Pharmacokinetics of efavirenz 400 mg once-daily co-administered with isoniazid and rifampicin in HIV-infected individuals.

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RUNNING TITLE: Efavirenz 400 mg with isoniazid/rifampicin

KEY WORDS: Low dose efavirenz; pharmacokinetics; tuberculosis; isoniazid/rifampicin; HIV

SUMMARY OF THE ARTICLE'S MAIN POINT: Efavirenz 400 mg (EFV400) is an option for the treatment of HIV. However, no data on EFV400 with INH/RIF are available. Following INH/RIF we observed limited changes in EFV400 exposure, irrespective of *CYP2B6* genotype.

ABSTRACT

BACKGROUND: WHO recommend efavirenz 400mg (EFV400) as first-line antiretroviral (ARV), with a disclaimer that no data on EFV400 with anti-tuberculosis (TB) treatment exist. Many people living with HIV (PLWH) require tuberculosis (TB) treatment with isoniazid (INH) and rifampicin (RIF), which affect cytochrome P450 and ARV exposure.

METHODS: This open-label study investigated EFV400+INH/RIF pharmacokinetics (PK), efficacy, *CYP2B6* pharmacogenetics in PLWH without TB. Patients receiving tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/EFV 600mg with a viral load (VL)<50copies/mL were switched to TDF/FTC/EFV400. Weekly therapeutic drug monitoring (TDM) and steady-state PK profiles of EFV400 without (PK1) and with INH/RIF following 4 (PK2) and 12 (PK3) weeks of co-administration, were evaluated.

RESULTS: Thirty-two PLWH were screened and 26 baselined, 22 completed PK2. All maintained VL<50copies/mL throughout the study. Geometric mean ratios (GMR) (90%CI) PK2/PK1, of EFV400 C_{max}, area under the curve (AUC), and C_{24h} were 0.91 (0.83-0.99), 0.91 (0.79-1.05), 0.85 (0.72-0.99). GMR (90%CI) of PK3/PK2 and PK3/PK1 C_{max}, AUC, and C_{24h} were 0.95 (0.86-1.05), 0.92 (0.83-1.01), 0.88 (0.75-1.03) and 0.84 (0.75-0.93), 0.84 (0.72-0.99), 0.75 (0.62-0.92). Eleven/22 subjects were carriers of 516T (n=10) and/or 938C (n=3) polymorphisms in the *CYP2B6* gene associated with slow EFV metabolism.

CONCLUSIONS: INH/RIF co-administration in TB-negative PLWH was associated with limited changes in EFV400 AUC (<25%) and EFV400 concentrations were maintained within ranges of those measured in PLWH in the ENCORE-1 study, irrespective of *CYP2B6* genotype. We conclude that the co-administration of EFV400 with anti-TB treatment can be considered. This is being confirmed in PLWH co-infected with TB.

Introduction

Tuberculosis (TB) remains one of the leading causes of death among people living with HIV (PLWH). The WHO estimates that PLWH are 16-27 times more likely to develop TB than HIV negative individuals and that approximately one million PLWH developed TB in 2016, resulting in 0.4 million deaths. The dual burden of HIV-associated TB is particularly high in the African region, where 81% of patients with notified TB presented with HIV infection [1].

The WHO guidelines recommend antiretroviral treatment (ARV) be initiated as early as possible in all PLWH, especially if co-infected with TB to reduce mortality [2]. The preferred first-line regimen currently recommended by the WHO consists of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) or lamivudine (3TC) and efavirenz (EFV) 600 mg as a fixed-dose combination [2]. It is recognised that CNS (central nervous system) symptoms and psychiatric adverse effects such as dizziness, vivid dreams, headache, sleep disturbance, depression, and suicidal ideation affect almost half of the individuals taking EFV and can often impede adherence and lead to treatment discontinuation [3,4]. EFV exposure as well as genetic polymorphism have been shown to predict these neuropsychiatric toxicity [5,6]. The ENCORE-1 clinical trial, an international Phase III, double blind and randomized study, showed the non-inferiority of EFV 400 mg (EFV400) relative to the 600 mg dose in terms of virological suppression. Furthermore, individuals randomized to EFV400 presented significantly lower rate of treatment discontinuation due to adverse events [7–9]. EFV400 use becomes even more appealing when considering the potential significant cost reduction in drug manufacture, as ARV dose reductions compensate for finite global manufacturing capacity and allow access programmes to reach larger numbers of PLWH.

Nevertheless, the lack of pharmacokinetic (PK) and efficacy data of EFV400 in pregnant women and when co-administered with anti-TB treatment have, so far, limited its implementation [10]. Multiple factors have been investigated to better understand the PK of EFV and these are crucial to consider in order to better understand the potential efficacy and

role of EFV400 in clinical practice. Pharmacogenomics studies have shown that EFV plasma concentrations are affected by the polymorphic enzyme cytochrome P450 2B6 (*CYP2B6*), the main metabolic pathway for converting EFV to inactive metabolites. Individuals classified as slow metabolisers present significantly higher EFV concentrations that may result in increased CNS adverse events even in the presence of co-administered rifampicin (RIF)-containing anti-TB treatment [7,10–12]. Moreover, other factors such as low body weight have been associated with increased EFV plasma exposure [13]

The standard anti-TB regimen recommended for PLWH is complex and consists of two months of daily isoniazid (INH), RIF, pyrazinamide, and ethambutol, followed by four months of INH/RIF [14]. RIF is a potent inducer of drug metabolising enzymes, including *CYP2B6*, which is mainly responsible for EFV metabolism [15]. By contrast, INH demonstrates potent inhibition of *CYP2A6*, an alternate pathway of EFV hydroxylation [16]. Moreover, long-term administration of EFV results in an induction of its own metabolism and consequent reduction of its exposure (auto-induction) [17,18]. Several studies have investigated the effect of INH/RIF on EFV 600 mg and found no significant difference in EFV plasma concentrations, reporting in contrary a trend towards higher EFV exposure with co-administration of RIF and INH [12,19–21]. However, data on EFV400 co-administered with INH and RIF are not available.

Therefore, the primary objective of this study was to evaluate the PK of EFV400 during co-administration with INH and RIF in PLWH. Secondary objectives were to assess the safety and tolerability of EFV400 in combination with TDF/FTC in HIV-infected subjects receiving INH and RIF and to describe the pharmacogenetics of *CYP2B6* in the studied individuals.

Methods

Study population

This open-label, PK study was registered at ClinicalTrials.gov (NCT02832778). Regulatory and ethical approvals were obtained before initiating the study. Subjects signed written informed consent prior to being enrolled in the study. Participants enrolled were PLWH without TB who were receiving TDF, FTC or 3TC plus EFV 600 mg for at least 12 weeks. INH 300 mg and RIF 600 mg were given in subjects ≥ 50 Kg, RIF 450 mg and INH 300 mg if weight was < 50 Kg.

Eligible patients were male or non-pregnant and non-lactating females, aged between 18 to 60 years, with confirmed HIV-infection, CD4 count higher than 100 cells/mm3, undetectable viral load for at least 12 weeks, body mass index (BMI) of 18 to 35 kg/m^2, using adequate and effective double barrier method of contraception. Patients were latent TB negative by ELISpot testing (if documented history of previous successful treatment for TB ELISpot results could be positive). Subject exclusion criteria were: evidence of organ dysfunction, hepatitis B/C co-infection, use of medications and herbal preparations known to interfere with EFV metabolism.

Study procedures

On day 1 the EFV dose was reduced from 600 mg to 400 mg once-daily (OD) until day 14 (PK1). On days 15 to 98 INH/RIF co-formulated OD were added to the EFV400. EFV therapeutic drug monitoring (TDM) was performed between 10-14 hours post dose, twice-weekly from baseline to day 42, then reduced to once weekly in selected subjects whose concentrations remained stable. To promptly assess EFV concentration reductions that could potentially lead to viral rebound, TDM samples were analysed and reported to the study team to be reviewed in real-time. In consideration of the INH/RIF potential hepatotoxicity, liver function tests (LFTs) including serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were performed at every TDM visit. HIV-RNA

measurement and safety blood determinations were performed every two weeks. Study subjects were withdrawn according to predefined stopping criteria: (i) significant liver toxicity defined as ALT and/or AST ≥ Grade 2 and symptomatic, ALT and/or AST ≥ Grade 3 and asymptomatic or ALT and/or AST ≥ Grade 2 and bilirubin ≥ than Grade 2; (ii) viral load (VL) detectable on two consecutive occasions; (iii) EFV concentrations below 20% of the suggested minimum effective concentration (MEC) of 1000 ng/mL on three consecutive occasions. The study cut-off of 800 ng/mL was derived by the receiver operating characteristic (ROC) curve analysis performed during the ENCORE-1 study [7]. Adverse events were reported according to the Division of AIDS (DAIDS) grading scale (December 2004).

Intensive pharmacokinetic assessments

Intensive PK visits with serial blood sample collection over 24 hours for measurement of EFV concentrations were performed on three occasions: after 14 days of treatment with EFV400 and prior to initiation of INH/RIF (day 14, PK1), four weeks into EFV400 and INH/RIF co-administration (day 42, PK2) and 12 weeks after EFV 400 mg and INH/RIF co-administration (day 98, PK3).EFV plasma concentrations were evaluated from blood drawn from intravenous catheter inserted into an arm vein at pre-dose, 2, 4, 8, 12, and 24 hours post-dose, in a fasted state under direct observation by the clinical study staff.

Efavirenz concentration analysis

EFV plasma concentrations for a full profile and TDM measurements were by a validated reversed-phase ultra performance liquid chromatography (UPLC) method modified from a method previously published at Jefferiss Research Trust Laboratories [22]. EFV was measured at a wavelength of 246 nm and the assay was validated over a calibration range of 250–10,000 ng/mL. The laboratory adheres to the International Inter laboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma [23].

Sample size calculation and data analysis

The sample size was determined based on the effect of INH/RIF on EFV concentrations. The EFV C_{24} (concentration at 24 hours post-dose) from each patient was compared between the two phases using geometric mean ratios (GMR) (log_{10} transformed data). For this sequential design, a sample size of 25 patients (this includes a 10% drop-out rate) was calculated to provide at least 80% power to detect a decrease in EFV C_{24} of 20% during combined EFV400-INH/RIF administration compared to the EFV400 alone. All participants who completed PK1 and PK2 were included in the final data analysis. Withdrawn subjects and subjects who did not complete PK2 were replaced in order to maintain statistical power. Non-compartmental modelling techniques (WinNonlin®Phoenix, version 7.0; Pharsight Corp, Mountain View, CA, USA) were applied to plasma EFV concentration-time data to obtain: C_{24h}, maximum plasma concentration (C_{max}), and area under plasma concentration-time curve from 0-24 hours (AUC_{0-24}). Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (CI), were calculated for all parameters.

Changes in within-subject EFV plasma concentrations (PK2 versus PK1, PK3 versus PK2, PK3 versus PK1) were assessed by calculating GMR and 90% CI. Inter individual variability in EFV PK parameters was expressed as a percentage coefficient of variation [CV, (standard deviation/mean)x100].

Pharmacogenetics assays and analysis

Genomic DNA was extracted from whole blood and quantified using NanoDrop (ThermoFisher Scientific, Wilmington, DE) following specific written consent utilising the manufacturers protocols (E.Z.N.A Blood DNA Mini Kit, Omega Bio-tek, Norcross, GA). Genotyping of known functional polymorphisms recognised to be linked with increased steady state EFV exposure *CYP2B6* 516G>T (*rs3745274, CYP2B6*6*) and 983T>C (*rs28399499, CYP2B6*18*) were performed using a real-time PCR-based allelic discrimination with a DNA Engine Chromo4 System as described previously [24]

Composite *CYP2B6* genotypes were assigned as follows: extensive metaboliser (no variant allele at position 516 or 983); intermediate metaboliser (single variant allele at position 516 or 983, but not both); slow metaboliser (two variant alleles, e.g. either 516 T/T, 983 C/C, or 516 G/T plus 983 T/C) [25]. Although the sample size of this study is small for statistical analysis to assess differences in drug exposure among the three metaboliser groups described above, for completion unpaired t-test was performed to assess whether these differences were significant.

Results

Study population

A total of 32 PLWH on EFV 600 mg in combination with TDF and FTC were screened for the study. Three subjects were excluded as they were lost to follow up before baseline, one withdrew consent before baseline because of personal reasons, one for pre-existing steatohepatitis and consequent excessive risk of hepatotoxicity in the opinion of the investigators and one was excluded due to positive TB ELISpot. Twenty-six subjects were considered eligible for the study and started EFV400 intake. After baseline, a total of four individuals withdrew from the study: three because of EFV400 TDM results < 800 ng/mL in more than three consecutive visits (two subjects had EFV concentrations < 800 ng/mL from baseline while they were still on EFV 600 mg and therefore they were withdrawn before commencing INH/RIF, one subject was discontinued due to EFV concentrations < 800 ng/mL after two weeks of co-administration of EFV400 and INH/RIF) and one individual withdrew because of onset of non-drug related liver toxicity before INH/RIF initiation. Therefore, 22 subjects completed at least four weeks of EFV400 plus INH/RIF co-administration (PK2) and were considered for PK analysis. Demographic and laboratory characteristics of the evaluable population are presented in Table 1. Eighteen/22 subjects completed the study to day 99 (PK3), as four discontinued between PK2 and PK3: two subjects developed liver toxicity, one had EFV400 TDM results < 800 ng/mL, and one was confirmed pregnant.

Pharmacokinetics of EFV400 during co-administration with isoniazid/rifampicin

EFV TDM results for the 22 PLWH who completed the PK2 are shown in Figure 1. Each individual attended between 15 and 32 TDM visits. In four subjects, EFV concentrations were detected below the study cut off of 800 ng/mL only at a single occasion, with other EFV TDM measurements being above the threshold, therefore they were not discontinued and were included in the analysis. EFV PK parameters and GMR (90% CI) measured on PK1,

PK2 and PK3 are illustrated in Table 2. The concentration-time profile of EFV400 alone and with INH/RIF are shown in Figure 2. EFV C_{max}, C_{24h} and AUC_{0-24} were 9%, 15% and 9% lower after four weeks of co-administration with INH/RIF (PK2) *versus* EFV400 alone (PK1). After further eight weeks of INH/RIF intake (PK3), EFV C_{max}, C_{24h} and AUC_{0-24} were 5%, 12%, and 8% lower compared to PK2 and 16%, 25% and 16% lower compared to PK1.

Efavirenz pharmacogenetics

Among the 26 subjects baselined for the study and signed the appropriate consent, 25 were genotyped. Fourteen were extensive metabolisers, seven intermediate and four slow metabolisers. The metaboliser status of these 22 patients who were considered evaluable for PK analysis are presented in Table 1. The relationship between EFV TDM results and metaboliser status is illustrated in Figure 1.

At PK1, AUC_{0-24} was significantly lower in intermediate (38,611.2 ± 11,923.9 ng*h/mL; P = 0.003) and extensive (45,117.8 ± 17,045.4 ng*h/mL; P = 0.0003) metabolisers defined by CYP2B6 alleles than in slow metabolisers (204,913.0 ± 101,668.4 ng*h/mL). Similarly for PK2, AUC_{0-24} was significantly lower in intermediate (49,138.6 ± 18,523.3 ng*h/mL; P = 0.002) and extensive (34,799.5 ± 15,226.1 ng*h/mL; P = 0.00004) metabolisers than in slow metabolisers (195,032.8 ± 81,017.1 ng*h/mL). This CYP2B6 genotype effect was also seen at PK3, where AUC_{0-24} was significantly lower in intermediate (42,428.8 ± 14,001.9 ng*h/mL; P = 0.007) and extensive (25,945.2 ± 5,512.0 ng*h/mL; P = 0.0003) metabolisers than in slow metabolisers (179,646.1 ± 82,873.8 ng*h/mL).

Characteristics of subjects with EFV concentrations below the protocol driven concentration cut off of 800 ng/mL

A total of four subjects out of 26 included in the study were withdrawn due to EFV levels less than 800 ng/mL in more than three consecutive visits. Two subjects had EFV levels < 800 ng/mL detected since baseline visit, when the EFV TDM was performed while they were still on EFV 600 mg. In detail, one subject (subject 104) was White British, had a baseline BMI of

27 Kg/m^2 and had a baseline EFV concentration of 766 ng/mL, which dropped to 422 ng/mL after 11 days of EFV400. The other subject (subject 134) was of Hispanic origin, with a BMI of 35.9 Kg/m^2, and an EFV TDM at baseline of 667 ng/mL, that decreased to 578 ng/mL after 14 days of EFV400. Both were male, extensive metabolisers and did not receive INH/RIF as they discontinued the trial before the first dose of anti-TB treatment. A third subject (subject 131), with a baseline EFV 600 mg concentration of 969 ng/mL had a first detection of EFV TDM < 800 ng/mL (733 ng/mL) after eight days of EFV400 alone that further dropped to 456 ng/mL after a week of EFV400 plus INH/RIF; he was discontinued after two weeks of INH/RIF when EFV concentrations were 423 ng/mL. He was an Hispanic male, extensive metaboliser and with a BMI of 27 Kg/m^2. A fourth individual (subject 105) was a White male, intermediate metaboliser with a BMI of 25 Kg/m^2 with EFV levels down to 673 ng/mL after two weeks and discontinued after almost 8 weeks of INH/RIF. Importantly, all subjects maintained an undetectable VL throughout the study. Two subjects (both extensive metabolisers) were found having EFV TDM levels between 700 and 774 ng/mL at 12 hours post dose at PK 2 visit; interestingly the same two subjects when tested at 12 hours post dose at PK 3 visits presented higher levels of EFV, above 800 ng/mL

Safety and tolerability

Overall EFV400 was well tolerated during co-administration with INH/RIF, with no serious adverse events reported. Two subjects were discontinued due to INH/RIF-related liver toxicity as per protocol stopping criteria. They were followed up until full normalization of the LFTs. One subject was withdrawn from the trial due to onset of transient grade 3 ALT increase with unknown cause before starting on INH/RIF, being viral hepatitis infections and autoimmune liver diseases excluded. Finally, one subject was discontinued and switched to EFV 600 mg as confirmed pregnant; subject's HIV viral load remained undetectable throughout the pregnancy and delivery. Grade 3 hypertension was observed in one subject with previous history of high blood pressure, unlikely related to the study drugs. No other

Grade 3 or 4 drug-related adverse events were reported. *CYP2B6* polymorphism were not linked to drug-related hepatotoxicity.

Discussion

We investigated EFV plasma PK following the administration of EFV400 with and without INH/RIF in PLWH. Genetic differences linked to EFV metabolism were also studied in order to better explain EFV concentration changes over the study period. For ethical and safety reasons we enrolled PLWH not co-infected with TB, with an undetectable VL on TDF/FTC or 3TC and EFV 600 mg and we established a concentration cut off of 800 ng/mL.

Although EFV400 C_{24h} was 25% lower after 12 weeks of co-administration with INH/RIF (PK3) compared to EFV 400 mg alone, the plasma concentrations of EFV were maintained above the cut-off extrapolated by the ENCORE-1 study [7]. Importantly, the EFV dose reduction was observed to be adequate in maintaining virological suppression during co-administration with anti-TB treatment in all individuals enrolled in the study.

We also observed four subjects (two before and two while on INH/RIF intake) with EFV concentrations below the protocol established cut off of 800 ng/mL in multiple consecutive occasions who were withdrawn from the study. The protocol was designed to restrict remarkable decreases in EFV concentrations to protect the HIV-positive subjects without TB who volunteered for the study. Importantly, these subjects had concentrations within the ranges of those measured by the ENCORE-1 PK sub-study and the majority of concentrations measured in these four subjects (none < 400 ng/mL) were also within the proposed ROC range associated to virological response proposed by Dickinson et al. [7].

RIF is a strong CYP450 inducer that has been shown to reduce EFV concentrations in healthy volunteers studies [26]. However, subjects with HIV-TB co-infection are exposed to multiple drugs, leading to complex PK interactions. Several studies showed that EFV concentrations may increase during co-administration with a RIF-based anti-TB treatment [12,21,27,28]. This is due to the fact that the metabolism of EFV in co-administration with anti-TB treatment does not follow a simple pathway but it is a result of multiple factors. Furthermore, *CYP2B6* polymorphism is known to be linked with plasma levels of EFV,

explaining for greater EFV exposures observed in populations with high rates of EFV slow metabolizers [29,30]. In addition, INH is a *CYP2A6* inhibitor; by a concentration-dependant inhibitory effect on EFV, INH metabolism may counterbalance the EFV clearance induced by RIF and therefore explain the increase in EFV exposure especially in slow metabolisers [16,21].

In this study, none of the subjects weighted <60 Kg and therefore we could not confirm previous results from the STRIDE trial that found a significant lower EFV C_{24h} in patient weighing ≥60 Kg versus <60 Kg [12]. However, large individual variability in EFV exposure without and with INH/RIF was consistent with previous studies [12], where the addition to INH/RIF in PLWH on ARVs led to both a decrease or an increase in EFV exposure in different subjects. Finally, although the majority of study subjects were males, these data should still be transferrable to both sexes, as differences in EFV exposure between males and females were not highlighted in the PK sub-study of ENCORE-1, where 191 (32%) women were studied.

Although our findings are being confirmed by EFV PK determinations in PLWH co-infected with TB, we here demonstrate for the first time that EFV400 can be co-administered with INH/RIF-containing anti-TB treatment and it can be used extensively in low- and middle-income countries (LMIC) to reduce drug manufacture costs and HIV treatment discontinuations due to adverse events.

Ultimately, while there is a trend towards shifting from EFV-containing ARV combinations to dolutegravir-containing first-line treatment for HIV in LMIC, the process is slow and may take numerous years, especially in countries in Sub-Saharan Africa or South-East Asia that do not have access to dolutegravir yet and may benefit from EFV 400 mg use [31].. Furthermore, WHO guidelines update is on-going and allowing use of EFV 400 mg extensively will allow such countries to select only this dose of EFV without concerns regarding pregnancy and co-administration with anti-TB treatment.

Funding

This work was supported by a research grant from Mylan through OPTIMIZE, a global partnership unifying distinct voices to achieve a common goal: accelerating access to simpler, safer and more affordable HIV treatment. OPTIMIZE is funded by the United States Agency for International Development (USAID) through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

Acknowledgements

The authors would like to thank David Back (University of Liverpool, Liverpool, UK), Laura Waters (University College London, London, UK) and Freya Chapman (SSAT, Chelsea and Westminster Hospital, London, UK), for their advice on study design and being part of the protocol steering committee; Melynda Watkins and Paul Domanico from Clinton Health Access Initiative (CHAI) for their support on study design and completion; the research teams at St Stephen's Clinical Research for their hard work and the volunteers who took part in the study.

We are grateful to the NIHR BRC at Imperial College for its support of this study and to Bryony Simmons for reviewing the statistical analysis.

Some of the results of this study were presented at the Conference on Retroviruses and Opportunistic Infections (CROI), 3 - 7 March 2018, Boston, MA, USA.

Transparency declarations

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MC has received travel grant from Gilead

XW no conflicts

MN no conflicts

CW no conflicts

SF no conflicts

IDW no conflict

AO has received research funding from Merck, AstraZeneca, Pfizer, ViiV Healthcare and Janssen and consultancy for Merck and ViiV Healthcare. He is also co-inventor of patents relating to nanotechnology-based drug delivery systems

AH no conflicts

MMC no conflicts

MB has received travel and research grants from and has been advisor for Janssen, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva.

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Tables

Table 1: Subject baseline characteristics.

Characteristic	Evaluable subjects (n= 22)
Male, n (%)	14 (64)
Age, years (range)	47 (22-60)
Ethnicity	
White, n (%)	8 (36)
Black African, n (%)	10 (45)
Other, n (%)	4 (18)
CD4 T (cell/mm^3), median (range)	591 (223-1159)
CD4 T-cell (%), median (range)	34 (20-51)
VL < 20 (copies/mL), n (%)	22 (100)
BMI, median (range)	25 (20-35)
Completed the study (PK3 visit)	18 (82)
***CYP2B6* metaboliser status**	
Extensive, n (%)	10 (45)
Intermediate, n (%)	7 (32)
Slow, n (%)	4 (18)

n = number, VL = viral load, BMI = body mass index, *CYPB6* = cytochrome P450 2B6

Table 2: Plasma efavirenz (EFV) pharmacokinetic (PK) parameters following 14 days of administration of EFV 400 mg once daily (PK1), co-administration of EFV 400 mg and isoniazid/rifampicin for four weeks (PK2) and 12 weeks (PK3) in people living with HIV non co-infected with tuberculosis (TB).

	GM(95%CI)			GMR(90%CI)		
PKparameter	**PK1**	**PK2**	**PK3**	**PK2/PK1**	**PK3/PK2**	**PK3/PK1**
C_{max}ng/mL CV%	3257(2554-4154) 83	2953(2293-3804) 80	2791(2020-3857) 87	0.91(0.83-0.99)	0.95(0.86-1.05)	0.84(0.75-0.93)
C_{24h}ng/mL CV%	1703(1180-2457) 124	1441(948-2191) 128	1301(790-2141) 133	0.85(0.72-0.99)	0.88(0.75-1.03)	0.75(0.62-0.92)
$AUC_{0\text{-}24}$ng*h/mL CV%	52259(38284-71335) 107	47618(33979-66732) 106	44004(29442-65767) 113	0.91(0.79-1.05)	0.92(0.83-1.01)	0.84(0.72-0.99)

GM = geometric mean, CI = confidence intervals, C_{max} = maximum concentration, AUC = area under the curve, C_{24h}= 24 hour post-dose concentration, CV= coefficient of variation

Figures

Figure 1. Study enrolment and analysis population flow chart. All subjects enrolled in the study were considered for safety analysis. Subjects who completed co-administration of efavirenz 400 mg (EFV400) plus isoniazid/rifampin (INH/RIF) for at least 4 weeks (PK2) and 12 weeks (PK3) were considered for pharmacokinetics (PK) analysis. Subjects discontinued due to EFV levels < 800 ng/mL are classified as slow, intermediate and extensive depending of composite *CYP2B6* genotypes. TDM, therapeutic drug monitoring.

TB, tuberculosis

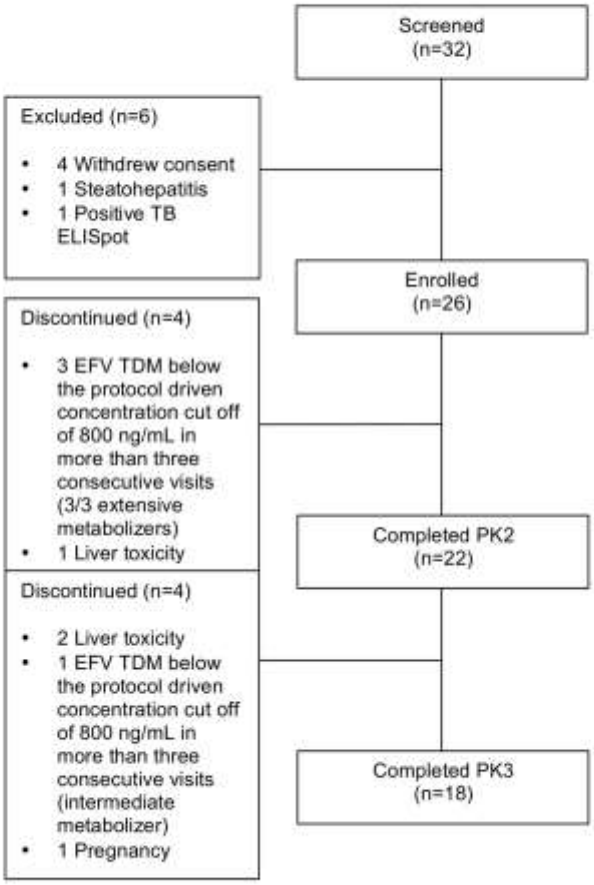
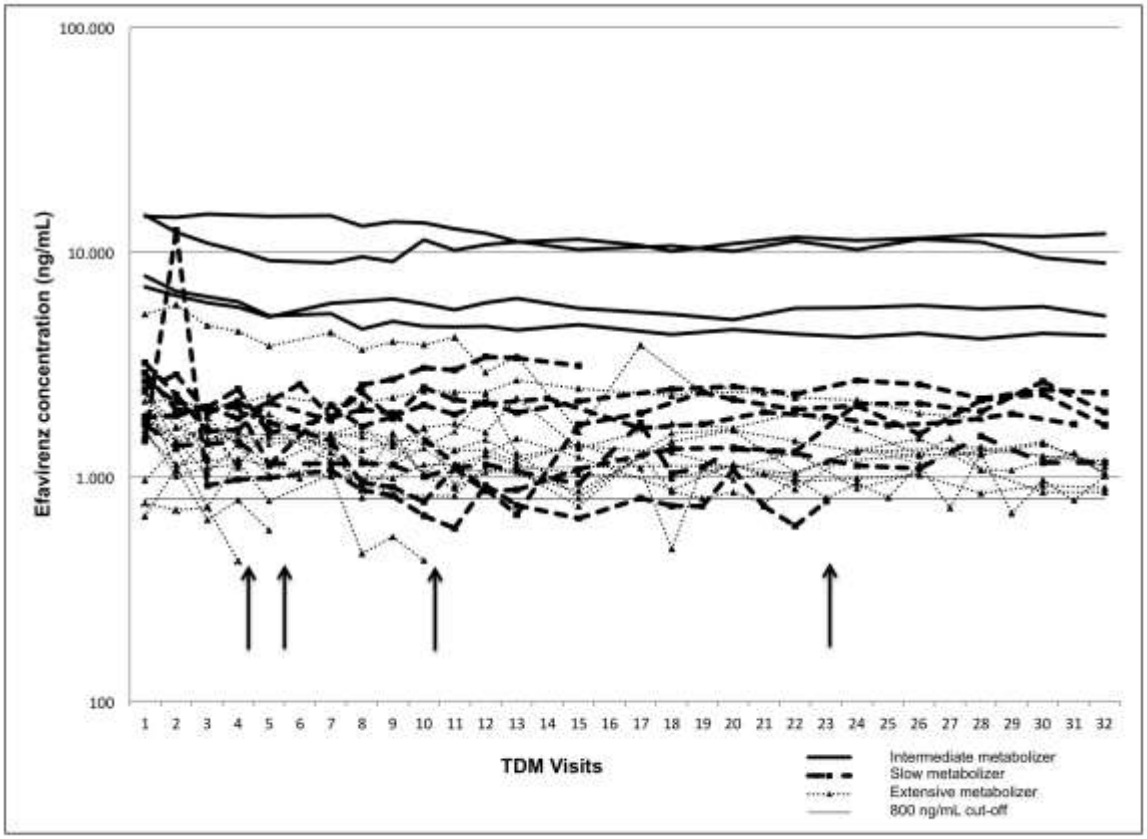
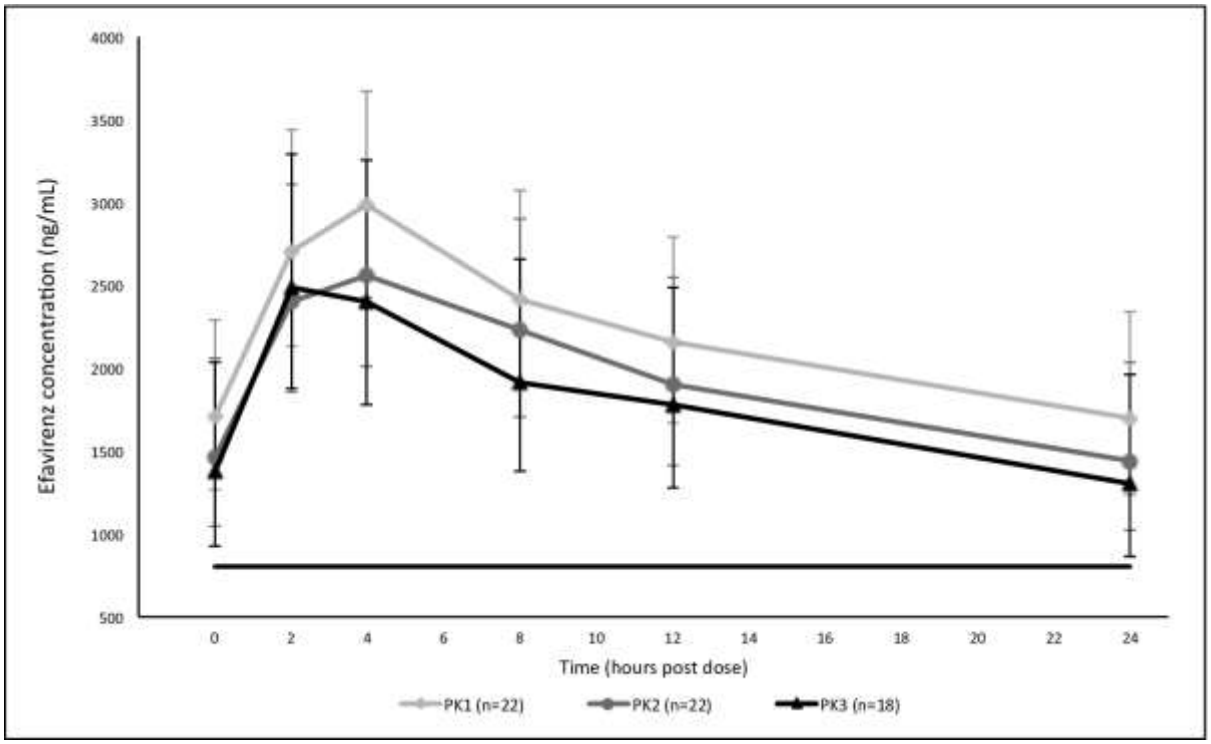

Screened
(n=32)
Excluded (n=6)
• 4 Withdrew consent
• 1 Steatohepatitis
• 1 Positive TB ELISpot
Enrolled
(n=26)
Discontinued (n=4)
• 3 EFV TDM below the protocol driven concentration cut off of 800 ng/mL in more than three consecutive visits (3/3 extensive metabolizers)
• 1 Liver toxicity
Completed PK2
(n=22)
Discontinued (n=4)
• 2 Liver toxicity
• 1 EFV TDM below the protocol driven concentration cut off of 800 ng/mL in more than three consecutive visits (intermediate metabolizer)
• 1 Pregnancy
Completed PK3
(n=18)

Figure 2: Efavirenz (EFV) therapeutic drug monitoring (TDM) results stratified by efavirenz (EFV) metabolizer status according to *CYP2B6* polymorphism (intermediate, slow and extensive). The black straight line indicates the EFV concentration cut off (800 ng/mL) established by the study protocol. Black arrows indicate four individuals who discontinued the study due to EFV levels < 800 ng/mL.



F**igure 3:** Geometric mean drug concentration-time curves of efavirenz (EFV) following the administration of EFV 400 mg once daily (PK1, light grey line), two weeks of co-administration with isoniazid (INH) and rifampicin (RIF) (PK2, dark grey line) and four weeks of co-administration with INH/RIF (PK3, black line). Error bars represent 90% confident intervals calculated for each time point. The dark black straight line indicates the 800 ng/mL EFV concentration cut off.


Efavirenz concentration (ng/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours post dose)
PK1 (n=22)
PK2 (n=22)
PK3 (n=18)