Original article

Efavirenz and rifampicin in the South African context: is there a need to dose-increase efavirenz with concurrent rifampicin therapy?

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Background: Increasing efavirenz (EFV) dose from 600 mg to 800 mg daily has been suggested with concomitant rifampicin (RFN), as induction of cytochrome P450 isoenzymes may reduce EFV plasma concentrations
Methods: Individuals from the CIPRA-South Africa cohort taking EFV-based antiretroviral therapy with concomitant tuberculosis (TB) were dosed with either increased (800 mg) or standard (600 mg) dose EFV during TB treatment. After TB therapy, all individuals took 600 mg EFV. Two mid-dosing interval EFV concentrations were determined from each individual: after 4 weeks of concomitant EFV and RFN therapy, and ≥4 weeks after TB therapy completion. Mid-dosing interval EFV concentrations were compared within individuals using the Wilcoxon signed–rank test.
Results: Paired samples were collected from 72 individuals. Overall, 45 (63%) were women and median weight was 59 kg (IQR 52–67). At antiretroviral therapy start, median $CD4^+$ T-cell count was 114 cells/mm^3 (IQR 37–165), median viral load was 5.5 log (IQR 5.1–5.9). A total of 38 (53%) individuals took 800 mg EFV during TB treatment and 34 (47%) took 600 mg. EFV concentrations in the 800 mg group were higher with RFN (2.9 mg/l [IQR 1.8–5.6]) than without (2.1 mg/l [IQR 1.4–3.0]; *P*=0.0003). There was no significant difference in EFV concentrations with RFN (2.4 mg/l [IQR 1.2–5.1]) or without (2.2 mg/l [IQR 1.4–3.7]) in the 600 mg group. There was no increase in EFV-linked adverse effects in either group. The proportion of virologically suppressed individuals at 48 weeks was similar in both groups.
Conclusions: EFV concentrations were significantly increased in the EFV 800 mg group on RFN. There was no significant decrease in EFV concentrations when on RFN in the 600 mg group. Dose escalation of EFV 600 mg to 800 mg is not required during concomitant TB therapy in South Africa.

Introduction

The South African antiretroviral treatment programme uses a standardized first-line regimen that is non-nucleoside reverse transcriptase inhibitor (NNRTI)-based [1,2]. Efavirenz (EFV) is the preferred NNRTI, except for women of childbearing potential. The standard dose for EFV used is 600 mg daily. According to South African guidelines, this dose remains unchanged with concomitant tuberculosis (TB) therapy, but there are limited data during coadministration [1].

EFV plasma concentrations show marked inter-individual variability [3]. In 2001, Marzolini *et al.* [4] obtained blood samples from 130 Swiss people on 600 mg EFV. EFV concentrations varied from 125 to 15,230 μg/l at the mid-dose interval (normal range 1–4 mg/l). Lower concentrations were linked with virological failure and high concentrations with significant central nervous system toxicity. Other studies have linked higher EFV concentrations both with neuropsychiatric side effects and abnormalities of liver function [5–7]. Adding a drug that may potentiate EFV metabolism, thus lowering plasma concentrations, could result in failure of antiretroviral therapy (ART). This would be particularly harmful in a resource-poor setting where therapeutic options are limited.

South Africa has one of the highest incidences of TB in the developing world, due to a large extent to

the HIV epidemic. The numbers of people presenting with TB continue to increase in Africa, in contrast to the decrease in TB cases worldwide. The probability of someone with HIV developing TB is 10% per annum in developed countries and likely to be much higher in the developing world [8]. The South African National Tuberculosis guidelines use rifampicin (RFN) as a core antimycobacterial in both initial and re-treatment regimens [9].

In South Africa, many people with symptomatic HIV have TB and many more develop TB soon after commencing therapy, thus necessitating the concomitant use of TB therapy, including RFN, and ART, including EFV [10]. These two commonly used medications have had previously documented interactions as they are both metabolized by and induce the cytochrome P450 enzyme system (particularly isoenzymes 3A4 and 2B6). While studies revealed that EFV had no effect on RFN pharmacokinetics, the reverse did not apply [11,12].

At least two studies raised concerns for virological breakthrough due to reduced EFV concentrations when dosed at 600 mg in the presence of RFN. Data from López-Cortés *et al.* [12] in 24 HIV-positive individuals revealed a 24% reduction in EFV maximum concentration (C_{max}) and a 22% reduction in the area under the concentration–time curve (AUC) in a Caucasian population on TB therapy. They noted that an 800 mg dose returned serum EFV concentrations to those achieved with 600 mg without RFN. Information from another 12 healthy normal volunteers, again Caucasian, showed induction of EFV metabolism in the presence of RFN [11]. EFV product information states that a 20% reduction in EFV C_{max} and a 26% reduction in AUC may be expected with the addition of RFN, but that the clinical relevance of this decrease in EFV concentrations had not been established [13].

A logical step would be to reduce the risk of virological breakthrough by increasing EFV dose when on concomitant RFN therapy. However, this seems to result in increased drug levels and thus a potential increase in toxicity. A large, as yet unpublished, study (n=65) noted an increase in EFV trough concentrations when a dose of 800 or 1,000 mg of EFV was given to people on RFN, as compared to the 600 mg dose without TB treatment [14]. In a further small series, 7 of 9 HIV-positive individuals treated with 800 mg of EFV concurrently with RFN in 2004 experienced significant central nervous system side effects on this higher dose. Trough EFV concentrations were noted to be high [15]. Others noted central nervous system toxicity with higher EFV concentrations [7].

There remains room for debate to whether the 600 mg or 800 mg dose of EFV is appropriate when on concurrent TB therapy. The need to achieve adequate EFV concentrations and maintain viral suppression must be weighed against the increased risk of central nervous system toxicity when a higher dose is used. Differing polymorphisms in the 2B6 cytochrome P450 isoenzyme of an African population compared to the Caucasian populations, where the majority of pharmacokinetic work has been completed, may explain some of the variation seen. What is true for one population may not hold true for another [16]. While support for staying with the 600 mg dose in developing countries stems from five studies (from South Africa, Brazil, Thailand and India) that have noted good clinical and virological outcomes in people with TB treated with ART containing EFV at the standard 600 mg dose, to date there is no information on EFV concentrations at the 800 mg dose in an African population, with or without RFN [16–20].

This study compared intraindividual steady-state mid-dosing interval plasma concentrations of EFV at 800 mg or at 600 mg during concurrent use of RFN, to the standard 600 mg EFV dose while on ART alone in a South African population. It also examined adherence and virological outcomes for both groups as well as any difference in recorded central nervous system or hepatic adverse events.

Methods

This study is a substudy of project 1 of the Comprehensive International Programme for research on AIDS, South Africa (CIPRA-SA project 1), called 'Safeguard the household', a study of HIV antiviral therapy treatment strategies appropriate for a resource-poor country (NCT-0255840) [21]. CIPRA-SA project 1 recruited 810 individuals with $CD4^+$ T-cell counts of <350 cells/μl onto ART between February 2005 and January 2007. Individuals were from two South African sites, one large urban site in Gauteng and one small community in the South Peninsula region of Cape Town.

ART was given according to the South African National Antiretroviral Guidelines [1,2] with an initial NNRTI-based regimen followed by a protease inhibitor-based regimen. EFV is the preferred NNRTI for people taking concurrent TB therapy. First-line NNRTIs usually given at the time of this study were stavudine and lamivudine. Scheduled trial visits occurred monthly until week 12 and every 12 weeks thereafter. Viral loads, $CD4^+$ T-cell counts and adherence assessment by counting of tablet returns were performed at every visit. All adverse event data were recorded. The DAIDS tables for grading the severity of adult and paediatric adverse events were used to assess each adverse event [22].

During initial recruitment to the CIPRA-SA project 1 study, from February to November 2005, all participants with concomitant TB were dosed with 800 mg of EFV. Later this was amended to allow the investigators to match the South African National ART Guidelines

and from December 2005 until January 2007, all people recruited to the same cohort with TB were commenced on the 600 mg EFV dose. These doses were specified by the study protocol and amendments and were not left to investigator discretion.

RFN is used for the full duration of TB therapy in South Africa. The initial TB treatment regimen comprises 2 months of four-drug therapy (RFN, isoniazid, pyrazinamide and ethambutol) followed by 4 months of RFN and isoniazid alone. RFN is dosed according to body weight, that is, 450 mg for patients <50 kg and 600 mg for patients >50 kg. Re-treatment of TB comprises 8 months of therapy and RFN is again included for the duration of treatment.

Substudy

All individuals in the CIPRA-SA project 1 cohort who were taking RFN-based TB treatment at the time of commencing EFV-based ART were eligible for this substudy. No extra visits or blood samples were required.

Individuals were divided into two groups: those on 800 mg EFV during TB treatment (and 600 mg thereafter) and those who remained on 600 mg EFV throughout. Demographic information was collected at commencement of ART for each individual, including gender, weight and WHO stage of HIV infection. Dates of commencement and completion of TB treatment were recorded, as was date of commencement of ART. The date and time of the EFV dose immediately prior to the each sample required was also recorded, as were the date and time of the sample used for mid-dosing interval EFV concentrations. EFV is routinely dosed at night and bloods drawn in the mornings. $CD4^+$ T-cell counts and viral loads were collected for the first 48 weeks on ART and all adverse events noted were noted during the same time period.

At each scheduled visit during the CIPRA-SA project 1 study, plasma was drawn for storage. Samples required for this substudy were drawn retrospectively from a bank of stored plasma samples after review of each individual's clinical details to determine which samples were required. Each individual required paired samples for the mid-dosing interval EFV assay. The first sample was selected from a visit ≥4 weeks into concurrent TB and ART. The second sample was selected from a visit ≥4 weeks after TB therapy had been discontinued, but while still on ART. As these paired samples were drawn retrospectively, they were not matched with regard to dose to sampling time.

Selected stored samples were pulled from the bank of samples and analysed for EFV mid-dosing interval concentrations at the Division of Clinical Pharmacology laboratory at the University of Cape Town, which is ISO17025 accredited for this purpose. EFV concentrations were done using validated HPLC methods with a mass spectrometer.

Sampling

Due to the large interindividual variability in EFV concentrations (coefficient of variability 118%), but lower intraindividual variability (coefficient of variability 30%) [4], a study using paired observations from one individual is more appropriate for an EFV pharmacokinetic study than one making comparisons between individuals. To detect a >30% change in mid-dosing interval EFV concentrations with a power of 90%, at a significance level of 0.05, a sample size of 40 people was required in the EFV 800 mg group. Another sample of 40 was required for the EFV 600 mg group.

Statistical analyses

Statistical analyses were performed using STATA version 10 (STATA Corporation, College Station, TX, USA). Undetectable viral load was defined as a viral load <400 copies/ml. EFV concentrations were classified as subtherapeutic if they were <1 mg/l.

Continuous variables were summarized using means and standard deviations if normally distributed, and medians and ranges if not normally distributed. Within-group comparisons of continuous variables were made using a paired *t*-test if parametrically distributed and the Wilcoxon signed-rank test for paired observations if non-parametrically distributed. Between-group comparisons were made using a Student's *t*-test if parametrically distributed and the Wilcoxon/Mann–Whitney rank-sum test if non-parametrically distributed.

Pharmacokinetic analyses

EFV concentrations were determined by validated liquid chromatography–tandem mass spectrometry (LC/MS/MS), as previously described [23,24], in the Division of Clinical Pharmacology Laboratory, University of Cape Town (Cape Town, South Africa). The calibration curve was linear over the range of 0.1–15 mg/l. Where initial results were >15 mg/ml, specimens were diluted to quantify the concentration.

Ethical considerations

All individuals signed informed consent allowing the use of stored samples for pharmacokinetic work at the commencement of the CIPRA-SA project 1 study. Informed consent documents were approved by both the University of Cape Town and the University of Witwatersrand Ethics Committees. The study was run in accordance with South African Good Clinical Practice Guidelines.

Results

There were 87 participants in the CIPRA-SA project 1 cohort (n=810) who commenced ART while on therapy for TB and as such were eligible for entry into this substudy. Seven of these individuals had no second visit

Table 1. Baseline demographic characteristics of individuals in the 72 paired samples

Characteristic	All participants	Participants on 800 mg EFV during RFN-based antitubercular therapy	Participants on 600 mg EFV during RFN-based antitubercular therapy
Participants, *n*	72	38	34
Female, *n* (%)	45 (63)	23 (61)	22 (65)
Median bodyweight, kg (IQR)	58.8 (51.9–66.9)	57.9 (51.9–67.4)	60.0 (51.4–65.2)
Median baseline CD4$^+$ T-cell count, cells/mm^3 (IQR)	114 (37–165)	122 (32–161)	91 (40–165)
Median baseline viral load, log (IQR)	5.5 (5.1–5.9)	5.5 (5.1–5.9)	5.7 (5.3–5.9)

EFV, efavirenz; RFN, rifampicin.

Table 2. EFV plasma concentration in mg/l on and after antitubercular therapy with mean post-dose sampling times

Parameter	On antitubercular therapy	After antitubercular therapy	*P*-value
EFV 800/600 (*n*=38)			
Median EFV plasma concentration, mg/l (IQR)	2.9 (1.8–5.6)	2.1 (1.4–3.0)	0.0003[a]
Proportion subtherapeutic, *n* (%)	1 (3)	5 (13)	0.089[b]
Mean post-dose sampling time, h (±SD)	14.0 (±1.5)	14.3 (±1.7)	0.628[c]
EFV 600/600 (*n*=34)			
Median EFV plasma concentration, mg/l (IQR)	2.4 (1.2–5.1)	2.2 (1.4–3.7)	0.669[a]
Proportion subtherapeutic, *n* (%)	4 (12)	3 (9)	0.690[b]
Mean post-dose sampling time, h (±SD)	13.8 (±1.7)	13.8 (±1.8)	0.208[c]

The efavirenz (EFV) therapeutic range is 1.0–4.0 mg/l. [a]Wilcoxon sign-rank test. [b]χ^2 test. [c]Paired *t*-test.

for collection of a paired sample either due to death (*n*=1), transfer to another clinic (*n*=1), prolonged TB treatment (*n*=1) or loss to follow-up (*n*=4) and so were excluded. A further seven individuals with both samples available had no recorded time of EFV dosing. These 14 individuals were excluded from the analysis, leaving 72 individuals with paired samples.

Baseline characteristics

The demographics of these groups are described in Table 1. There were 38 people who commenced ART with 800 mg EFV and 34 people who were on 600 mg EFV throughout. The majority of the cohort were women (63%), with a median weight of 59 kg (IQR 52–67). Overall, 47% of the cohort weighed 60 kg or more. Baseline CD4$^+$ T-cell counts were low (122 cells/mm^3 [IQR 35–161] for those in the 800 mg EFV group and 91 cells/mm^3 [IQR 40–165] in the 600 mg EFV group) and viral load >5 logs at baseline. Baseline characteristics in the two groups were similar.

EFV concentrations

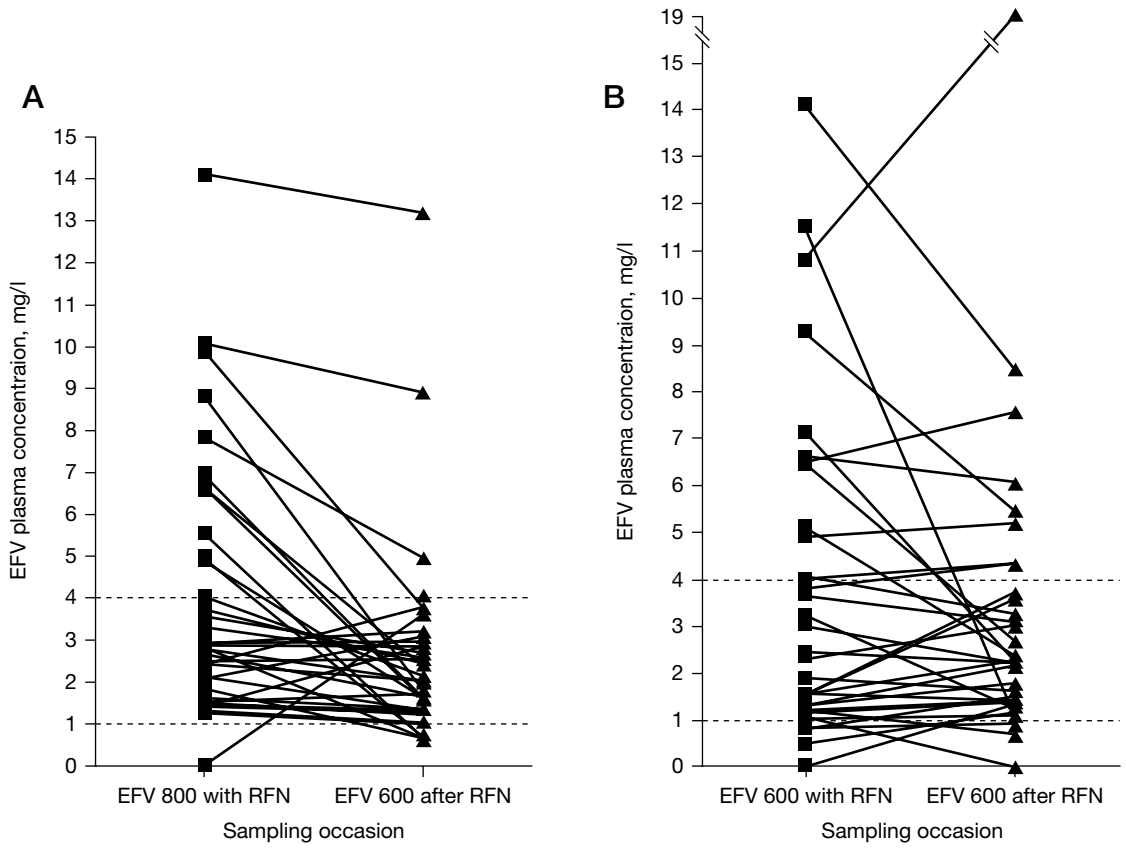
The majority of the participants (92%) had their first sample taken at week 4, 8 or 12 of ART. The majority of the second samples (90%) were taken between week 24 and week 48 on ART.

Table 2 describes the median EFV concentrations in the 800/600 and 600/600 groups. The median concentration of EFV in individuals on 800 mg EFV was 2.9 mg/l (IQR 1.8–5.6 mg/l). The median EFV concentration was 2.1 mg/l (IQR 1.4–3.0 mg/l) in these individuals when they had completed TB therapy, after they were changed to the 600 mg EFV dose. EFV concentrations were significantly higher on 800 mg than that on 600 mg (Wilcoxon signed-rank *P*=0.003).

The median concentration of EFV in individuals on 600 mg EFV during TB therapy was 2.4 mg/l (IQR 1.2–5.1 mg/l) compared to 2.2 mg/l (IQR 1.4–3.7 mg/l) in the same individuals after TB therapy was complete. EFV concentrations were similar on and off TB treatment in this group (Wilcoxon signed-rank *P*=0.669). Mean post-dose sampling times were close to 14 h and there was no significant difference in post-dose sampling times by group (Table 2).

Figure 1 shows the paired values for all individuals, both in the 800/600 group (Figure 1A) and in the 600/600 group (Figure 1B). The great majority of individuals had stable or decreasing concentrations of EFV once RFN treatment was completed. In the 800/600 group there was less variability in the EFV concentrations and only one individual had a subtherapeutic EFV concentration while on RFN. In the 600/600 group the variability of EFV concentrations was greater on RFN and four individuals had subtherapeutic concentrations, however, there was no significant difference in the proportion of those

Figure 1. Paired graphs of individual efavirenz concentrations in the 800/600 and 600/600 groups



Paired graphs showing individual efavirenz (EFV) concentrations in **(A)** the 800/600 EFV group (n=38) and **(B)** the 600/600 EFV group (n=34). Dotted lines represent the normal range (1–4 mg/l). RFN, rifampicin.

who were subtherapeutic either within or across the groups (Table 2).

Using linear regression, there was no correlation found between weight as a continuous variable and EFV concentration at either time point, in either group. Participants were also categorized into those weighing <60 kg and those weighing ≥60 kg within each dosing group while on RFN therapy, and although EFV levels in the ≥60 kg group were slightly lower, there was no significant difference in median EFV concentrations (600 mg group: <60 kg, median EFV level 2.5 mg/l [IQR 1.3–4.0]; ≥60 kg, median EFV level 1.5 mg/l [IQR 1.2–5.1]; 800 mg group: <60 kg, median EFV level 3.6 mg/l [IQR 2.7–7.0; P=0.593]; ≥60 kg, median EFV level 2.4 mg/l [IQR 1.5–3.7; P=0.103]).

Virological and adherence outcomes

Overall, 92% of the group were suppressed to <50 copies/ml at 48 weeks of ART. There was no significant difference by group. There was no association between EFV concentrations of <1 mg/l and a detectable viral load at the time of EFV sampling (χ^2 test P=0.979 for first sample and P=0.276 for second sample).

Adherence by tablet count of EFV returns was uniformly excellent, with a median adherence of 100% (IQR 96–100%) at 12 weeks as well as at 48 weeks (IQR 96.5–100%), and no significant difference was noted by group. There was no evidence of a difference in adherence at week 12 and week 48 between those with subtherapeutic EFV levels and those with levels >1 mg/l (CO *et al.*, data not shown).

Adverse events

During the first 60 weeks on ART, 105 adverse events were reported in this cohort. A total of 33 (32%) adverse events in 21 individuals were thought to be possibly or probably related to the ART: 2 (2%) due to EFV and 31 (30%) due to the use of stavudine. Both EFV-related events were elevations in transaminase concentrations, one to ACTG grade 2 (2.5–5× the

upper limit of normal) and the other to ACTG grade 3 (5–10× the upper limit of normal) [22]. Both occurred in individuals who were only exposed to 600 mg doses of EFV and both occurred during concomitant TB therapy. Both individuals had EFV levels outside of the 75% IQR at the time of the toxicity, namely 9.3 mg/l and 10.8 mg/l, respectively. In general, adverse events were evenly distributed across the two groups with 11 (28%) individuals in the 600/600 group and 10 (22%) individuals in the 800/600 group experiencing an adverse event.

Discussion

Although current recommendations suggest that EFV dosage should be increased during concomitant antitubercular therapy, particularly in individuals weighing >60 kg [25,26], this remains a point of debate [16]. Current evidence suggests a dose increase may not be necessary in the South African context [17,19]. A comparison of intraindividual mid-dose EFV concentrations in our population revealed that EFV concentrations did not decrease when using standard 600 mg dosing during concomitant RFN-containing antitubercular therapy across a range of weights. These data complement the recently published data from Cohen *et al*. [19], which similarly describes no significant difference in EFV concentrations in individuals dosed with 600 mg EFV throughout TB treatment in a very similar population, as well as data from Boulle *et al*. [17], which showed no effect on virological outcomes in individuals treated for TB while on a standard 600 mg dose of EFV .

In addition, data from this study show that EFV concentrations were significantly increased when individuals were exposed to the recommended increased dose of EFV (800 mg) during therapy with RFN as compared to standard 600 mg EFV on completion of TB treatment. Despite these increased concentrations, no particular increase in EFV-related toxicity was noted, although the EFV concentrations in the two individuals experiencing an EFV-related adverse event during concomitant RFN therapy were higher than expected. Although adverse event data was collected throughout the CIPRA study, only ACTG grade 3 and 4 events were captured in the database. It is possible that an increased frequency of minor (ACTG Grade 1 and 2) adverse effects was missed through the data capture process, but it is clear that no serious EFV-related toxicity was reported. The clinicians were not required to enquire specifically for EFV toxicities. Raised EFV concentrations do, however, still cause anxiety about potential EFV toxicity, especially if the higher EFV dose is used [7,18].

Virological suppression was maintained throughout RFN treatment in both the EFV 800 mg and EFV 600 mg groups, despite a minority of individuals having subtherapeutic concentrations noted. This is consistent with other recent studies in the same population, where no difference was noted in virological outcome in a large group of individuals commencing EFV-based ART with or without concomitant TB therapy [17]. Adherence to EFV in these subtherapeutic individuals did not differ from those with therapeutic levels, but adherence as assessed by tablet returns is not a sensitive enough measure to note a missed dose immediately prior to a study visit. One of the strengths of this study is the tight control of visit schedule and monitoring due to being a substudy of a larger randomized controlled study, reflected in the consistency in post-dose sampling times [21]. Most individuals with TB were retained on the study for the duration of their treatment so the majority who entered the study had a paired sample available for intraindividual analysis as preferred for EFV pharmacokinetic sampling due to large interindividual variability [3].

This study has several limitations. Recent data on EFV suggests that the pharmacogenetic profile of the cytochrome P450 enzyme system, in particular the 2B6 G526T polymorphism, may have a greater effect on the metabolism of EFV than RFN [16,19,27]. This study could not determine relationships between the 2B6 polymorphisms and EFV concentrations as genetic samples were not available for the majority of individuals. Individuals were not randomized to the study arms, but enrolled sequentially into the 800 mg and then the 600 mg EFV groups. This may have led to a bias, such as the more ill individuals enrolling early; however, we have shown that the baseline clinical data of the groups did not differ (Table 1). The use of samples collected at routine clinical visits did not allow us to examine the effect of RFN on EFV at time points other than mid-dosing, although mid-dosing concentrations are accepted as the standard pharmacokinetic measure for EFV therapeutic drug monitoring. Our recorded time for EFV dosing was based on subjective patient reporting and was not objectively observed or standardized. We only collected one sample from each individual while taking RFN and another sample after RFN treatment, thus we could not control for intraindividual variability, which may have been a source of error when assessing a single sample without objective dosing times. Furthermore, we did not collect data on RFN adherence as it was assumed to be uniformly adequate due to daily TB therapy being directly observed either in the clinic or by community supporters in South Africa.

The suggestion to increase EFV dose during concomitant TB and HIV therapy has been based on relatively scant data, largely from non-African populations, and data as to the correct dosing remains limited [11–14,28]. Data from this CIPRA-SA substudy,

together with recent published data from two other South African studies, demonstrate that the 600 mg dose of EFV maintains adequate drug concentrations during concomitant TB therapy, even in those weighing >60 kg, and that the dose escalation to 800 mg is not required in a South African population.

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