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Effect of high-dose rifampicin on efavirenz pharmacokinetics: drug–drug interaction randomized trial

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Background: High-dose rifampicin is considered to shorten anti-TB treatment duration but its effect on antiretroviral metabolism is unknown.

Objectives: To assess the effect of doubling the rifampicin dose (to 20 mg/kg/day, R20) on efavirenz pharmacokinetics (PK) in HIV/TB coinfected patients.

Methods: Open-label Phase 2 drug–drug interaction randomized trial. Pulmonary TB, ART-naive adults were randomized to R20 and either efavirenz 600 mg (EFV600) or 800 mg (EFV800), or rifampicin 10 mg/kg/day (R10) and EFV600 with a 1:1:1 ratio. Patients were first started on TB treatment and 2–4 weeks later started on ART. They were switched to R10 and EFV600 after 8 weeks. Full PK sampling was done 4 weeks (on rifampicin) and 24 weeks (off rifampicin) after ART initiation. Transaminases, plasma HIV-1 RNA and sputum cultures were monitored. The efavirenz geometric mean ratio (GMR) of AUC at 4 and 24 weeks after ART initiation within the same patient was calculated in each arm and its 90% CI was compared with a preset range (0.70–1.43).

Results: Of 98 enrolled patients (32 in the R20EFV600 arm, 33 in the R20EFV800 arm and 33 in the R10EFV600 arm), 87 had full PK sampling. For the R20EFV600, R20EFV800 and R10EFV600 arms, GMRs of efavirenz AUC were 0.87 (90% CI: 0.75–1.00), 1.12 (90% CI: 0.96–1.30) and 0.96 (90% CI: 0.84–1.10). Twelve weeks after ART initiation, 78.6%, 77.4% and 72.4% of patients had HIV-1 RNA below 100 copies/mL and 85.7%, 86.7% and 80.0% had Week 8 culture conversion, respectively. Two patients per arm experienced a severe increase in transaminases.

Conclusions: Doubling the rifampicin dose had a small effect on efavirenz concentrations and was well tolerated.

Introduction

TB is the leading cause of death worldwide with 10 million estimated cases in 2018.[1] Despite its good efficacy and tolerability, only 82% of patients complete the standard 6 month anti-TB treatment (ATT) in routine conditions.[1] Shorter, effective and safe treatment strategies are needed to optimize patient adherence. In HIV/TB-coinfected patients, shorter regimens could reduce the duration of ATT and ART coadministration thus reducing the risk of toxicity[2] and duration of exposure to rifampicin, which is a potent inducer of many drug-metabolizing enzymes. Previous studies, conducted mostly among HIV-negative patients, have shown the potential value of high-dose rifampicin in the shortening of ATT duration.[3–8]

Among antiretroviral drugs, efavirenz, which is part of the first-line ART regimen in HIV high-burden countries,[9] has its plasma concentration slightly reduced (20%–30%) when coadministered

with rifampicin. This is as a result of rifampicin induction of cytochrome P450 (CYP), especially in *CYP2B6* extensive metabolizers. *In vitro* studies have suggested that rifampicin enzyme induction is a concentration-dependent process. Although most studies focused on CYP3A4, one demonstrated a CYP2B6 dose–response effect with inducers.[10,11] Although such a reduction in plasma concentration of efavirenz does not affect ART efficacy with the usual 600 mg once-daily dose of efavirenz recommended among HIV/TB patients,[12,13] additional clinical data are still needed on the effect of the rifampicin dose increase on efavirenz pharmacokinetics (PK).

The ANRS 12292 RIFAVIRENZ trial's primary objective was to compare the PK of efavirenz within the same HIV/TB-coinfected patients, with and without rifampicin coadministration, when using two different dosing regimens: rifampicin [10 mg/kg/day (R10) and 20 mg/kg/day (R20)] and efavirenz [600 mg daily (EFV600) and 800 mg daily (EFV800)]. Secondary objectives were to assess the ART and ATT efficacy and safety of concurrent administration of ATT and ART.

Patients and methods

Population and design

The RIFAVIRENZ trial was a Phase 2, open-label, drug–drug interaction, parallel, randomized clinical trial conducted in Mbarara, South Western Uganda (Figure S1, available as Supplementary data at *JAC* Online). Adult patients with rifampicin-susceptible pulmonary TB confirmed by the XpertMTB/RIF test, who were HIV-positive, ART-naive with CD4 counts between 50 and 250 cells/mm^3, body weight >45 kg and without medical contraindications, were enrolled in the study. Later on, protocol amendments were made, reducing the body weight cut-off to >35 kg and removing the CD4 cell count limit (Table S1). The study received approval from Mbarara University of Science and Technology research ethics committee, Uganda National Council of Science and Technology and National Drug Authority for Uganda. The study was registered with ClinicalTrials.gov (NCT01986543).

The primary endpoints were the efavirenz PK parameters: concentration before drug intake (C_{min}), maximal concentration (C_{max}), time to achieve the C_{max} (T_{max}) and AUC at steady-state during a 24 h dosing interval (AUC_{0-24}), with and without rifampicin. Secondary endpoints included: the rifampicin C_{max}; genetic polymorphism of enzymes involved in efavirenz metabolism; ART and ATT efficacy endpoints; treatment adherence; and safety endpoints.

Patients were randomly assigned to one of the three arms (R10EFV600, R20EFV600 or R20EFV800) in a 1:1:1 ratio. The arm using standard rifampicin and efavirenz doses (R10EFV600) was added to support the interpretation of the PK findings from the two high-dose rifampicin arms, knowing the interpatient variability of efavirenz PK and the limited PK data in HIV/TB-coinfected Ugandan patients. The randomization list was generated by the trial statistician using a fixed randomization method with mixed block sizes between three and six (nQuery Advisor v. 7.0 software). Sealed and serially numbered opaque envelopes, each containing the allocated regimen, were sent to the study site. At enrolment, eligible participants were randomized by the clinical investigator.

After randomization, patients were started on an ethambutol (E), isoniazid (H), pyrazinamide (Z) and rifampicin fixed-dose combination (FDC) (275 mg/75 mg/150 mg/400 mg) supplemented with rifampicin 150 mg or 300 mg tablets (Lupin; Mumbai, India) if allocated to R20EFV600 or R20EFV800 arms. Doses were calculated according to WHO weight-band recommendation.[14] ART was initiated after 2 or 4 weeks of ATT for patients with baseline CD4 <50 and >50 cells/mm^3, respectively, using EFV600 (Merck; Hertfordshire, UK) together with tenofovir disoproxil fumarate/lamivudine (Hetero labs; Telengana, India) and supplemented with efavirenz 200 mg tablets (Strides Arcolab; Bangalore, India) for patients allocated to the R20EFV800 arm. Eight weeks after starting ATT, all patients were switched to the standard dose of rifampicin and efavirenz, coadministered with HR (75 mg/150 mg)(Lupin; Mumbai, India) until completion of ATT (Week 24) and ART alone until the last study visit (Week 28). Patients took ART in the evening during the first 2 weeks to facilitate tolerance to efavirenz and then switched to morning intake to allow PK sampling during the day until Week 28. Pyridoxine and co-trimoxazole were administered to all patients. Treatment intake was directly observed by a domiciliary treatment monitor.

Symptom assessment, physical examination and collection of blood for complete blood counts, ALT, AST and bilirubin were performed at baseline and at completion of Weeks 2, 4 and 8. Hepatitis B surface antigen and hepatitis C antibody tests were performed at baseline. Sputum specimens collected at baseline and Weeks 8, 16 and 24 were first tested using microscopy with auramine staining and then processed using conventional *N*-acetyl-L-cysteine/sodium hydroxide and cultured on both Löwenstein–Jensen (LJ) agar and in a Mycobacterial Growth Indicator Tube (MGIT).[15] CD4 cell counts were determined at Week 24 post-ART initiation using the BD FACSCount™ system (BD Biosciences, San Jose, USA). Viral load quantification was done at baseline, then 4, 12 and 24 weeks post-ART initiation at the Makerere University - Johns Hopkins University Research Collaboration (MU-JHU Care Ltd) laboratory in Kampala (Uganda) using a COBAS® AMPLICOR Analyzer (Roche Molecular Diagnostics, Indianapolis, USA). In patients with HIV-1 RNA more than 500 copies/mL at Week 28, resistance mutations to NNRTI and NRTI were sought at the WHO-accredited regional HIV drug resistance laboratory of the MRC in Entebbe (Uganda). Drug resistance interpretation was performed using the Stanford University HIV drug resistance database (http://hivdb.stanford.edu).

Adverse events (AEs) were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (v. 2.0, November 2014).

PK analysis

Intensive PK sampling (30 min before and 1, 2, 3, 4, 8, 12 and 24 h after treatment administration) was done 2 weeks after starting ATT (for rifampicin PK without ART), 4 weeks after starting ART (efavirenz and rifampicin PK) and 4 weeks after completion of ATT (efavirenz PK without rifampicin). After centrifugation, plasma was stored at −80°C. A sample of whole blood was collected at baseline for pharmacogenetics and stored at −80°C. Early morning blood samples were also collected for trough concentration (C_{min}) measurement at 2 and 12 weeks post-ART initiation. Samples were shipped to an accredited pharmacology laboratory in Paris (France) that adheres to an interlaboratory quality control programme. Assays of efavirenz and rifampicin were performed using validated HPLC techniques with lower limits of quantification of 0.1 μg/mL and 0.25 mg/mL, respectively.[16–19] The inter-run variabilities of the low, medium and high quality controls inserted in each analytical run were below 15%. PK parameters were estimated using non-compartmental analysis with the software WinNonlin v. 6.1 (Pharsight Corporation). The genetic polymorphisms of *CYP2B6* that were analysed were *CYP2B6 516 G > T rs3745274, 983 T > C rs28399499* and *785 A > G rs2279343*. Patients with three or four low-activity alleles were classified as slow metabolizers, with two or one as intermediate metabolizers and WT genotype as extensive metabolizers.[20]

Statistical analysis

Based on a 26% efavirenz AUC reduction when efavirenz is given with R10 in healthy volunteers (efavirenz manufacturer's data) and a lower reduction (13%) in coinfected patients (previous data from our group), we assumed a 20% reduction of the efavirenz AUC_{0-24} when given with rifampicin compared with efavirenz alone (efavirenz +

rifampicin – efavirenz alone/efavirenz alone).[21,22] Therefore, the sample size was calculated to be able to detect a 20% reduction in efavirenz AUC_{0-24} with the standard rifampicin dose compared with efavirenz alone and to show that the decrease in efavirenz AUC_{0-24} when the rifampicin dose was doubled was not greater than 30% (a clinically acceptable reduction). Using a 5% significance level (one-sided), a standard deviation of the differences of the log AUC of 0.29 (reflecting the 15% intrapatient variability of efavirenz clearance), 80% power (nQuery Advisor v. 6.01 software) and an inflation to take into account a 20% dropout rate, the target sample size was 34 patients for each study arm.[23] Due to slow recruitment and subsequent independent data monitoring committee (IDMC) recommendations, patient enrolment was terminated after randomization of 98 patients.

Data were reviewed by the IDMC every 6 months. Presentation of patients' characteristics and analyses of the secondary endpoints were done in the modified ITT population (mITT), which included all randomized patients confirmed to be HIV-infected and without resistance to rifampicin. The PK population for the primary analysis included all patients from the mITT population who had the full PK assessment. The safety analysis included all enrolled patients who had at least one dose of drug intake of ATT and/or ART. Data were analysed using Stata software v. 13.0 (StataCorp LP, College Station, TX, USA).

The geometric mean ratios (GMRs) of log-transformed AUC_{0-24} and C_{min} of efavirenz with ATT over the log-transformed AUC_{0-24} and C_{min} of efavirenz without ATT, respectively, were calculated in each arm. The corresponding 90% CIs of the GMRs were compared with the preset 0.70–1.43 interval following the 2017 guidance of the US FDA for clinical drug interaction studies.[24] Other PK parameters on and off ATT were described using median and IQR by treatment arm. Proportions of patients with mid-dose subtherapeutic concentrations (<1000 ng/mL) were calculated.[25] The proportion of patients with an HIV-1 RNA reduction of >1 log at 4 weeks after starting ART and with HIV-1 RNA below 400 and 100 copies/mL at 12 and 24 weeks after ART initiation, respectively, the proportion with sputum culture conversion at Week 8 and end-of-treatment outcomes were calculated. The proportion of patients with serious AEs (SAEs), treatment-emergent AEs (TEAEs) Grade ≥3, elevation in transaminases and CNS AE Grade ≥3 were described. The treatment adherence rates for both ATT and ART between-visit time intervals were calculated as a percentage of the total dose intake, under direct observation, compared with the total dose prescribed to the patient. *Ad hoc* comparisons of secondary critical endpoints were made between the high-dose rifampicin arms and the standard-dose rifampicin arm using the chi-squared or Fisher's exact test for proportion and Wilcoxon matched-pairs signed-ranks test for continuous variables, where appropriate, at an alpha level of 5%.

Results

Between March 2014 and August 2016, 98 patients were randomized, of whom one patient tested HIV negative on PCR and was excluded from the mITT population. Overall, 87 patients were included in the primary endpoint analysis (Figure 1). More patients in the R10EFV600 arm had an extensive or slow *CYP2B6* genetic polymorphism than in other high-dose rifampicin arms (Table 1). Adherence rate to ATT remained 100% throughout the 24 weeks of treatment for all intervisit time intervals in the three arms. Only

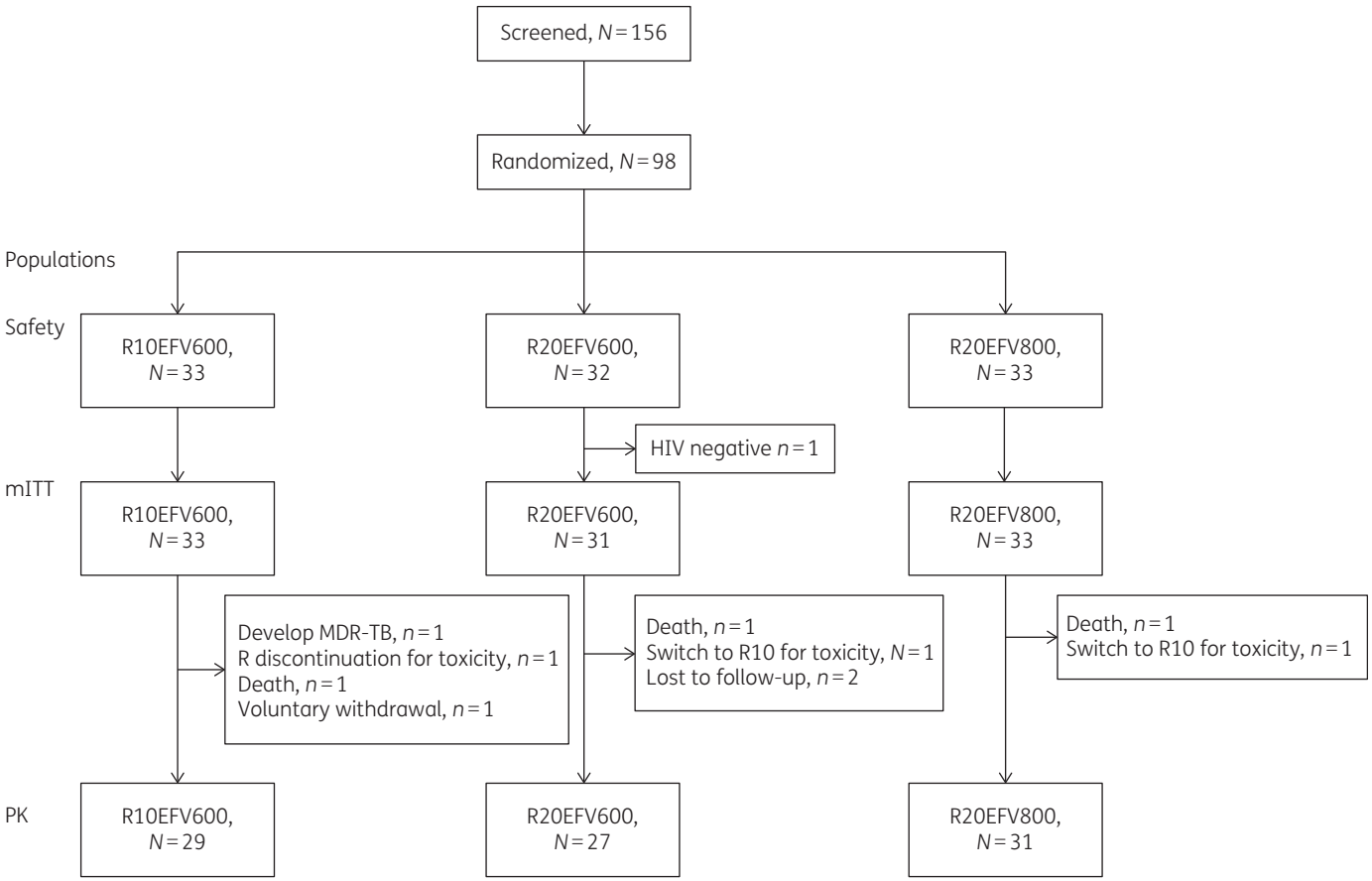

Figure 1. Study profile.

Table 1. Baseline participant characteristics

	R10EFV600 ($N = 33$)	R20EFV600 ($N = 31$)	R20EFV800 ($N = 33$)	*P* value
Males, *n* (%)	29 (87.9)	22 (71.0)	20 (60.6)	0.034
Age, years, median (IQR)	34.1 (29.6–38.1)	33.4 (28.0–36.6)	32.3 (27.8–43.1)	
Weight, kg, median (IQR)	51.9 (49.2–56.0)	53.8 (48.2–59.1)	54.1 (50.6–58.0)	
BMI, kg/m^2, median (IQR)	18.6 (17.9–20.6)	20.5 (17.5–21.0)	19.6 (18.3–21.4)	
MTB culture positive, *n* (%)				
LJ	27 (81.8)	24 (77.4)	26 (78.8)	0.905
MGIT	31 (93.9)	28 (90.3)	27 (81.8)	0.315
Haemoglobin, g/dL, median (IQR)	11.1 (9.0–12.6)	12.4 (10.7–13.8)	10.7 (9.5–12.4)	
CD4 count, cells/mm^3, median (IQR)	120 (66–252)	211 (69–334)	144 (86–367)	
HIV-1 RNA, log copies/mL, median (IQR)	5.5 (4.6–5.8)	5.2 (4.5–5.7)	5.1 (4.8–5.9)	
HBV, n/N (%)	2 (6.1)	1 (3.2)	1/32 (3.1)	1.000
HCV, n/N (%)	1/33 (3.0)	0/30	0/33	1.000
ALT, IU/L, median (IQR)[a]	22 (15–29)	19 (13–37)	19 (11–35)	
Presence of cavities, *n* (%)	14 (42.4)	16 (51.6)	12 (36.4)	0.465
Smear-positive microscopy	30 (90.9)	27 (87.1)	24/32 (75.0)	0.243
CYP2B6 genetic polymorphism				0.059
slow metabolizers	7 (21.2)	4 (12.9)	4 (12.2)	
intermediate metabolizers	14 (42.4)	22 (71.0)	19 (57.6)	
extensive metabolizers	11 (33.3)	3 (9.7)	5 (15.2)	
missing	1 (3.0)	2 (6.5)	5 (15.2)	

MTB, *M. tuberculosis*.
[a]ALT normal range: male = 0–45 IU/L; female = 0–34 IU/L.

in the R20EFV800 arm was a decrease in adherence rate to ART below 95% between Weeks 16 and 20 (93.3%) observed. There was increased exposure to rifampicin with the dose increase, as shown by the median (IQR) C_{max} at Week 2: 16.0 μg/mL (10.7–20.0), 15.6 μg/mL (12.2–19.0) and 5.3 μg/mL (3.5–6.9) for the R20EFV600, R20EFV800 and the R10EFV600 arms, respectively.

The lower bounds of the 90% CI of the GMR of the AUC_{0-24} (0.75 for R20EFV600, 0.96 for R20EFV800 and 0.84 for R10EFV600) were within the preset interval (0.70–1.43) (Table 2).

As compared with the R10EFV600 arm, a subtherapeutic efavirenz mid-dose concentration (C_{12} <1000 ng/mL) in the R20EFV600 and R20EFV800 arms was noted in 4/28 (14.3%) and 9/31 (29.0%) versus 9/31 (29.0%) ($P = 0.218$ and $P = 1.000$) patients on rifampicin and in 2/27 (7.4%) and 6/30 (20.0%) versus 6/28 21.4%) ($P = 0.252$ and $P = 0.893$) patients off rifampicin, respectively.

There was a high interpatient variability in the efavirenz plasma concentrations, as shown by the individual efavirenz C_{12} at Week 6/8 (on rifampicin) and Week 28 (off rifampicin) (Figure 2). Efavirenz concentrations were higher on rifampicin than off rifampicin, mostly among the slow-metabolizer patients (Figure 3).

There were significantly fewer patients with HIV-1 RNA below 100 copies/mL in the R20EFV800 arm after 24 weeks, as shown in Table 3. All six samples tested for drug resistance mutations at Week 24 revealed NNRTI resistance mutations, but in two of them resistance was already present at baseline. At Week 8, between 88.5% and 90.3% of patients had no detectable *Mycobacterium tuberculosis* on sputum culture using LJ and between 80.0% and 86.7% using MGIT. Treatment success was noted in 28/31 (90.3%) of patients on R20EFV600 and 31/33 (93.9%) on R20EFV800 versus 29/33 (87.9%) on R10EFV600 (Table 4).

Of the 98 patients included in the safety population, 18 (18.4%) (6 per treatment arm) developed at least one SAE, 15 of them (5 per treatment arm) during the first 8 weeks. Six patients (two per treatment arm) had Grade ≥3 elevation in transaminases, all within the first 8 weeks. Of these, two had their treatment interrupted with subsequent decrease in rifampicin dose from 20 mg/kg to 10 mg/kg. No Grade 3 or 4 CNS AEs were reported (Table 5). Three patients died (one per arm), of which one was as a result of disseminated TB, and two had severe sepsis of digestive origin.

Discussion

To the best of our knowledge, this is the first study to assess the effect of doubling the rifampicin dose on efavirenz PK in an HIV/TB-coinfected population. Despite a slight decrease in efavirenz AUC_{0-24} with higher rifampicin doses, the GMR remained within the preset interval of 0.70–1.43. As expected, the proportion of patients with subtherapeutic efavirenz concentrations was slightly higher during rifampicin coadministration.[26] However, the reduction was small and this could be explained at least in part by the reported inhibiting effect of isoniazid on the efavirenz accessory metabolic pathway by *CYP2A6* in the *CYP2B6* slow metabolizers.[23,27] Of note, we used the alleged mid-dose cut-off of 1 mg/L. Indeed, this lower limit of the currently recommended therapeutic range (1–4 mg/L) for efavirenz is controversial. Data from the ENCORE1 study noted that only a small proportion of those failing treatment had mid-dose efavirenz concentrations of <1.0 mg/L.[28] More recently the efavirenz mid-dose concentration of 0.7 mg/L was selected as the cut-off value for prediction of non-viral suppression.[29] Interestingly, four, none and four patients had

Table 2. PK parameters of efavirenz at Week 8 and Week 28

PK parameters	Regimen		
	R10EFV600	R20EFV600	R20EFV800
Week 8 (subjects on rifampicin coadministration)	31	28	31
AUC_{0-24}, ng·h/mL, median (IQR)	40 198 (13 406–314 509)	47 505 (16 180–308 410)	44 466 (12 943–326 311)
C_{12}, ng/mL, median (IQR)	1605 (983–3593)	1822.2 (1191–2671)	1896.4 (939–3270)
C_{min}, ng/mL, median (IQR)	10 780 (576–3216)	1163 (803–1995)	1032 (762–2253)
C_{min}<750 ng/mL, *n*/*N* (%)	9/31 (29.0)	6/28 (21.4)*	7/31 (22.6)**
C_{max}, ng/mL, median (IQR)	2325 (939–19 819)	2953 (786–14 027)	2877 (952–14 872)
T_{max}, h, median (IQR)	3.1 (2.5–4.1)	4.0 (3.3–4.0)	4.0 (3.0–4.0)
Week 28 (subjects off rifampicin coadministration)	29	27	31
AUC_{0-24}, ng·h/mL, median (IQR)	38 918 (14 346–214 301)	49 574 (13 365–486 759)	35 169 (14 236–265 682)
C_{12}, ng/mL, median (IQR)	1629 (1050–2686)[a]	1989 (1336–2845)	1420 (1042–2920)[b]
C_{min}, ng/mL, median (IQR)	1137 (783–2080)	1496 (1110–2171)	1028 (690–2310)
C_{min}<750 ng/mL, *n*/*N* (%)	9/31 (29.0)	6/28 (21.4)***	7/31 (22.6)****
C_{max}, ng/mL, median (IQR)	2692 (945–11 935)	3105 (841–22 128)	2300 (966–13 203)
T_{max}, h, median (IQR)	3.2 (3.0–4.0)	4.0 (2.1–4.0)	3.0 (3.0–4.0)
GMR (Week 8/Week 28), *n*	29	27	31
AUC_{0-24} (90% CI)	0.96 (0.84–1.10)	0.87 (0.75–1.00)	1.12 (0.96–1.30)
C_{min} (90% CI)	0.92 (0.79–1.08)	0.83 (0.72–0.96)	1.16 (0.97–1.39)

*P = 0.503 (Pearson's chi-squared); **P = 0.772 (Pearson's chi-squared); ***P = 0.731 (Fisher's exact); ****P = 0.204 (Pearson's chi-squared).
[a]Number of observations used to calculate the median C_{12} (ng/mL) at week 28 in patients on R10EFV600 (n = 28).
[b]Number of observations used to calculate the median C_{12} (ng/mL) at week 28 in patients on R20EFV800 (n = 30).

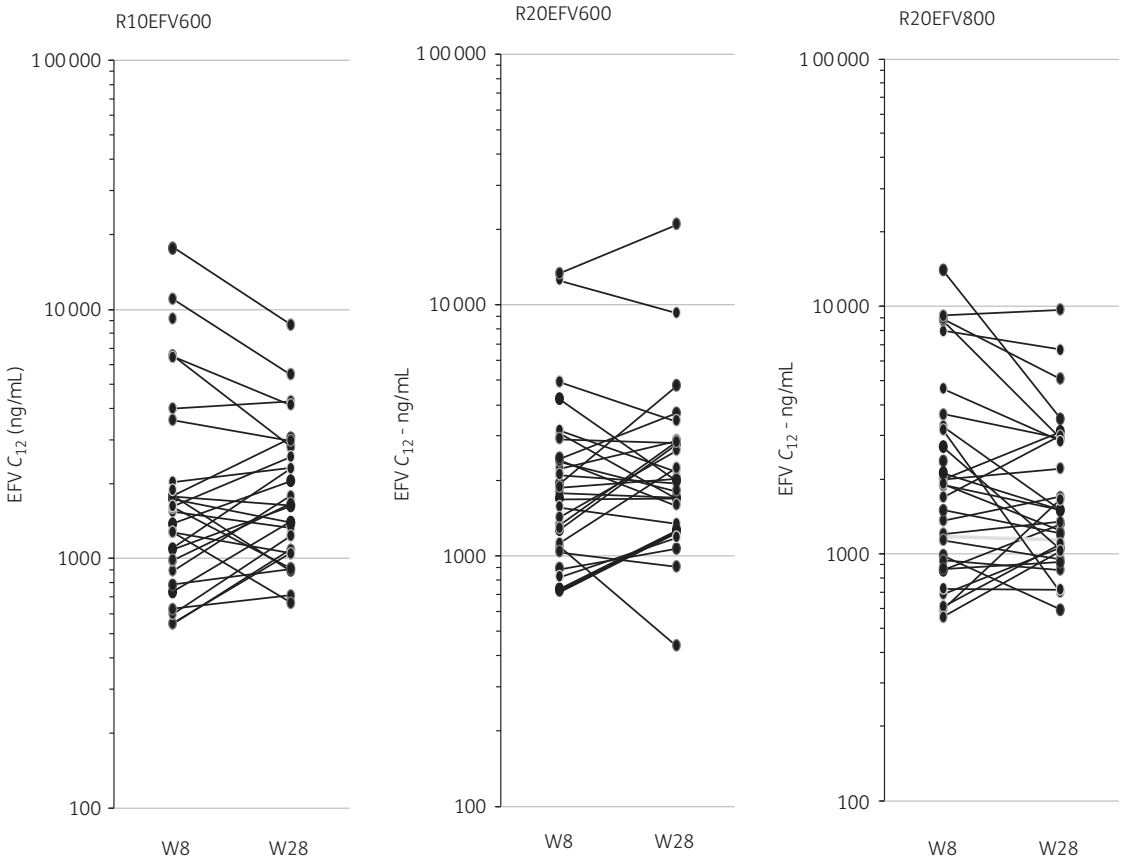

Figure 2. Efavirenz C_{12} for individual patients by treatment arm.

efavirenz mid-dose concentrations below this cut-off at Week 8 in the R10EFV600, R20EFV600 and R20EFV800 arms, respectively. The absence of an increase in the proportion of patients with sub-therapeutic efavirenz concentrations within the two high-rifampicin-dose arms (14% and 29%) as compared with the standard-rifampicin-dose arm (29%) during rifampicin coadministration could suggest a non-increased induction of CYP2B6 isoenzymes with higher rifampicin doses. In addition, we cannot exclude an effect caused by a pharmacogenetics imbalance between the arms.

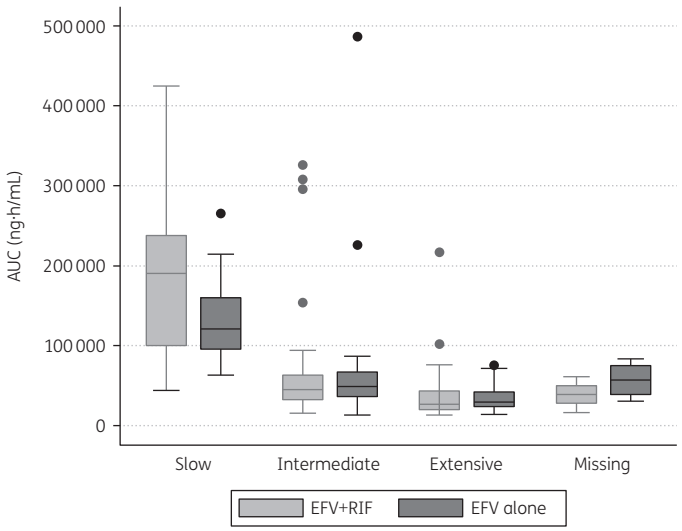

Figure 3. Efavirenz AUC according to the *CYP2B6* genetic polymorphism. Light grey boxes, with rifampicin; dark grey boxes, without rifampicin. *P* values based on Wilcoxon matched-pairs signed-ranks test for comparisons within each type of *CYP2B6* genetic polymorphism: $P = 0.062$, 0.827, 0.612 and 0.068 for slow, intermediate, extensive and missing, respectively.

The increase in rifampicin dose does not seem to affect the virological response during the first 12 weeks after ART initiation, knowing that all patients had been switched to the standard dose of rifampicin and efavirenz after Week 8. Despite these reassuring data, there was an unexpected lower response after 24 weeks among patients in the high-rifampicin-dose arms (R20EFV600 and R20EFV800) versus those on standard dosing (R10EFV600) and the difference was significant for patients in the R20EFV800 arm. We have limited evidence from our data to explain this difference. One possible explanation could be related to treatment adherence. We observed a mild decrease in the average adherence rate to below 95% (93%) between Weeks 16 and 20 in the R20EFV800 arm for both rifampicin and ART whereas the adherence rate overall was very good and always above 95% in the two other arms. This could potentially explain the reduction of virological efficacy at Week 28 as compared with Week 12.[30] Of note, in four patients there was acquisition of the K103N viral mutation at Week 28.

Although non-significant, we observed a trend for a slight increase in the Week 8 culture conversion rate (+5.7% and 6.7%) using MGIT for patients in the R20EFV600 and R20EFV800 arms, respectively, a finding that supports the rifampicin dose-dependent bactericidal effect already demonstrated in HIV-negative TB patients.[3,6] However, our trial was not powered to compare the ATT efficacy.

Coadministration of a doubled dose of rifampicin with efavirenz among HIV/TB-coinfected patients was well tolerated.

Table 3. Virological response at 4, 12 and 24 weeks post-ART initiation

Characteristic	R10EFV600 ($N = 33$)	R20EFV600 ($N = 31$)	*P* value[a]	R20EFV800 ($N = 33$)	*P* value[a]
4 weeks reduction HIV-1 RNA ≥1 log[b]	28/32 (87.5)	26/28 (92.9)	0.675	28/29 (96.6)	0.357
HIV-1 RNA <400 copies/mL					
12 weeks after ART initiation	26/29 (89.7)	26/28 (92.9)	1	26/31 (83.9)	0.708
24 weeks after ART initiation	28/29 (96.6)	22/27 (81.5)	0.096	26/31 (83.9)	0.196
HIV-1 RNA <100 copies/mL					
12 weeks after ART initiation	21/29 (72.4)	22/28 (78.6)	0.589	24/31 (77.4)	0.655
24 weeks after ART initiation	27/29 (93.1)	20/27 (74.1)	0.073	21/31 (67.7)	0.022
Failures 24 weeks after ART initiation (HIV-1 RNA ≥1000 copies/mL)	1/29 (3.5)	4/27 (14.8)	0.154	2/31 (6.5)	0.525
Resistance mutations at Week 28 for patients with HIV-1 RNA >500 copies/mL					
samples tested (*n*)	1	4		3	
no amplification	0	2		0	
NRTI/NNRTI resistance mutations (*n*)	1[c]	2		3[d]	
NRTI/NNRTI resistance mutations	K65R, T215D, Y115FY, G190A	K65R, K103N, G190A V179T		M184V, K103N K70KEQ, L100I, P225H	

[a]Fisher's exact test, R10EFV600 control group.
[b]After exclusion of patients with undetectable viral load at inclusion.
[c]Same resistance mutation at baseline.
[d]Two with resistance at baseline: two acquired a 184V mutation and one acquired thymidine analogue mutations (TAMs). One had TAMs at baseline and not at Week 28.

Table 4. Eight week sputum culture conversion and end-of-ATT outcomes

	R10EFV600	R20EFV600	*P* value[a]	R20EFV800	*P* value[a]
Week 8 culture conversion[b]					
LJ, *n*/*N* (%)	28/31 (90.3)	23/26 (88.5)	1.000	24/27 (88.9)	1.000
MGIT, *n*/*N* (%)	24/30 (80.0)	24/28 (85.7)	0.732	26/30 (86.7)	0.731
Treatment outcome (*n*)	33	31		33	
cured	22 (66.7)	19 (61.3)		24 (72.7)	
treatment completed	7 (21.2)	9 (29.0)		7 (21.2)	
treatment failure[c]	1 (3.0)	0		0	
death	1 (3.0)	1 (3.2)		1 (3.0)	
default	1 (3.0)	1 (3.2)		0	
transferred out[d]	1 (3.0)	1 (3.2)		1 (3.0)	
treatment success (cured + completed)	29 (87.9)	28 (90.3)	1.000	31 (93.9)	0.672

[a]*P* values based on Fisher's exact test.
[b]After exclusion of contaminated, 'not done' and non-mycobacteria culture results.
[c]One patient was diagnosed with MDR TB in the bone marrow on Xpert but with complete RH susceptibility on culture and drug susceptibility testing and negative sputum smear, all at Week 6 of TB treatment follow-up.
[d]The three patients transferred out were patients withdrawn by the study investigator due to safety reasons.

The proportion of patients with Grade ≥3 increase of transaminase on rifampicin 20 mg/kg (6.1%) is comparable to that reported among HIV-negative TB patients on the same rifampicin dose (7%) and among HIV/TB-coinfected patients on the standard rifampicin dose in larger trials.[3,31] We did not observe severe CNS AEs (Grade ≥3) despite the use of efavirenz at 800 mg daily in one arm.

This study had some limitations. First, despite the randomization, there was an imbalance in genotypic polymorphism distribution between study arms. There were more slow metabolizers and extensive metabolizers randomized to the standard-rifampicin-dose arm and more intermediate metabolizers randomized to the high-rifampicin-dose arms (71% and 58%, respectively, versus 42%). This imbalance could potentially influence the primary endpoint findings. However, due to this distribution and the fact that there were more missing metabolizers in the R20EFV800 arm, it is difficult to predict the size and direction of the bias. There was also an imbalance of gender between arms, with more women in the R20EFV800 arm compared with the two other arms. One study that presented plasma efavirenz concentrations stratified by gender during coadministration with anti-TB drugs reported lower mean C_{min} for males than for females (1870 ng/mL versus 2370 ng/mL), which was explained by the differences in patients' body weight.[32] However, in our study, there was no difference in mean body weight between males and females across treatment regimens (data not shown). Second, the study design has the limitation of increasing the risk of interpatient variability as compared with a within-subject design assessing the effect of the different rifampicin doses in the same patients. However, this design would require antiretroviral washout periods, which is not advisable in these patients. Also, knowing that the time to reach steady-state efavirenz concentrations might be long, we cannot exclude that the induction effect of one rifampicin dose would alter the effect of the other dose. This design allowed assessment of very important secondary clinical outcomes (ATT and ART response), which would not be assessed with a within-subject design. Third, the trial only evaluated rifampicin doses up to 20 mg/kg based on available background efficacy and safety information in HIV-negative patients at the time of the trial implementation. However, a recent dose-optimization study in HIV-negative TB patients has demonstrated that rifampicin doses as high as 35 mg/kg administered for 3 months were well tolerated and had a faster time to stable culture conversion. There was no difference of time to culture conversion at the dose of 20 mg/kg.[6] This has led to the evaluation of a rifampicin 35 mg/kg dose among HIV-negative TB patients in an ongoing Phase 3 treatment-shortening trial (RIFASHORT trial; NCT02581527). Although we cannot generalize our findings to the effect of rifampicin doses higher than 20 mg/kg, our data suggest that increasing the rifampicin dose has little effect on efavirenz concentrations and that induction could be maximal at the lower doses. Fourth, the study was not powered for the comparison of secondary efficacy and safety endpoints between the arms. Therefore, the absence of difference in the few secondary endpoints that were compared between the arms could be due to lack of power.

In conclusion, doubling the rifampicin dose resulted in a small reduction of efavirenz exposure in HIV/TB-coinfected patients, appeared safe and had good ATT and early ART efficacy. This coadministration could be considered in future evaluation of high-dose rifampicin regimens in HIV/TB-coinfected patients but would require close monitoring of the virological response.

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Table 5. Major TEAEs (Grade 3 or 4) among patients by treatment arm

System organ class[a]/ TEAE preferred term	R10EFV600 (*N* = 33)	R20EFV600 (*N* = 32)	R20EFV800 (*N* = 33)
Blood and lymphatic system disorders, *n* (%)			
anaemia	1 (3.0)	1 (3.1)	0
leucopenia	2 (6.1)	1 (3.1)	2 (6.1)
neutropenia	1 (3.0)	0	0
thrombocytopenia	4 (12.1)	2 (6.3)	3 (9.1)
Gastrointestinal disorders, *n* (%)			
vomiting	1 (3.0)	0	0
General disorders, administration site conditions			
pyrexia	1 (3.0)	0	0
Hepatobiliary disorders, *n* (%)			
hyperbilirubinaemia	3 (9.1)	2 (6.3)	0
Infections and infestations, *n* (%)			
disseminated TB	1 (3.0)	0	0
sepsis	0	0	1 (3.0)
septic shock	3 (9.1)	2 (6.3)	3 (9.1)
Investigations, *n* (%)			
ALT increased	1 (3.0)	2 (6.3)	1 (3.0)
AST increased	3 (9.1)	2 (6.3)	2 (6.1)
haemoglobin decreased	0	0	1 (3.0)
Metabolism and nutrition disorders			
dehydration	0	1 (3.1)	0
hyponatraemia	1 (3.0)	0	0
Respiratory, thoracic and mediastinal disorders, *n* (%)			
dyspnoea	0	0	1 (3.0)
pleural effusion	1 (3.0)	0	0
pulmonary hypertension	0	0	1 (3.0)
respiratory distress	0	1 (3.1)	0
Vascular disorders, *n* (%)			
hypertension	0	0	1 (3.0)

[a]AE terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA v. 19.1).

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Transparency declarations

None to declare.

Author contributions

M.B., D.A., A-M.T., E.B., V.F., and C.V. were involved in the conception and design of the study. D.A., M.B., A.M.T., E.B., W.M., K.M., R.K., K.K., P.O., D.N., D.K.T.N., T.G., and A.B-T. were involved in study implementation. E.B., M.B., A.M.T. and D.A. did the data analysis. V.F. and C.V. interpreted the data and provided important intellectual input. D.A., M.B., A.M.T. and E.B. wrote the first draft. The Rifavirenz study group members participated in study implementation. All authors reviewed the final draft of the manuscript.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at *JAC* Online.

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