plasma exposure. Accordingly there is no need to increase the dose of EFV during RIF-based anti-TB cotreatment in black population. The current maximum effective dose of 600 mg EFV that was licensed to avoid the risk of emergence of viral resistance is presumed to be high [36]. A recent randomized clinical trial in HIV-only infected patients reported that a reduced dose of 400 mg EFV is noninferior to the standard dose of 600 mg and recommended a lower dose EFV to be used as part of routine care but this remain to be investigated in TB–HIV patients during receiving anti-TB therapy [36]. In line with our finding several studies reported that *CYP2B6* genotype but not RIF-based anti-TB therapy is the major determinant for between patient variability in EFV plasma exposure [6,30,32,34]. Recently *CYP2B6* genotype-based EFV dose recommendations for sub-Saharan Africa population is published [37] and currently studies are going on to evaluate this.

The reason for the observation of high plasma EFV exposure in patients cotreated with RIF-based anti-TB treatment in the present study is not clear. Nevertheless, a putative mechanism is suggested [6,18]. One of the plausible reasons could be inhibition of EFV metabolism by the other anti-TB drugs such as isoniazid. Apart from CYP2B6 and CYP3A that catalyze 8-hydroxyefavirenz formations, CYP2A6 mediates EFV 7-hydroxylation accounting for approximately 23% of total EFV metabolism [38]. Isoniazid is inhibitor of CYP2A6 and CYP3A4 activities *in vitro* [39,40]. Thus isoniazid, which is part of the standard RIF-based anti-TB regimen given to the TB–HIV coinfecting patients, may inhibit EFV metabolism by CYP2A6. Whereas this effect is absent in patients treated with EFV-based ART only.

EFV dosage recommendations during RIF-based anti-TB therapy need to consider not only the effect on EFV plasma exposure but also the resulting effect on ART treatment outcome. Regardless of baseline bodyweight category or *CYP2B6* genotype group, the percentage change in CD4 cell count from baseline was much higher in TB–HIV patients receiving RIF-based anti-TB cotreatment than HIV patients receiving ART only. The higher immunologic recovery is consistent with the observed higher plasma concentrations of EFV in TB–HIV patients treated with RIF-based anti-TB treatment. Concomitant anti-TB therapy during ART may also enhance immune recovery in HIV patients. In line with our finding, a previous study reported improved CD4 cell recovery in TB–HIV coinfecting patients receiving dual anti-TB and ART therapy compared with HIV patients receiving ART only [41]. TB coinfection augments the immunologic deterioration caused by HIV. Indeed at baseline, the CD4 cell counts before the start of treatment was significantly lower in TB–HIV coinfecting patients. Apparently the greater improvement in CD4 cell count among TB–HIV patients following cotreatment may indicate a role for immune reconstitution following ART and may also indicate contribution of anti-TB therapy for immune restoration.

The time to reach virological success during ART was longer in TB–HIV coinfecting patients than HIV patients without active TB coinfection. At week 24 of ART, significantly higher proportion of patients had detectable HIV RNA viral load (>50 copies/ml) or virologic failure (>200 copies/ml) in TB–HIV patients treated with concomitant EFV-based ART with RIF-based anti-TB therapy than HIV-only patients treated with EFV-based ART. This observation was irrespective of baseline bodyweight category. However, no difference in proportion of viral responders between the two treatment groups was observed by week 48; indicating that it

takes longer time to reach virology success during dual TB–HIV coinfection as compared to HIV-only infection. The immune environment created by *Mycobacterium* TB promotes HIV viral replication and hence the delayed viral response in TB–HIV coinfecting patients

Figure 4. Comparison of change in the median CD4 cell count between HIV patients treated with efavirenz-based antiretroviral therapy only versus tuberculosis–HIV coinfecting patients treated with concomitant efavirenz-based antiretroviral therapy and rifampicin-based anti-tuberculosis therapy, stratified by baseline bodyweight group. Statistical analysis was done using repeated-measure ANOVA. (A) All patients. (B) Patients with a baseline bodyweight of >50 kg. (C) Patients with a baseline bodyweight of ≤50 kg. ART: Antiretroviral therapy; EFV: Efavirenz; RIF: Rifampicin.

Table 5. Comparison of virologic outcome by week 24 and 48 of antiretroviral therapy between HIV patients treated with efavirenz-based antiretroviral therapy alone vs tuberculosis-HIV co-infected patients treated with efavirenz-based antiretroviral therapy together with rifampicin-based anti-tuberculosis therapy, stratified by baseline bodyweight group.

Time on ART	Baseline weight group	HIV RNA	EFV-based ART		EFV-based ART + RIF based anti-TB		Total	p-value	Odds ratio (95% CI)
			n (%)	p-value	n (%)	p-value			
Week 24	All	D	19 (9.0)		27 (23.7)		46 (14.1)	0.001	3.15 (1.66–5.97)
		ND	193 (91.0)		87 (76.3)		280 (85.9)		
	BW ≤50 kg	D	4 (3.4)	0.003	10 (16.4)	0.049	14 (7.9)	0.002	5.54 (1.65–18.49)
		ND	113 (96.6)		51 (83.6)		164 (92.1)		
	BW >50 kg	D	15 (15.8)		17 (32.1)		32 (21.6)	0.02	2.52 (1.13–5.59)
		ND	80 (84.2)		36 (67.9)		116 (78.4)		
Week 48	All	D	19 (10.5)		13 (15.9)		32 (12.2)	0.22	1.61 (0.75–3.43)
		ND	162 (89.5)		69 (84.1)		231 (87.8)		
	BW ≤50 kg	D	7 (7.3)	0.11	6 (12.2)	0.21	13 (9)	0.32	1.77 (0.56–5.60)
		ND	89 (92.7)		43 (87.8)		132 (91)		
	BW >50 kg	D	12 (14.1)		7 (21.2)		19 (16.1)	0.35	1.64 (0.58–4.61)
		ND	73 (85.9)		26 (78.8)		99 (83.9)		

ART: Antiretroviral therapy; BW: Bodyweight; D: Detectable HIV RNA viral load >50 copies/ml; EFV: Efavirenz; IQR: Interquartile range; ND: Nondetectable; HIV RNA ≤50 copies/ml; RIF: Rifampicin.

might rather be due to TB coinfection and not by RIF-based anti-TB treatment *per se*. Interestingly, in both treatment groups, higher proportion of patients with detectable HIV RNA viral load was observed in patients with pretreatment bodyweight of >50 kg as compared with those weighing ≤50 kg. Thus the effect of pretreatment bodyweight on viral response is not specific to the presence or absence of RIF-based anti-TB treatment, because it was also observed in HIV patients without active TB treated with EFV-based ART only. Besides, plasma EFV concentration was a significant predictor of viral response in HIV patients treated with EFV based ART only but not in TB–HIV patients treated with concomitant EFV based ART plus RIF based anti-TB therapy. This may indicate that in the presence of TB comorbidity and concomitant use of anti-TB drugs, which are enzyme inducers and/or inhibitors, plasma EFV concentration alone may not be a reliable surrogate marker to predict virological response.

The incidence of drug liver toxicity in TB–HIV coinfecting patients receiving concomitant ARV and anti-TB therapy was significantly higher than HIV patient receiving ART only. In addition to the disease burden, overlapping or additive toxicity from antiretroviral and anti-TB drugs may account for this observation. Indeed we found association of higher EFV plasma concentration and *CYP2B6**6/*6 genotype to be associated with higher incidence of drug-induced liver toxicity in both treatment groups [2,28], a finding later

observed in Tanzania TB–HIV patients [3]. Recently we reported a higher incidence of drug-induced liver toxicity in the order of TB–HIV patients receiving dual TB–HIV therapy >TB–HIV patients treated with anti-TB alone >HIV patients treated with ART alone >TB only patients treated with anti-TB alone [42]. This indicates that TB–HIV patients receiving dual anti-TB and ART are the most vulnerable group of patients to develop drug-induced liver toxicity. Given the fact that EFV cause concentration dependent liver injury, increasing the dose of EFV to 800 mg during anti-TB drugs may further exacerbates the risk for drug-induced liver toxicity without any additional efficacy benefit.

The limitation our study includes that this study was done in highly immune suppressed patients with pretreatment CD4 count <200 cells per mm³. When patients were enrolled into the study, only HIV patients with <200 cell count were eligible to receive ART according the previous WHO and Ethiopian national HIV treatment guidelines, which is modified now to include patients with CD4 count >200 cells. Thus our result may not be applicable to patients with less immune compromised patients, although TB coinfection is most associated with rapid progression of HIV disease with a higher HIV viral load and low CD4 cell count. Furthermore EFV pharmacokinetics display wide interethnic variability within sub-Saharan African populations partly due to pharmacogenetic diversity [21] and hence studies from one population may not

Variable	Week 24				Week 48			
	Univariate		Multivariate		Univariate		Multivariate	
	p-value	Exp(β) (95% CI)	p-value	Exp(β) (95% CI)	p-value	Exp(β) (95% CI)	p-value	Exp(β) (95% CI)
Treatment group (reference for comparison: EFV-based ART only)	0.001	3.15 (1.66–5.97)	0.02	3.90 (1.05–14.53)	0.22	1.61 (0.75–3.43)	0.18	1.69 (0.79–3.66)
Sex (reference for comparison: male)	0.13	0.61 (0.2–1.15)	0.39	0.57 (0.16–2.05)	0.86	0.68 (0.42–2.04)	–	–
Baseline bodyweight (reference for comparison: < 50 kg)	0.001	3.23 (1.65–6.32)	0.01	5.88 (1.52–22.85)	0.08	1.95 (0.92–4.13)	0.08	2.05 (0.95–4.31)
HIV stage (reference for comparison: stage 4)	0.15	–	0.47	–	0.45	–	–	–
Stage 1	0.99	0.44 (0.05–3.49)	1.00	0.38 (2.93–0.26)	0.99	1.11 (0.29–4.32)	–	–
Stage 2	0.43	1.93 (0.99–3.72)	0.38	0.12 (2.58–0.76)	0.87	0.53 (0.24–1.19)	–	–
Stage 3	0.05	–	0.13	–	0.12	–	–	–
Type of ART (reference for comparison: ZDV/3TC/EFV)	0.04	–	0.08	–	0.57	–	–	–
d4T/3TC/EFV	0.69	0.86 (0.41–1.80)	0.79	0.83 (0.26–2.65)	0.66	0.66 (0.30–1.45)	–	–
TDF/3TC/EFV	0.01	3.25 (1.37–7.71)	0.04	32.4 (1.92–604)	0.67	0.67 (0.18–2.55)	–	–
WBC count $\times 10^3$	0.37	0.82 (0.54–1.23)	–	–	0.39	0.54 (0.13–2.22)	–	–
Hepatitis B surface antigen (reference for comparison: -ve)	0.26	1.95 (0.61–6.28)	–	–	0.56	1.85 (0.23–14.62)	–	–
Log EFV plasma concentration week 4	0.56	0.66 (0.16–2.67)	–	–	–	–	–	–
Log EFV plasma concentration week 16	0.09	0.23 (0.04–1.30)	0.04	0.13 (0.21–0.87)	–	–	–	–
CYP2B6*6 carrier (reference for comparison: absence of *6)	0.37	1.33 (0.71–2.52)	–	–	0.39	1.38 (0.65–2.91)	–	–

3TC: Lamivudine; ART: Antiretroviral therapy; d4T: Stavudine; EFV: Efavirenz; RIF: Rifampicin; TDF: Tenofovir; WBC: White blood cell; ZDV: Zidovudine.

be directly extrapolated to another population within the continent, although our finding is in line with other studies from sub-Saharan Africa.

Conclusion

EFV plasma exposure is mainly influenced by *CYP2B6**6 genotype. Despite improved immunologic recovery, the time to reach virological success is longer in dual TB–HIV coinfecting patients receiving RIF-based anti-TB therapy and EFV-based ART than HIV patients receiving EFV-based ART only. However, there is no significant difference in the long-term virological response between the two treatment groups. RIF-based anti-TB cotreatment has no significant influence on the long-term EFV plasma exposure and virological response. Hence, we conclude that there is no need to increase the dose of EFV during RIF-based anti-TB cotreatment in black African population. Our finding supports the current WHO HIV treatment guideline that recommends no EFV dosage adjustment during concomitant RIF-based anti-TB therapy. Our study provides evidence-based recommendation for policy makers to develop effective TB–HIV treatment guidelines particularly in resource-limited settings.

Future perspective

The burden of TB and HIV/AIDS is highest in sub-Saharan Africa and treatment of the two dis-

eases is challenging because of drug interactions and overlapping toxicities. Studies in black African populations including ours' demonstrate the importance of *CYP2B6* genotype but not RIF cotreatment for between patient variability in EFV plasma exposure and associated adverse events such as liver enzyme abnormality and neuropsychiatric manifestations [2,3,6,14,21,28,30,37,43]. Due to its high allele frequency distribution and its impact on EFV metabolism, *CYP2B6**6 genotype is one of the most important factor to be considered for EFV dose optimization in sub-Saharan Africa population [37]. Ongoing and future randomized clinical trials evaluating the safety and efficacy of *CYP2B6* genotype-based EFV dose modification in adult and children may lay ground for future application of pharmacogenetics for patient care in HIV clinics. Sub-Saharan African populations display wide pharmacogenetic diversity than any other population [44]. Hence, more pharmacogenetic, pharmacokinetic and safety/efficacy studies are needed and result from one population may not be directly extrapolated to another population within the continent. Likewise dose optimization studies conducted in whites and Asians may not be directly applicable for black African populations. Pharmacogenetics and pharmacokinetics characterization of interactions between RIF-based anti-TB and EFV-based ART in different population may form a base

Executive summary

Background

- Tuberculosis (TB) is the most common opportunistic infection in HIV patients and cotreatment of the two diseases is marred by drug–drug interactions and overlapping toxicities.
- Efavirenz (EFV) plasma exposure is influenced by *CYP2B6* genotype and ethnicity.
- Rifampicin (RIF), a potent CYP enzyme inducer, is reported to lower plasma EFV concentration by 20–30% particularly in white population. However, studies from black and Asian populations report insignificant effect or even quite contrary effect.
- The current HIV treatment guidelines are inconsistent about whether to increase the dose of EFV during concomitant RIF-based anti-TB treatment or not, particularly in patients weighing more than 50 kg.

Patient & methods

- We performed a comparative observational study to investigate the effect of RIF-based anti-TB therapy on plasma EFV concentrations, treatment outcome (safety and efficacy) and the implications of *CYP2B6* genotype and bodyweight.

Results

- Long-term EFV plasma exposure was mainly influenced by *CYP2B6* genotype but not RIF-based anti-TB therapy.
- There was no significant bodyweight-dependent effect of RIF-based anti-TB treatment on the efficacy of 600 mg/day EFV-based antiretroviral therapy in Ethiopian HIV patients
- Incidence of drug-induced liver injury was significantly higher in the TB–HIV coinfecting patients mainly due to TB–HIV coinfection and overlapping anti-TB and antiretroviral drugs toxicity hence increasing EFV dose in TB–HIV patients may even further exacerbate the risk for treatment-associated liver toxicity.

Conclusion

- There is no need to increase the dose of EFV during concomitant RIF-based anti-TB therapy in TB–HIV coinfecting patients. Our result supports the current WHO TB–HIV treatment guideline which recommends no EFV dose adjustment during RIF-based anti-TB cotreatment.

for future population specific dosing strategies and to establish optimal treatment guidelines.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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