Pharmacokinetics of efavirenz in patients on antituberculosis treatment in high HIV and tuberculosis burden countries: a systematic review

Authors:

Daniel Atwine[1, 2, 4], Maryline Bonnet[1, 3, 4] and Anne-Marie Taburet[5,6]

Affiliations:

[1]Epicentre Mbarara Research Centre, Mbarara, Uganda

[2]Mbarara University of Science and Technology, Mbarara, Uganda

[3]IRD UMI233 TransVIHMI-INSERM U1175, Montpellier, France

[4]University of Montpellier, Montpellier, France

[5]Bicetre hospital, Paris, France

[6] UMR 1184, INSERM, CEA, Université Paris-Sud

Running head: Pharmacokinetics of efavirenz with anti-tuberculosis treatment

Address reprint requests to: Daniel Atwine, Epicentre Mbarara Research Centre, P.O Box 1956, Mbarara, Uganda. Tel: + 256793328410.

Email: daniel.atwine@epicentre.msf.org or daniel.atwine@must.ac.ug

ORCID ID: 0000-0002-3373-1999

Co-Authors contact details:

Maryline Bonnet : maryline.bonnet@epicentre.msf.org

Anne-Marie Taburet: amtaburet@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.13600

Abstract

Aims: Efavirenz (EFV) and Rifampicin-Isoniazid (RH) are cornerstone drugs in HIV-tuberculosis (TB) co-infection treatment but with complex drug interactions, efficacy and safety challenges. We reviewed recent data on EFV and RH interaction in TB/HIV high-burden countries.

Methods: We conducted a systematic review of studies conducted in the high TB/HIV-burden countries between 1990 and 2016 on EFV pharmacokinetics during RH co-administration in co-infected patients. Two reviewers conducted article screening and data collection.

Results: Of 119 records retrieved, 22 were included (2 conducted in children), reporting either EFV mid-dose or pre-dose concentrations. In 19 studies, median or mean concentrations on RH range between 1000-4000ng/mL, the so called therapeutic range. The proportion of patients with sub-therapeutic concentration on RH ranged between 3.1 to 72.2%, in 12 studies including 1 conducted in children. The proportion of patients with supra-therapeutic concentration ranged between 19.6 to 48.0% in 6 adult studies and 1 child study. Five of 8 studies reported virological suppression > 80%. The association between any grade hepatic and central nervous system adverse effects with EFV / RH interaction was demonstrated in 2 and 3 studies, respectively. The frequency of the *CYP2B6 516G>T* polymorphism ranged from 10 to 28% and was associated with higher plasma EFV concentrations, irrespective of ethnicity.

Conclusions:

Anti-tuberculosis drug co-administration minimally affect the EFV exposure, efficacy and safety among TB-HIV co-infected African and Asian patients. This supports the current 600 mg EFV dosing when co administered with antituberculosis drugs.

INTRODUCTION

HIV infection is still a global public health concern, especially in Africa and Asia (1). Sub-Saharan Africa remains most severely affected, accounting for nearly 70% of the people living with HIV worldwide (1). The estimated risk of developing tuberculosis (TB) in people living with HIV ranges between 26 and 31 times greater than in those without HIV infection (2). The highest TB incidence rates among HIV patients are reported in Africa and Asia. The overall TB mortality rate among HIV patients is about 6 times higher in Africa (30 per 100,000 population) than the global average (5.3 per 100,000 population), with approximately 75% of all deaths occurring in Sub-Saharan Africa (3).

The recommended first-line antiretroviral treatment for adults and adolescents consists of two nucleoside analogs, reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI)(4). Recommended WHO NRTI backbone was zidovudine + lamivudine (3TC) and recently tenofovir disoproxyl fumarate (TDF) + 3TC. TDF and 3TC are eliminated unchanged through the kidney, and are substrates of uptake and efflux transporters. Consequently, they are less likely to exhibit potent drug-drug interactions with anti-tuberculosis treatment than drugs whose elimination involves drug metabolizing enzymes such as cytochrome P-450 (CYP) (4). The recommended NNRTI is efavirenz (EFV) given its proven high virological efficacy, its availability as a fixed-dose combination (FDC) administered at 600mg dose once-daily, under generic formulation and preferably in the night so as to minimize central nervous system (CNS) adverse events, and to ensure good adherence. EFV is well incorporated within the low income and high HIV burden countries' national guidelines (5-7). There is reassuring data regarding its safety in pregnancy (8) and improved efficacy compared to the former widely used NNRTI, nevirapine (9). Although dolutegravir an HIV-integrase inhibitor has been found more tolerable compared to EFV, and with increasing availability in resource limited countries, limited experience of its use in HIV-TB co-infected patients will make EFV-based ART regimen the corner stone of HIV treatment in those patients for many years (4, 10).

EFV is mostly metabolized by CYP2B6 through hydroxylation to inactive metabolite 8-hydroxy EFV, and to a lesser extent by CYP2A6 into7-hydroxy EFV (11, 12), with CYP3A4/5 and CYP1A2 playing a minor role in this step (12, 13). The main metabolite, 8- hydroxy EFV is further hydroxylated primarily by CYP2B6 to form 8, 14-hydroxy EFV. The oxidative metabolites undergo conjugation by UDP-glucuronyltransferase (UGT2B7) pathway (14) and

are excreted in the urine as glucuronides (15). There are reports that CYP2A6 and UGT2B7 only play a significant role in the efavirenz pathway when CYP2B6 activity is impaired (16). EFV plasma concentrations below 1000 ng/mL in samples collected between 8-20h post intake, have been associated with increased risk of virological failure in HIV-infected patients, while concentrations above 4000 ng/mL have been associated with risk of CNS adverse effects (17, 18). There is a wide inter-individual variability in EFV concentrations (18) that is partially explained by genetic factors as shown by the strong association between *CYP2B6 516G>T* single nucleotide polymorphism (SNP) and EFV exposure (19). The *CYP2B6 516G>T* is a common polymorphism that has been consistently associated with reduced enzyme activity, higher EFV exposure and increased toxicity (11, 19, 20). On the other hand, there is no clear evidence supporting the association with gender and body weight (15, 21).

With regard to drug susceptible TB, a six-month regimen is broken down into an intensive two-month phase involving isoniazid (H, 5 mg/kg), rifampicin (R, 10 mg/kg), pyrazinamide (Z, 25 mg/kg) and ethambutol (E, 15 mg/kg) followed by four months of continuation phase with R and H (22). Both R and H are the cornerstone drugs within this regimen (23, 24) that has a very good efficacy (25). This regimen is used with FDC, and administered once daily (24).

Rifampicin has a strong bactericidal activity (25, 26) given its ability to inhibit transcription by binding with high affinity to bacterial DNA-dependent RNA polymerase (27-29) and the best sterilizing drug to prevent relapses of TB. R is also a potent inducer of several liver or gut drug metabolizing enzymes, especially isoenzymes of CYP, mainly isoenzyme CYP3A4 and CYP2B6. This results in enhanced NNRTI drug metabolism and may lead to sub-therapeutic NNRTI plasma concentration during co-administration (30). In healthy volunteers, EFV Area Under the Curve (AUC), maximum concentration (C_{max}) and minimum concentration (C_{min}) are reduced by 26, 20 and 32% when co-administered with R as compared to EFV alone, respectively, which led to the Food and Drug Authority (FDA) recommendation of an increase in EFV dosing to 800 mg once a day when combined with TB drugs (30, 31). However, due to the potential of increased risk of CNS toxicity with the increase of EFV dose and reassuring virological response in co-infected patients receiving EFV at 600mg once daily in high HIV burden countries, it is recommended to maintain EFV at usual dose (600mg/day once daily) (17, 32-36). The other cornerstone anti-TB drug, isoniazid, is metabolized mainly through N-acetyltransferase type 2 (NAT2) and was demonstrated *in vitro* to have an inhibitory effect on several cytochrome P450 enzymes (CYP2C19, CYP1A2, CYP2A6, CYP2C19, and CYP3A4)

(37), and especially through its effect on CYP2A6 metabolic pathway, could impact the relationship between RH and EFV, rendering the inducing effect of combined R and H (RH) less potent than R alone (38, 39). Such effect could be different according to patient's *CYP2B6 516 G>T* genetic polymorphism (40).

Although the goal of providing antiretroviral therapy (ART) has over time expanded from saving lives to include long-term virus control and to reduce transmission (41), but the effects of ART co-administration with other treatments that risk impairment of the ART blood concentrations may impend the attainment of this goal. A strong evidence base to support such public health approaches is needed to ensure good results from delivery of treatment at scale without compromising quality (41) but also safety and efficacy. Although attempts have been made in describing the pharmacokinetics (PK) and pharmacogenetics of EFV with RH co-administration (15, 42-44), an extensive focus on the world's highest HIV/TB burden countries that may be affected most by drug-drug interactions is lacking.

We conducted a systematic review to gather existing information on the pharmacokinetics of EFV during RH co-administration among TB and HIV high-burden countries. We assessed the effect of body weight, gender, EFV dosing and the CYP2B6 homozygous slow metabolizer genetic polymorphism, *CYP2B6 516 G>T*, on the EFV concentrations during RH co-administration, and the effect of the EFV PK results on the virological response, CNS and hepatic toxicity.

METHODS

Study eligibility criteria

A study was considered eligible for inclusion if it was a randomized controlled trial, cohort, case-control or cross-sectional study, that report PK parameters of EFV (minimum or mid-dose concentrations at least) following co-administration with RH in TB/HIV co-infected patients for at least 4 weeks (that is to ensure a minimum steady state) and conducted in one of the World Health Organization (WHO) TB/HIV high burden countries (45). Studies that enrolled patients with comorbidities that require co-administration of other drugs with known interaction with EFV, and studies enrolling patients on anti-TB prophylaxis, or using other rifamycins like rifapentine and rifabutin were excluded. Only studies published in English were included.

Search strategy

We conducted this review according to PRISMA guidelines (46). We identified relevant articles through a systematic search of Cochrane Library, EMBASE.COM and MEDLINE (via OvidSP) published from 1st January 1990 to 31st August 2016 in the English language. The choice of 1990 as start point was based on the consideration that in most of the TB/HIV high-burden countries, access to antiretroviral treatment took place after 1990, with EFV receiving FDA approval in 1998 (47). We also searched the Web-of-science and carried out manual searches (hand searching) to retrieve other reports of studies that are reported in journals, conference proceedings, bibliographies of review articles and retrieved articles, monographs, and sources other than those mentioned above. We used the following abbreviated search strategy: ("Efavirenz" or "Stocrin" or "Sustiva") and ("Rifampicin" or "RIFAFOUR" or "RIFAMPIN" or "RIFAMYCIN") and ("pharmacokinetics" or "drug assay" or "plasma drug concentration" or "Ctrough" or "pharmacology" or "drug interaction" or "drug-drug interaction" or "Efavirenz concentration" or "Rifampicin concentration" or "non-nucleoside reverse transcriptase inhibitors concentration").

Bibliography search and screening of titles and abstracts were done by one reviewer (DA), duplicate records were eliminated and full texts of potentially relevant articles retrieved. The selection was validated by a second reviewer (MB), blinded to the initial assessment. Full texts retained through this process were independently screened by two reviewers (DA and AMT). Disagreements were examined by the third reviewer (MB).

Records with inaccessible full text but with author contact details were retrieved after contacting authors by email. Abstract only records were excluded from further data collection processes.

Data collection and analysis

Data collected from each study were recorded by one reviewer (DA) in a standardized data extraction form (see Appendix 1) and validated by the second reviewer (AMT). Authors were contacted for clarification whenever needed. All discrepancies were discussed and resolved by consensus between the three reviewers (DA, AMT, and MB).

Data extraction forms were entered into a database using Epi Info™ software (V7.2, 1600 Clifton Road Atlanta, GA 30329-4027 USA) and analysis used the Stata software (v. 13, College Station, Texas, USA). We performed descriptive presentation of the studies' and patients' characteristics. EFV mid-dose concentrations measured 12h post dose (C_{12}) or pre-

dose concentration (C_{min}) measured before next dose intake were the PK parameters chosen as a surrogate of EFV exposure based on their availability in all selected articles. They were presented with or without RH co-administration globally, by gender, body weight, and EFV dose. Proportions of patients with sub-therapeutic (<1000 ng/mL) or supra-therapeutic EFV concentrations (>4000 ng/mL)(18) were presented graphically per study and geographical region. EFV concentrations in homozygous slow metabolizer patients carrying *CYP2B6 516TT* gene and extensive metabolizers carrying CYP2B6 516GG gene (48), were presented graphically by study. Results for heterozygous patients (CYP2B6 516GT) were not shown.

RESULTS

Of the total 119 records retrieved, 22 records were included in the analysis (Fig 1). Of these, 20 studies had data on at least mean or median EFV C_{12} (n=16) or pre-dose C_{min} (n=6) measured either in the morning (n=4) or evening (n=2) during RH co-administration (17, 35, 38, 49-65), while 1 study only reported body weight-specific EFV C_{12} data during RH co-administration (66) and one reported only proportions of patients with sub-therapeutic EFV concentrations (67).

General characteristics of studies

Table 1 shows characteristics of the 22 included studies. All were published between 2006 and 2016with 14 (64%) versus 7 (32%) conducted exclusively in Africa and Asia respectively. The majority of studies included adult patients (91%). The 2 children studies were conducted in South Africa. In adults, EFV was systematically administered at a dose of 600 mg/day of which one study also had EFV 800 mg/day dose administered to a selected comparative group of patients (35). EFV was administered at bed-time to improve the tolerability and reduce adverse events (68), except for 4 adult studies when it was taken in the morning (51, 53, 61, 69)and a 6-month anti-TB treatment was used and administered daily at recommended dosing in all studies except one with intermittent administration (53). Thirteen studies (59%) reported EFV concentrations on and off RH within the same patients. All studies had EFV concentrations during RH co-administration, with sampling done at steady state during intensive phase or continuation phase of TB treatment. Individual study-specific characteristics are shown in Appendix 2.

Effect of RH co-administration on the PK of EFV in HIV/TB co-infected patients

Overall, 19/20 studies reported the median or mean EFV C_{12} or C_{min} within the allegated therapeutic window (1000-4000 ng/mL) during RH co-administration irrespective of the geographical region (Table 2). One study in Thai patients (50) reported median or mean EFV C_{12} or C_{min} >4000 ng/mL although without specifying the proportion of patients with supratherapeutic concentrations. Of the 14 studies conducted among adult patients that reported EFV concentrations on and off RH, 10 were in Africa and 4 in Asia. Notably, among the 10 adult studies conducted in Africa, 6 reported higher EFV concentration during RH co-administration compared to the off RH period, although the difference is highly variable, ranging from 3.7% to 33.3% across studies and countries (35, 51, 60, 62, 65, 69). The remaining 4/10 adult African studies reported a lower EFV concentration while on RH, still with a difference that is highly variable, ranging from -16·3 to -33·3% (54-56, 64). Higher EFV concentrations during RH co-administration was also observed in 2 adult studies conducted in South-East Asia (50, 53), with the remaining 2 studies (57, 63) reporting reduced EFV concentrations.

Of the two studies among the South African children, the earlier study by Ren (52) indicated unchanged median C_{12} with RH co-administration (0.8%), while a recent study by McIlleron (38) indicated a decrease of 16.3%.

Sub-therapeutic EFV concentration and virological response

Fig 2 shows the 13 studies reporting the proportion of patients with sub-therapeutic EFV levels on or off RH. The proportion of patients with sub-therapeutic EFV concentration (<1000ng/ml) on RH range between 3·1 to 72·2% in 12 studies including 1 conducted in children.

Ten studies, had proportions for both on and off RH, with 9 reporting higher proportions of patients with EFV<1000ng/ml during RH co-administration than without RH, although the difference was highly variable, ranging between 1·1 to 21·1%. Only 2 studies, 1 in Thai patients (57) and 1 in South Africans (61) reported a lower proportion of patients with EFV<1000ng/ml during RH co-administration than without RH, with a difference <5%.

Two studies (one in adult and one in children) reported a very high proportion of patients (>50%) with sub-therapeutic concentrations either with or without RH (52, 67). These striking results could possibly be due to an adherence issue, genetic polymorphism or low EFV dosing in the children study.

Table 3 shows results of virological response with EFV and RH co-administration. Out of 10 studies (8 in adults, 2 in children) reporting both EFV exposure and virological suppression, 6 adult studies reported a proportion of patients with subtherapeutic EFV concentrations ranging from 3% to 32% although the virological suppression was ≥ 80% between 6 and 12 months follow-up. Of them, 4 studies had less than 20% of patients with sub-therapeutic concentrations. In contrast, both studies (all in adults) with virological suppression lower than 80% had more than 20% [range: 27-72%] of patients with sub-therapeutic levels (59, 67). Although both children studies reported a high virological suppression (~ ≥85%). In the study by Ren, 2009(52) there was an obvious miss-match between the reported proportion of children with subtherapeutic EFV Cmin (60%) and the reported high virological suppression (84·6%).

Supra-therapeutic EFV concentration and safety

Figure 3 shows all the 7 studies that reported a proportion of patients having supra-therapeutic EFV concentrations (>4000 ng/mL) on RH. Five studies had data on proportion of patients with EFV>4000 ng/ml during and without RH co-administration. All the 5 studies (59, 61, 63, 65, 69), all in adults reported higher proportions of patients with EFV>4000 ng/ml during RH as compared to off RH, although the difference was highly variable, ranging between 3·0 to 23·1%.

Table 4 shows the hepatic adverse events among HIV-TB co-infected patients. Of the 8 studies that assessed and reported data on hepatic events, the 4 African adult studies reported incidence of any grade alanine aminotransferase (ALT) rises ranging between 2.8-30% among TB-HIV co-infected patients (35, 51, 60, 61), although a relationship between ALT rise and EFV/RH co-administration was demonstrated in only one study (60). Among the 3 Asian studies (58, 63, 67), incidence of any grade ALT rises ranged between 0-16.7%, with a significant relationship with EFV/RH co-administration reported only in one study (63). The only children study conducted in South Africa reported all grade ALT rises in 2.5% of children (38).

Table 4 shows the CNS adverse events among HIV-TB co-infected patients. Nine studies that is, 6 African, 2 Asian, 1 international study assessed and reported data on incidence of any grade CNS symptoms. Among African studies, 2/6 showed a significant relationship between CNS adverse events and supratherapeutic EFV plasma concentrations (55, 62). Of the 2 Asian

studies 1 reported a significant relationship between developing incidence of CNS side-effects of any grade with having at least one-time supratherapeutic EFV concentrations (63).

EFV concentration by body weight, EFV dose, and Gender

Three studies reported plasma EFV concentrations stratified by body weight when given at a 600 mg dose with anti-TB drugs co-administration (59, 60, 66). Two studies reported lower EFV concentrations in patients with weight > 50kg than in patients with weight < 50kg, with median C_{12} (interquartile range, IQR) of 2060 ng/mL [IQR: 1425, 3575] vs 2859 ng/mL [IQR: 1787, 4749] in Cambodian patients (66) and mean C_{min} of 1860 ng/mL vs 2080 ng/mL in a study that included African, Latin American and Asian sites (59). On the other hand, in the study conducted in Ethiopia, the median (IQR) C_{12} was slightly higher in patients with weight > 50 kg compared to those with weight < 50kg: 1515 ng/mL [962, 3019] vs 1345 ng/mL [765, 3058] (60). However, in the same study, without co-administration, there was a trend towards lower concentrations in patients with higher body weight: 1233 ng/ml [848, 1670] vs 1410 ng/mL [1067, 2155] (60).

Only one study in South Africa included patients on high EFV dose (800 mg) (35). A higher median (IQR) C_{12} of EFV during RH co-administration was noted in the patients on 800mg EFV (2900 ng/mL, IQR: 1800, 5600) as compared to those on 600mg EFV (2400 ng/mL, IQR: 1200, 5100).

Only one study presented plasma EFV concentrations stratified by gender during co-administration with anti-TB drugs. The mean C_{min} was lower for males than for females (1870 ng/mL vs 2370 ng/mL) which could be related to differences in patients body weight (59).

The frequency of CYP2B6 slow and extensive metabolizers, and effect on EFV concentration during anti-TB treatment co-administration.

A total of 9 studies (6 from Africa and 3 from Asia) reported EFV concentrations according to the *CYP2B6 G516T* genetic polymorphism encoding for a defective enzyme, and 8/9 studies (5 from Africa and 3 from Asia) reported the frequency of CYP2B6 homozygous slow metabolizer genetic polymorphism within the studies' populations. Most of the studies reported only frequencies for the most frequent polymorphism *CYP2B6 516 G>T* (*CYP2B6*6* allele). In all studies, except for one conducted in Tanzania (54), patients who carried this loss of function allele had higher EFV concentrations both off and on RH as compared to those carrying the wild-type gene as shown in figure 4, panels A and B respectively. The frequency of slow metabolizers ranged between 10% in one study conducted in Rwanda (64) and 28% in

another study in Ethiopia (60), while the frequency of extensive metabolizers ranged from 34% to 50% across studies.

DISCUSSION

In this review, we note that, all selected studies, but one conducted in children (52), reported median or mean EFV C_{12} or C_{min} within the allegated therapeutic range [1000-4000 ng/mL] during RH-based standard TB drug co-administration, hence supporting the recommended 600mg EFV dosing in African or Asian HIV/TB co-infected patients. In addition, many of these studies also showed an increase in EFV concentrations during RH co-administration. Noteworthy, the two studies which enrolled more than 200 patients (63, 65) reported a very small difference (~4%) in median EFV C_{12} with versus without RH co-administration. Surprisingly, both studies reported some patients having higher EFV concentrations on vs off RH. This observation was demonstrated to be dependent on *CYP2B6* and *NAT2* genetic polymorphism. Indeed, patients who are CYP2B6 slow metabolizers, had higher concentrations of EFV (>4000 ng/ml). In those patients, R has little effect on minor drug metabolizing enzymes involved in EFV biotransformation, although H which is metabolized by the polymorphic NAT2 was demonstrated to inhibit these enzymes (40, 70) leading to higher EFV concentrations on RH versus off RH as shown in Fig 4, panel A. In contrast, extensive metabolizers have lower EFV concentrations with little or no effect of RH as shown in Fig 4, panel B. In summary, this drug-drug interaction is complex and owing to the difference in frequencies of genetic polymorphism of CYP2B6 and NAT2 enzymes, EFV concentrations may be higher or lower when co-administered with RH or administered alone (33, 71).

Studies conducted among adult patients in Tanzania and Thailand or in children in South-Africa highlight within country variability with regard to effect of RH on EFV concentrations (38, 50-52, 54, 56, 57), which could partially be explained by the small sample size, or differences in methodology used and the pharmacogenetics within different ethnic groups. As highlighted in the review by Colic et al., (72), the reported inter-population variability in EFV exposure among African and Asian countries could be due to the higher genetic diversity with regard to *CYP2B6* among individuals in different population groups or ancestral origins (73). The influence of age on CYP2B6 expression has not been well established although previous studies hypothesized that it may also depend on sex, as significant increase in liver CYP2B6 is

more linked to only males at higher age (74). The lower EFV concentrations among males reported in one study (59) are in agreement with what has been reported in another study in Zimbabwe without anti-TB drugs co-administration that showed a mean EFV C_{12} lower in males than in females (75) although this study was excluded in this review given a non-specified timing of PK sampling. This might also be dependent on the *CYP2B6* genetic polymorphism and age (74).

With the few studies available, it was not possible to satisfactorily assess the effect of body weight and EFV dose during co-administration with anti-TB drugs. Nevertheless, the effect of body weight if any is small and does not warrant dose optimization.

Similarly no strong conclusions could be made with regard to the EFV exposure during RH co-administration in children, given that only two studies are available (38, 52). The observed differences in the effect of RH on EFV in these two studies conducted in South Africa could not be explained by age of the children but could have been driven, first by the differences in sample sizes with one study performed among 15 children (52) and the other among 40 children (38). Second, the dose difference of EFV used in the two studies. Third, the frequency of genetic polymorphism, given the genotype frequencies in different ethnic African populations as previously reported (72, 76).

Although the proportion of patients with sub-therapeutic EFV levels was very high in some studies, there were no major differences with and without anti-TB treatment. The frequency of CYP2B6 extensive metabolizers, could be a plausible explanation for these subtherapeutic EFV concentrations, although lack of adherence can not be ruled out (48, 77).

As expected, there was a trend of lower virological response in studies with very high proportion of patients with sub-therapeutic concentrations. However, some discordances between the EFV concentrations and the virological response observed in some studies (52, 60, 69), illustrate the difficulty to correlate the drug plasma concentration measured at one point of time with the virological response. This is in agreement with the pharmacokinetic/pharmacodynamic results of the ENCORE1 study where patients were randomized to receive EFV once daily either at 400 mg or 600 mg. It was shown that despite reported C_{12} <1000 ng/mL in 5% and 2% for EFV400 and EFV600 respectively, 1 patient in the EFV400 group and 3 in the EFV600 group had detectable plasma viral load at 48weeks of therapy (78). In addition, it also highlights the limitation of the commonly used sub-therapeutic threshold of 1000 ng/mL for mid-dose EFV concentration, which is based on very low level of

evidence (18). Furthermore, the use of the same threshold for studies reporting C_{min} (trough concentration) concentrations could have led to an overestimation of the proportion of patients with sub-therapeutic concentrations (52).

The occurrence of supratherapeutic EFV levels was very common both in African and Asian studies. Higher EFV concentrations during co-administration with anti-TB treatment could increase the occurrence of adverse events (11, 19, 20). EFV CNS adverse effects have been reported to be more common in those patients with higher EFV concentrations (18, 48, 79). However, due to the very low number of studies reporting both safety and PK data during co-administration with anti-TB treatment, it is very difficult to draw strong conclusions based on this current review. In addition, the lack of information or standardisation in reporting safety information between studies, especially for CNS adverse events, makes the interpretation even more difficult. Nevertheless, we note that no clear correlation could be made between EFV supratherapeutic levels and occurrence of CNS adverse events during RH co-administration within the exclusively African studies (17, 55, 65). This lack of association might also be biased by the other common causes of neuropsychiatric disorders besides EFV treatment in HIV infected patients (80, 81). Some studies have however attempted to explain this disparity between plasma EFV concentrations and onset of CNS adverse events on grounds of the high lipophillic nature of EFV which allows it to penetrate the blood brain barrier easily and so give disproportionate EFV concentrations between plasma and brain (67). Interestingly it was recently suggested that among 563 patients who had been initiated on EFV-containing regimens at an HIV primary care clinic in the South-eastern United States, slow metabolizer genotypes were significantly associated with EFV discontinuation due to onset of CNS symptoms although this association was considerably stronger in Whites than in Blacks (82).

Regarding, hepatotoxicity, the reported overall incidence of ALT rises to any grade among TB-HIV co-infected patients was higher among the African adult studies [2.8-30%] as compared to Asian studies [0-16.7%]. Nevertheless, only one adult study indicated a significant relationship between any grade ALT rise with EFV and RH co-administration (63). In this review, it was not possible to distinguish the individual drug contribution of R, H or EFV on ALT rises of any grade given that the timing of onset was not well clarified in all studies. In one children study conducted in South Africa, all grade ALT rises were noted in 2.5% of children, with only 1 child suffering a grade 3 elevation in ALT in the month after completion of anti-TB treatment, which turned to normal without treatment adjustment (38).

This systematic review has some limitations, i) the great heterogeneity between studies with regard to study designs, PK parameters explored, and reporting, hindered any potential meta-analysis; ii) The small sample sizes for TB-HIV co-infected populations in many studies, may have contributed to the observed variability in EFV exposure due to RH co-administration even within same country; iii) Most studies did not attempt to correlate sub-therapeutic and supra-therapeutic concentrations of EFV during RH co-administration with CYP2B6 genetic polymorphisms, and so hindered a clear explanation of the observed changes; iv) The few studies which enrolled children could not allow a thorough evaluation and conclusions on EFV exposure with RH co-administration. This needs to be highlighted as children are a vulnerable population who need optimized dosing for improved efficacy; v) Analysis of safety information was limited by the very few number of studies correlating both safety, body weight and gender and PK data and by the variability in the assessment of CNS adverse events, with only one study using a standard scale (55).

CONCLUSION

This systematic review shows a minimal effect of RH co-administration on EFV plasma concentrations, when EFV is used at a 600 mg dosing. This supports the current recommendation for co-administration of ART regimen with EFV 600 mg daily and anti-TB treatment in TB-HIV high burden countries. The CYP2B6 genetic polymorphism is the more likely explanation for the variability of EFV concentrations in African and Asian patients on co-administration with anti-tuberculosis treatment. The interpretation and management of elevations in ALT and CNS adverse events should be done not only in the context of EFV and RH interaction but also looking at other independent predictors like advanced disease, liver diseases, adherence and patients' demographic characteristics. This systematic review is important as ritonavir/cobicistat boosted PI cannot be used with R, and yet sufficient data is not yet available on potential use of raltegravir or dolutegravir (83, 84). Initial pharmacokinetic data for co-administration of EFV at 400 mg dose with RH were recently reported showing no major reduction in EFV concentration suggesting that EFV 400mg plus RH could be safe. However, the full report of the results is yet to be published (85). Since new TB drugs allowing shorter TB treatment regimen will not be available soon, there is need to optimize the current first line drugs for susceptible TB. Increasing the rifampicin dose is an option (86) raising the issue of the drug-drug interaction with EFV. The ANRS 12292 Rifavirenz trial has recently shown a minimal effect of rifampicin at 20 mg/kg dosing on EFV exposure (87). Owing the

discrepancies between the two children studies, there is a need for better evidence to guide on the EFV dosing during anti-tuberculosis drug co-administration in this population.

DECLARATIONS

Funding source

This systematic review had no funding.

Conflict of Interest

Author AD, Author MB and Author AMT declare that they have no conflict of interest.

References

1. World Health Organization. Global Health Observatory (GHO) data: HIV/AIDS Global situation and Trends 2016 [cited 2017 13th July]. Available from: http://www.who.int/gho/hiv/en/.

2. World Health Organization. Tuberculosis and HIV 2014 [cited 2017 12th July]. Available from: http://www.who.int/hiv/topics/tb/about_tb/en/.

3. World Health Organization. Global Tuberculosis Report. Geneva2016 [cited 2017 21st June]. Available from: http://www.who.int/tb/publications/global_report/en/.

4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing hiv infection: recommendations for a public health approach Geneva2016 [cited 2017 29th July]. 2nd [Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf.

5. Nelson LJ., Beusenberg M., Habiyambere V., Shaffer N., Vitoria MA., Montero RG., et al. Adoption of national recommendations related to use of antiretroviral therapy before and shortly following the launch of the 2013 WHO consolidated guidelines. AIDS. 2014;28(Suppl 2):S217-24.

6. AIDSinfo. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2016 [updated 28th January 2016; cited 2016 01/02].

7. Gulick RM., Ribaudo HJ., Shikuma CM., Lustgarten S., Squires KE., Meyer WA., et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004;350:1850-61.

8. Anon. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2013.

9. Shubber Z., Calmy A., Andrieux-Meyer I., Vitoria M., Renaud-Thery F., Shaffer N., et al. Adverse events associated with nevirapine and efavirenzbased first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS. 2013;27.:1403-12.

10. Clinton Health Access Initiative (CHAI). ARV Market Report: The State of the Antiretroviral Drug Market in Low- and Middle-Income Countries, 2014-2019 2015 [cited 2017 29th July]. Available from: http://www.clintonhealthaccess.org/content/uploads/2015/11/CHAI-ARV-Market-Report-2015_FINAL.pdf.

11. Desta Z., Saussele T., Ward B., Blievernicht J., Li L., Klein K. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. Pharmacogenomics. 2007;8(6):547-58.

12. Ward B.A., Gorski J.C., Jones D.R., Hall S.D., Flockhart D.A., Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism : implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther 2003;306:287-300.

13. Whirl-Carrillo M., McDonagh E.M., Herbert J.M. Pharmcaogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92:414-7.

14. Bélanger A.S., Caron P., Harvey M. Glucuronidation of the antiretroviral drug efavirenz by UGT2B7 and an in vitro investigation of drug-drug interaction with zidovudine. Drug Metab Dispos. 2009;37:1793-6.

15. Kwara A., Ramachandran G., Swaminathan S. Dose adjustment of the non-nucleoside reverse transcriptase inhibitors during concurrent rifampicin-containing tuberculosis therapy: one size does not fit all. l 6(1):55-68. Expert Opin Drug Metab Toxico. 2010 6(1):55-68.

16. Di Iulio J., Fayet A., Arab-Alameddine M. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. Pharmacogenet Genomics. 2009;19:300-9.

17. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. J Antimicrob Chemother 2006;58(6):1299-302.

18. Marzolin C., Telenti A., Decosterd L.A., Greub G., Biollaz J., Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1 infected patients. AIDS. 2001;15:71-5.

19. Motsinger AA., Ritchie MD., Shafer RW., Robbins GK., Morse GD., Labbe L. Multilocus genetic interactions and response to efavirenz-containing regimens: an adult AIDS clinical trials group study. . Pharmacogenet Genomics. 2006;16(11):837-45.

20. Gounden V., van NC., Snyman T., George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. . AIDS Res Ther. 2010;7:32.

21. Chou M, Bertrand J., Borand L., Verstuyft C., Laureillard D., Blanc F. X. Pharmacokinetics of efavirenz in combination with rifampicin in HIV-infected adults: results of the PECAN (ANRS 121454) study. . 13th IntWorkshop on ClinPharmacology of HIV pharmacology 2012.

22. World Health Organization. Treatment of Tuberculosis guidelines 2016 [cited 2017 30th July]. 4th [Available from: http://apps.who.int/iris/bitstream/10665/44165/1/9789241547833_eng.pdf.

23. World Health Organisation. Treatment of Tuberculosis Guidelines. Geneva: 2010 Fourth Edition.

24. World Health Organization. Treatment of tuberculosis: Guidelines for treatment of drug-susceptible tuberculosis and patient care2017 29th July 2017. Available from: http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1.

25. Jindani A., Nunn A.J., Enarson D.A. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. The Lancet. 2004;364:1244-51.

26. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. Int J Tuberc Lung Dis. 2000;4:796-806.

27. Hartmann G., Honikel K. O., Knüsel F., Nüesch J. The specific inhibition of the DNA-directed RNA synthesis by rifamycin. BiochimBiophys Acta. 1967;145:843–4.

28. Jin D. J., Gross C. A. RpoB8, a rifampicin-resistant termination-proficient RNA polymerase, has an increased Km for purine nucleotides during transcription elongation. J Biol Chem. 1991;266:14478–85.

29. Campbell E. A., Korzheva N., Mustaev A., Murakami K., Nair S., Goldfarb A. Structural mechanism for rifampicin inhibition of bacterial rna polymerase. Cell. 2001;104:901–12.

30. Piscitelli SC., Gallicano KD. Interactions among drugs for HIV and opportunistic infections. . N Engl J Med 2001;344(13):984-96.

31. Sustiva (efavirenz) highlights of prescribinhg information. http://packageinserts bms com/pi/pi_sustiva pdf 12 A.D. March 4. Available from: http://packageinserts.bms.com/pi/pi_sustiva.pdf.

32. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 rev. . 2010.

33. Manosuthi W., Sungkanuparph S., Thakkinstian A., Rattanasiri S., Chaovavanich A., Prasithsirikul W. Plasma nevirapine levels and 24-week efficacy in HIV-infected patients receiving nevirapine-based highly active antiretroviral therapy with or without rifampicin. . Clin Infect Dis. 2006 43(2):253-5.

34. Manosuthi W., Kiertiburanakul S., Sungkanuparph S., Ruxrungtham K., Vibhagool A., Rattanasiri S. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. . AIDS. 2006;20(1):131-2.

35. Orrell C., Cohen K., Conradie F., Zeinecker J , Ive P , Sanne I , et al. Efavirenz and rifampicin in the South African context: is there a need to dose-increase efavirenz with concurrent rifampicin therapy? Antivir Ther 2011;16(4):527-34.

36. Brennan-Benson P., Lyus R., Harrison T., Pakianathan M., Macallan D. Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. . AIDS 2005;19(14):1541-3.

37. Wen X., Wang J.S., Neuvonen P.J., Backman J.T. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes. . Eur J Clin Pharmacol 2002;57(11):799-804.

38. McIlleron HM., Schomaker M., Ren Y., Sinxadi P., Nuttall JJ., Gous H., et al. Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. AIDS 2013;27(12):1933-40.

39. Gengiah T.N., Holford N.H., Botha J.H., Gray AL., Naidoo K., bdool Karim S.S. The influence of tuberculosis treatment on efavirenz clearance in patients co-infected with HIV and tuberculosis. Eur J Clin Pharmacol 2012;68(5):689-95.

40. Bertrand J., verstuyft C., Chou M., Borand L., Chea P., Nay KH., et al. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6

and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. The Journal of infectious diseases. 2013;209(3):399-408.

41. Ford N., Ball A., Baggaley R., Vitoria M., Low-Beer D, Penazzato M., et al. The WHO public health approach to HIV treatment and care: looking back and looking ahead (In Press). Lancet Infect Dis. 2017.

42. DiGiacinto J.L., Chan-Tack K.M., S.M R, Reynolds K.S., Struble K. A. Are Literature References Sufficient for Dose Recommendations? An FDA Case Study of Efavirenz and Rifampin. Journal of Clinical Pharmacology. 2008;48:518-23.

43. Zanger U.M., Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6) : advances on polymorphisms ,mechanisms, and clinical relevance. Frontiers in Genetics. 2013;4(24):1-12.

44. Lang T., Klein K., Fischer J. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. . Pharmacogenetics 2001;11:399-415.

45. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. Geneva2015 [cited 2017 15th August]. Available from: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1.

46. Moher D., Shamseer L., Clarke M., Ghersi D., Liberati A., Petticrew M., et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4:1.

47. Tseng A., Seet J., Phillips E.J. The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future. British Journal of Clinical Pharmacology. 2014;79(2):182-94.

48. Mollan K.R., Tierney C., Hellwege J.N., Eron J.J., Hudgens M.G., Gulick R.M., et al. Race/Ethnicity and the Pharmacogenetics of Reported Suicidality With Efavirenz Among Clinical Trials Participants. The Journal of Infectious Diseases. 2017 216

49. Yimer G , Ueda N , Habtewold A , Amogne W , Suda A , Riedel K-D , et al. Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. PLoS One. 2011;6(12):e27810.

50. Uttayamakul S, Likanonsakul S, Manosuthi W, Wichukchinda N, Kalambaheti T, Nakayama EE, et al. Effects of CYP2B6 G516T polymorphisms on plasma efavirenz and nevirapine levels when co-administered with rifampicin in HIV/TB co-infected Thai adults. AIDS Res Ther 2010;7:8.

51. Semvua HH., Mtabho CM, Fillekes Q., van den Boogaard J., Kisonga RM., Mleoh L., et al. Efavirenz, tenofovir and emtricitabine combined with first-line tuberculosis treatment in tuberculosis-HIV-coinfected Tanzanian patients: a pharmacokinetic and safety study. Antivir Ther 2013;18(1):105-13.

52. Ren Y., Nuttall J.J., Eley B.S., Meyers T.M., Smith P.J., Maartens G., et al. Effect of rifampicin on efavirenz pharmacokinetics in HIV-infected children with tuberculosis. J Acquir Immune Defic Syndr 2009;50(5):439-43.

53. Ramachandran G, Hemanth Kumar AK, Ponnuraja C, Ramesh K, Rajesh L, Chandrasekharan C, et al. Lack of association between plasma levels of non-nucleoside reverse transcriptase inhibitors & virological outcomes during rifampicin co-administration in HIV-infected TB patients. . Indian J Med Res 2013;138(6):955-61.

54. Ngaimisi E., Mugusi S., Minzi O., Sasi P., Riedel K.D., Suda A., et al. Effect of rifampicin and CYP2B6 genotype on long-term efavirenz autoinduction and plasma exposure in HIV patients with or without tuberculosis. Clin Pharmacol Ther 2011;90(3):406-13.

55. Mukonzo JK., Okwera A., Nakasujja N., Luzze H., Sebuwufu D., Ogwal-Okeng J., et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study. BMC Infect Dis 2013;13:261.

56. Mukonzo JK., Nanzigu S., Waako P., Ogwal-Okeng J., Gustafson LL., Aklillu E. CYP2B6 genotype, but not rifampicin-based anti-TB cotreatments, explains variability in long-term efavirenz plasma exposure. Pharmacogenomics 2014;15(11):1423-35.

57. Manosuthi W., Sukasem C., Lueangniyomkul A., Mankatitham W., Thongyen S, Nilkamhang S., et al. Impact of pharmacogenetic markers of CYP2B6, clinical factors, and drug-drug interaction on efavirenz concentrations in HIV/tuberculosis-coinfected patients. Antimicrob Agents Chemother. 2013;57(2):1019-24.

58. Manosuthi W, Sungkanuparph S, Tantanathip P, Lueangniyomkul A, Mankatitham W, Prasithsirskul W, et al. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study. Clin Infect Dis 2009;48(12):1752-9.

59. Luetkemeyer A.F., Rosenkranz S.L., Lu D., Marzan F., Ive P., Hogg E., et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clin Infect Dis 2013;57(4):586-93.

60. Habtewold A., Makonnen E., Amogne W., Yimer G., Aderaye G., Bertilsson L., et al. 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. Pharmacogenomics 2015;16(10):1047-64.

61. Gengiah TN., Botha JH., Yende-Zuma N., Naidoo K., SS. AK. Efavirenz dosing: influence of drug metabolizing enzyme polymorphisms and concurrent tuberculosis treatment. Antivir Ther 2015;20(3):297-306.

62. Cohen K., Grant A., Dandara C., McIlleron H., Pemba L., Fielding K., et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. Antivir Ther 2009;14(5):687-95.

63. Borand L., Madec Y., Laureillard D., Chou M., Marcy O., Pheng P., et al. Plasma concentrations, efficacy and safety of efavirenz in HIV-infected adults treated for tuberculosis in Cambodia (ANRS 1295-CIPRA KH001 CAMELIA trial). PLoS One 2014;9(3):e90350. .

64. Bienvenu E., Swart M., Dandara C., Ashton M. The role of genetic polymorphisms in cytochrome P450 and effects of tuberculosis co-treatment on the predictive value of CYP2B6 SNPs and on efavirenz plasma levels in adult HIV patients. Antiviral Res 2014;102:44-53.

65. Bhatt NB, Baudin E, Meggi B, Silva C, Barrail-Tran A, Furlan V, et al. Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship. J Antimicrob Chemother. 2015;70:225-32.

66. Borand L, Laureillard D, Madec Y, Chou M, Pheng P, Marcy O, et al. Plasma concentrations of efavirenz with a 600 mg standard dose in Cambodian HIV-infected adults treated for tuberculosis with a body weight above 50 kg. Antiviral Therapy. 2013;18(3):419-23.

67. Mariana N., Purwantyastuti., Instiaty., A. R. Efavirenz Plasma Concentrations and HIV Viral Load in HIV/AIDS-tuberculosis Infection Patients Treated with Rifampicin. Acta Med Indones. 2016;48(1):10-6.

68. Sustiva. US Prescrition 2004. Princeton, NJ: Bristol-Myer Squibb; 1998. 2004.

69. Friedland G., Khoo S., Jack C., Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. Journal of Antimicrobial Chemotherapy. 2006 58 (6):1299-302

70. Luetkemeyer AF., Rosenkranz SL., Lu D., Grinsztejn B., Sanchez J., Ssemmanda M., et al. Combined effect of CYP2B6 and NAT2 genotype on plasma efavirenz exposure during rifampin-based antituberculosis therapy in the STRIDE study. . Clin Infect Dis. 2015;60(12):1860-3.

71. Helen M., Graeme M., William B.J. Complications of antiretroviral therapy in patients with tuberculosis: Drug interactions, toxicity, and immune reconstitution inflammatory syndrome. Journal of infectious diseases. 2007;196(Supplement: 1):S63-S75.

72. Colic A., Alessandrini M., Pepper M.S. Pharmacogenetics of CYP2B6, CYP2A6 and UGT2B7 in HIV treatment in African populations: focus on efavirenz and nevirapine. Drug Metab Rev. 2015;47(2):111-23.

73. Li J., Menard V., Benish R.L. Worldwide variation in himan drug-metabolism enzyme genes CYP2B6 and UGT2B7: Implications for HIV/AIDS treatment. Pharmacogenomics. 2012;13:555-70.

74. Yang X., Zhang B., Molony C., Chudin E., Hao K., Zhu J. Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver. . Genome Res 2010;20:1020-36.

75. Dhoro M., Zvada S., Ngara B., Nhachi C., Kadzirange G., Chonzi P., et al. CYP2B6*6, CYP2B6*18, Body weight and sex are predictors of efavirenz pharmacokinetics and treatment response: population pharmacokinetic modeling in an HIV/AIDS and TB cohort in Zimbabwe. . BMC Pharmacol Toxicol. 2015;16:4.

76. Swart M., Skelton M., Wonkam A. CYP1A2< CYP2A6, CYP2B6, CYP3A4 and CYP3A5 Polymorphisms in two Bontu-Speaking Populations from Cameroon and South Africa: Implications for Global Pharmacogenetics. Curr Pharmacogen Pers Med. 2012;10(43-53).
77. Lee K.Y., Lin S.W., Sun H.Y., Kuo C.H., Tsai M.S. Therapeutic Drug Monitoring and Pharmacogenetic Study of HIV-Infected Ethnic Chinese Receiving Efavirenz-Containing Antiretroviral Therapy with or without Rifampicin-Based Anti-Tuberculous Therapy. . PLoS ONE 2014;9(2):e88497.
78. Dickinson L., Amin J., Else L., Boffito M., Egan D., Owen A., et al. Pharmacokinetic and Pharmacodynamic Comparison of Once-Daily Efavirenz (400 mg vs. 600 mg) in treatment-Naıve HIV-Infected Patients: Results of the ENCORE1 Study. Clinical Pharmacology & Therapeutics. 2015;98(4):406-16.
79. Haas D.W., Ribaudo H.J., Kim R.B., Tierney C., Wilkinson G.R., Gulick R.M. Pharmacogenetics of efavirenz and central nervous system side effects : an Adult AIDS Clinical Trials Group study. AIDS. 2004;18:2391-400.
80. Dube B., Benton T., Cruess D.G., Evans D.L. Neuropsychiatric manifestations of HIV Infection and AIDS. J Psychiatry Neurosci. 2005;30(4):237-46.
81. Ciesla J. A., Roberts J. E. Meta-Analysis of the Relationship Between HIV Infection and Risk for Depressive Disorders The American Journal of Psychiatry. 2001;158(5):725-30.
82. Leger P., Chirwa S., Turner M., Richardson DM., Baker P., Leonard M., et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. . Pharmacogenet Genomics. 2016;26(10):473-80.
83. Dooley KE., Denti P., Martinson N., Cohn S., Mashabela F., Hoffmann J. Phamacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. . J Infect Dis. 2015;211(2):197-205.
84. Dooley KE., Sayre P., Borland J. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62:21 – 7.
85. Cerrone M., Wang X., Neary M., Weaver C., Fedele S., Day-Weber I., et al., editors. Pharmacokinetics of efavirenz 400mg with isoniazid/rifampicin in people with HIV. Conference on Retroviruses and Opportunistic Infections (CROI)[Abstract Number 457]; 2018 March 4–7, 2018; Boston, Massachusetts.
86. Jindani A., Borgulya G., Westermann de Patino., Gonzales T., de Fernandes R.A., Shrestha B., et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. The International Journal of Tuberc Lung Dis. 2016;20(6):832-8(7).
87. Atwine D., Baudin E., Gelé T., Muyindike W., Kenneth M., Kyohairwe R., et al., editors. Efavirenz pharmacokinetics with high-dose rifampin in TB-HIV infected patients. Conference on retroviruses and opportunistic infections (CROI) [Abstract number 456]; 2018 March 4–7, 2018; Boston, Massachusetts

Table 1. Characteristics of the selected studies and of the HIV-TB co-infected patients included

Characteristic	Number of studies	
Study types, n (%)	22	
Prospective non-randomized comparative study		6 (27.3)
Cohort from randomized clinical trial		8 (36.4)
Prospective cohort		6 (27.3)
Case-Control		1 (4.6)
Cross-sectional		1 (4.6)
Geographical setting of studies, n (%)	22	
Africa		14 (63.6)
Asia		7 (31.8)
Africa/Latin America		1 (4.6)
Study population, n (%)	22	
Adult		20 (90.9)
Children		2 (9.1)
Age in years, median [range]		
Adult studies	17	35 [31.0-40.5]
Children studies	2	7.4 [6.3-8.5]
Gender, male		
Adults, n (%)	20	
<50%		5 (25.0)
50-70%		11 (55.0)
>70%		4 (20.0)
Children, n (%)		
<50%	2	1 (50·0)
50-70%		1 (50·0)
Body weight in kilograms		
Adult studies, median [range]	15	53.3 [50.0-57.4]
Children studies, median [range]	2	20.7 [18-23.4]
Sample size for selected studies, median [IQR]	22	131 [45-270]
Adult studies, n (%)	20	
<30		3 (15.0)
30-100		5 (25.0)
>100		12 (60.0)
Children, n (%)	2	
<30		1 (50.0)
30-100		1 (50.0)
Patient groups, n (%)	22	
HIV-TB co-infected and HIV-mono infected (2 parallel groups)		7 (31.8)
HIV-TB co-infected on and off anti-TB drugs		13 (59.1)
HIV-TB co-infected on anti-TB drugs (no off anti-TB drugs period)		2 (9.1)
Anti-TB treatment administration frequency for 6 months, n (%)	22	
Daily		21 (95.5)
Thrice weekly		1 (4.5)
EFV intake, n (%)	22	
Evening		20 (90.9)
Morning		2 (9.1)
EFV Pharmacokinetic parameter reported*, n (%)	22	
C12 (mid-dose concentration)		16 (72.7)
Cmin (Ctrough, pre-dose concentration)		6 (27.3)
CNS toxicity assessed, n (%)	22	8 (36.4)
Hepatotoxicity assessed, n (%)	22	7 (31.8)
Virological response assessed following standard anti-TB drugs co-administration, n (%)	22	12 (54.5)

HIV: Human Immuno-virus; TB: Tuberculosis; EFV: Efavirenz; C12: Mid-dose concentration; Cmin: Ctrough, pre-dose concentration; CNS: Central Nervous System; IQR: inter-quartile range

Table 2. Concentrations of EFV co administered with RH and without RH or after the discontinuation of TB treatment, measured at steady state (≥ 4 weeks) in 20 selected studies. Concentrations (ng/mL) are reported as mean (SD), median (p25, p75) or median [range]

Region/study description	Author/Country	Ref.no	Comparison group	On RH			Off RH			% Difference in EFV concentration between on and off-RH‡
				n	Cmin	C12	n	Cmin	C12	
AFRICA										
5 Adult studies, with on/off RH data in same patient	Semvua, 2013; (Tanzania)	[46]	S	21	2600 (1600, 4200)		21	2400 (1600, 3500)		8.3%
	Bhatt, 2015 ; (Mozambique)	(65)	S	235		2700 (1701, 6965)	199		2604 (1742, 4412)	3.7%
	Bienvenu, 2014;(Rwanda)	(64)	S	21		1800 (1400, 2300)	21		2700 (1500, 3100)	-33.3%
	Friedland, 2006; (South Africa) †	(69)	S	19	1730 [350, 27180]		19	1380 [570, 3980]		25.4%
	Orrell, 2011;(South Africa)	(35)	S	34		2400 (1200, 5100)	34		2200 (1400, 3700)	9.1%
5 Adult studies, with on-RH data in TB-HIV co-infected group and off-RH data in HIV only patient group	Ngaimisi, 2011 ; (Tanzania)	(54)	P	54		1148 (895, 2270)	128		1614 (1140, 2692)	-28.9%
	Habtewold, 2015; (Ethiopia)	(60)	P	60		1515 (856, 3039)	187		1290 (934, 1869)	17.4%
	Cohen, 2009; (South Africa)	(62)	P	40		2400 (1300, 3100)	102		1800 (1400, 4400)	33.3%
	Mukonzo, 2014; (Uganda)	(56)	P	130		1916 (1467, 3098)	78		2312 (1638, 3063)	-17.1%
	Mukonzo, 2013; (Uganda)	(55)	P	118		1820 (1420, 3210)	50		2410 (1640, 3060)	-24.5%
2 Children studies with on/off RH data in same patient	Ren, 2009; (South Africa)	(52)	S	15	830 (590, 6570)	1240 (910, 7380)	15	860 (610, 3560)	1230 (850, 4180)	0.8%
	McIlleron, 2013 ; (South Africa)	(38)	S	32		1640 (1210, 4400)	32		1960 (1320, 2930)	-16.3
2 African studies in adults, without off RH data	Yimer, 2011 ; (Ethiopia)	(49)	S	67		1318 (977, 1995)				
	Gengiah, 2015 ; (South Africa)	(61)	S	29	3100 (2600, 4800)					
ASIA										
	Ramachandran, 2013[c] ; (India)	(53)	S	51	2300 (2500)		49	2100 (1900)		9.5%

3 Adult studies, with on/off-RH data in same patient	Uttayamakul, 2010 ; (Thailand)	(50)	S	65		4420 (5970)	65		3500 (2670)	26.3%
	Borand, 2014; (Cambodia)	(63)	S	401		2667 (1753,4494)	401		2766 (1941, 3976)	-3.6%
1 Adult study, with on-RH data in TB-HIV co-infected group and off-RH data in HIV only patient group	Manosuthi, 2013; (Thailand)	(57)	P	101		2100 (1300, 3500)	38		2700 (1800, 5400)	-22.2%
1 adult study without off-RH data	Manosuthi, 2009 ; (Thailand)	(58)	None	71		3540 (3780)				
AFRICAN/ LATIN AMERICA:										
1 study without off-RH data	Luetkemeyer, 2013; (International)	(59)	S	505	1960 (1240, 3790)					

† Geometric mean (90% confidence intervals) or geometric mean [range]); SD: standard deviation; IQR: interquartile range; EFV: Efavirenz; RH: rifampicin and Isoniazid; C12: mid-dose concentration; Cmin: Ctrough, pre-dose concentration; Ref.no: reference number corresponding to the cited study.
S= PK comparisons done in same patients; P= PK comparisons done in different patients;

‡ This was calculated as the difference in mean or median C12 or Cmin during on RH and off RH, as a fraction of the mean or median C12 or Cmin during on RH, and expressed as a percentage. This estimates the change in EFV plasma concentration attributable to RH co-administration.

Table 3. Presentation of virological response with EFV concentrations during RH co-administration

Studies	Reference number	VL threshold (copies/mL)	Follow-up (months)	% patients with Sub-therapeutic levels*	% patients with VL suppression
Adult studies, N=8					
Mariana, 2016 (Indonesia)	(67)	<40	3 to 6	72.2	27.8
Manosuthi, 2009 (Thailand)	(58)	<50	12	3.1	83.9
Habtewold Abiy, 2015 (Ethiopia)	(60)	<50	12	38.6	84.1
Bhatt, 2015 (Mozambique)	(65)	<50	6	8.9	85.5
Friedland, 2006. (South Africa)	(69)	<100	6	31.6	80
Borand, 2014 (Cambodia)	(63)	<250	6	5.3	91
Luetkemeyer, 2013 (Botswana, Brazil, Haiti, Kenya, Malawi, South Africa, Thailand, Uganda, Zimbabwe, Peru, USA)	(59)	<400	12	27.3*	71.4
Orrell, 2011 (South Africa)	(35)	<50	12	12	92
Children studies, N= 2					
Ren , 2009 (South Africa)	(52)	<50	6	60*	84.6
McIlleron, 2013 (South Africa)	(38)	<400	6	17.4	87.0

All results based on C12 unless otherwise indicated (*) in case of Cmin based results; VL: viral load;

RH: Rifampicin and Isoniazid

Table 4. Hepatic and Central nervous system adverse events among HIV-TB co-infected patients

Study	Ref no	Number of HIV-TB coinfected patients included in the analysis, N	% of patients with all grade ALT increase	% of patients with all grade CNS events	Relationship between ALT rise with EFV/R co-administration	Relationship between CNS events with EFV/R co-administration
Mariana, 2016; (Indonesia): P	(67)	18	16.7	55.6	No relationship despite the higher incidence of all-grade ALT rise among HIV-TB patients (16.7%) versus HIV alone (3.7%). No patient developed supratherapeutic EFV concentrations.	**No relationship noted**. Since no patient had supratherapeutic EFV plasma concentrations, Authors attributed the high onset of CNS events to EFV's high lipophillic nature allowing it to easily penetrate the blood brain barrier.
Habtewold, 2015; (Ethiopia): P	(60)	208	30.0	No data	Relationship with EFV/R co-administration noted. Incidence of grade ≥3 ALT rise higher in HIV-TB patients on EFV/R co-administration (30%) than in HIV patients on EFV alone (15.7%). The role of high EFV plasma concentration and CYP2B6*6 genotype noted in both patient groups. NAT2 slow-acetylator genotype, as determined by sequencing of NAT-2 coding region predicted liver toxicity in TB-HIV co-infected on isoniazid. Overlapping drug toxicity (ART and anti-TB drugs) and disease effect (TB-HIV coinfection) could not be ruled-out.	**Not applicable**
Borand, 2014; (Cambodia): S	(63)	540	8.7	0.9	No relationship noted with grade ≥3 transaminase elevation (p=0.30), instead a significant relationship was noted between the risk of any grade hepatotoxicity with having consistent supratherapeutic EFV concentrations (p<0.001, OR =1.52 [1.33-1.74] but not with intermittent EFV levels >4 000 ng/mL, as compared with those in normal ranges.	No relationship noted with CNS events grade ≥3, p=0.30, but a significant relationship was noted between developing a CNS side-effect irrespective of grade with having at least one time supratherapeutic EFV levels as compared to those with normal ranges, p<0.001, OR= 2.72 [2.05-3.62]
Mukonzo, 2013; (Uganda): P	(55)	138	No data	74.0	**Not applicable**	Relationship with EFV/R co-administration noted. All grade CNS symptoms during ART were significantly predicted by EFV plasma concentrations consistently. No significant differences in incidence of CNS symptoms between patients on EFV with R (74%) and those without R (72%) cotreatment (p=0.73) was noted. No treatment discontinuation occurred due to severe CNS events.
Luetkemeyer, 2013; (International): S	(59)	780	No data	5.9		No relationship with EFV/R co-administration noted. EFV Cmin >4 000ng/ml was not significantly associated with occurrence of grade 3 or higher CNS events.
Friedland, 2006; (South Africa): S	(69)	19	No data	36.8		No clear association was observed between onset of all grade CNS symptoms and plasma EFV levels.

McIlleron, 2013; (South Africa): S	(38)	40	2.5	0	No relationship with EFV/R co-administration noted. Only 1 child suffered a grade 3 elevation in ALT in the month after completion of anti-TB treatment, which turned to normal without treatment adjustment. This child had an average mid-dose interval concentration of 17.7 mg/l during anti-TB treatment, which dropped to 4.14 mg/l a month after stopping R and isoniazid. There was a low incidence of liver toxicity with use of R 10 mg/kg.	No relationship with EFV/R co-administration noted. Though assessed, no grade 3 or 4 CNS events recorded. Subtle effects were not recorded in the study. Lack of CNS events was linked to good tolerability given the night administration of EFV..
Bhatt, 2015 ; (Mozambique): S	(65)	302	No data	2.0	Not applicable	No relationship with EFV/R co-administration noted. No significant association between occurrence of grade 2 or higher CNS adverse events reported within the first 12 weeks of ART and EFV concentrations >4000 ng/ml at week 12 , p=0.293
Orrell, 2011; (South Africa): S	(35)	72	2.8	No data	No relationship with EFV/R co-administration noted. Both grade 2 and 3 events of raise in ALT occurred during EFV co-administration. The absence of ALT elevation events before ART initiation signified that these events were EFV-related. No direct link made to EFV interaction.	Not applicable
Cohen, 2009; (South Africa): P	(62)	137	No data	35.8	Not applicable	A relationship with EFV/R co-administration noted. About 31% of those with CNS symptoms (all grade) had high EFZ concentrations. No significant associations between EFV concentrations and other neuropsychiatric symptoms.
Semvua, 2013; (Tanzania): S	(51)	25	4.0	No data	No relationship with EFV/R co-administration noted. Only ALT rises of grade 1 noted, with no link with EFV interaction established.	Not applicable
Gengiah, 2015; (South Africa): S	(61)	20	9.0	5.0	No relationship with EFV/R co-administration noted. Approximately 67% of all events of transaminase rise (grade 3 or 4) occurred during ATT alone, and only 26.7% during ATT/ART. No link to interaction and events during ART resolved without drug cessation.	No relationship with EFV/R co-administration noted. All the reported 3 CNS toxicity events (all grade), were from 1 patient on EFV 800mg and had a Cmin=2100ng/ml at the time of onset of CNS events. Symptoms ceased with a switch from morning to night administration of EFV.
Manosuthi, 2009; (Thailand): S	(58)	71	0	No data	No relationship with EFV/R co-administration noted. No NNRTI-associated hepatitis with EFV co-administered with R.	Not applicable

S: same patient comparisons (only HIV-TB co-infected). P: Parallel patients' comparisons (both HIV only and HIV-TB co-infected)
ALT: Alkaline aminotransferase, CNS: Central nervous system, EFV: Efavirenz, R: Rifampicin, TB: tuberculosis,
ART: Antiretroviral therapy, Cmin: minimum EFV concentration Ref no: reference number

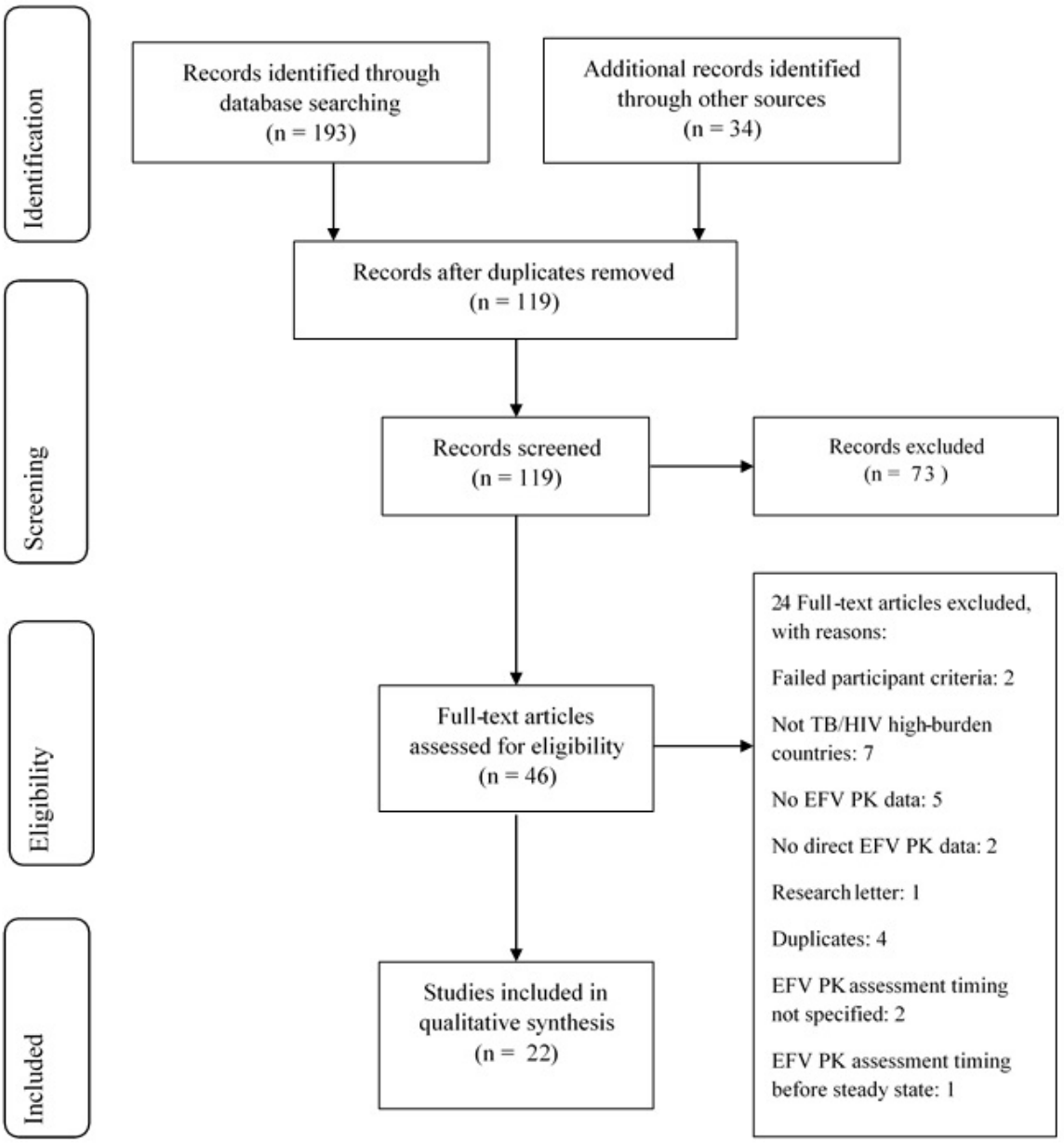

Fig 1. Flow chart showing the selection of relevant papers.

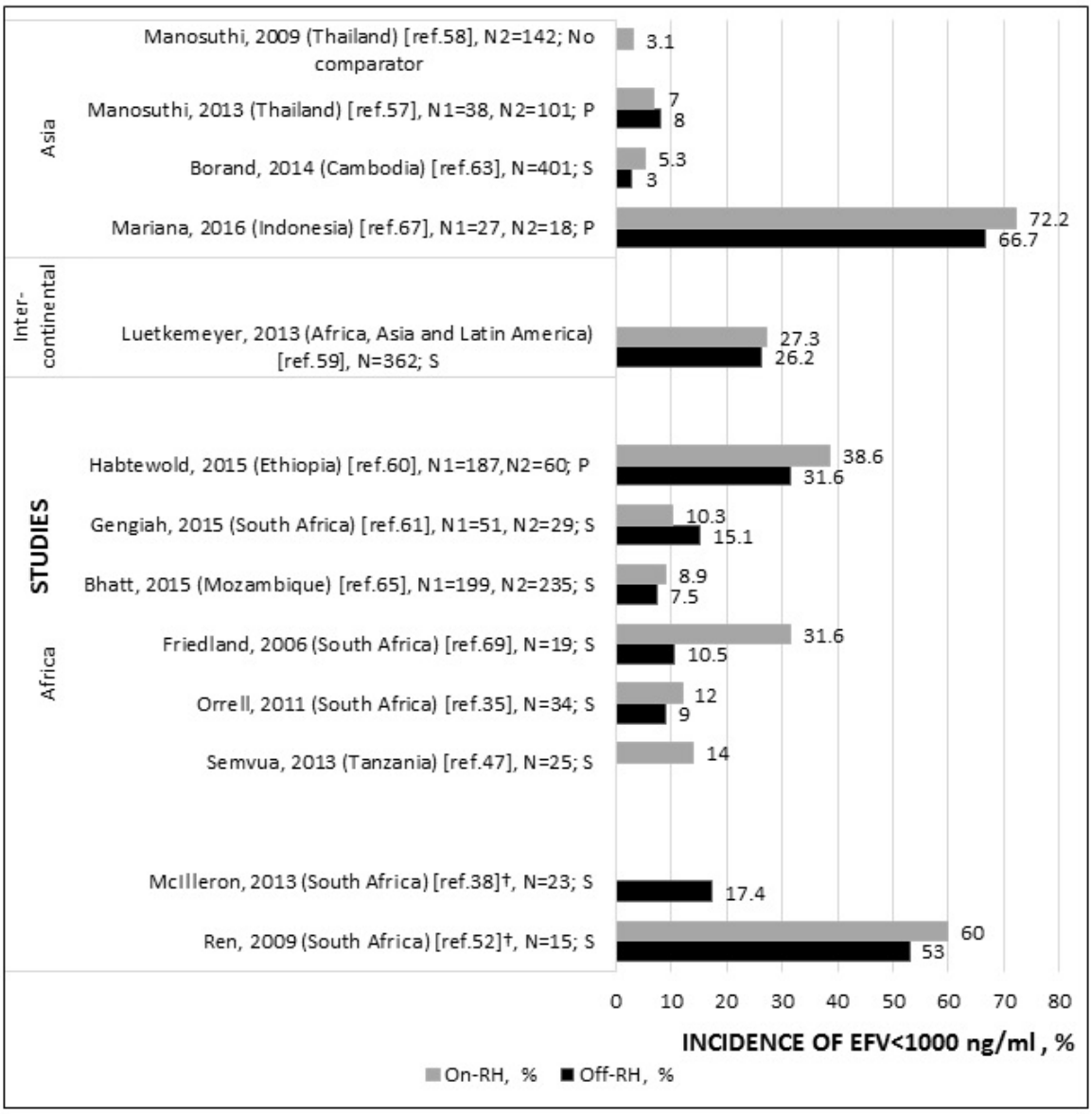

Fig 2. Proportion of patients with sub-therapeutic efavirenz plasma concentration.

†Children studies; S= on and off RH EFV sub-therapeutic concentrations assessed in the same patient; P= on and off RH EFV sub-therapeutic concentrations assessed in different patient groups (HIV-TB co-infected Versus HIV only). N= Sample size on which the EFV sub-therapeutic frequencies either with or without RH co-administration is based; N1= Sample size on which the EFV sub-therapeutic frequencies during ART without RH co-administration is based; N2= Sample size on which the EFV sub-therapeutic frequencies during ART with RH co-administration is based; ref = reference number

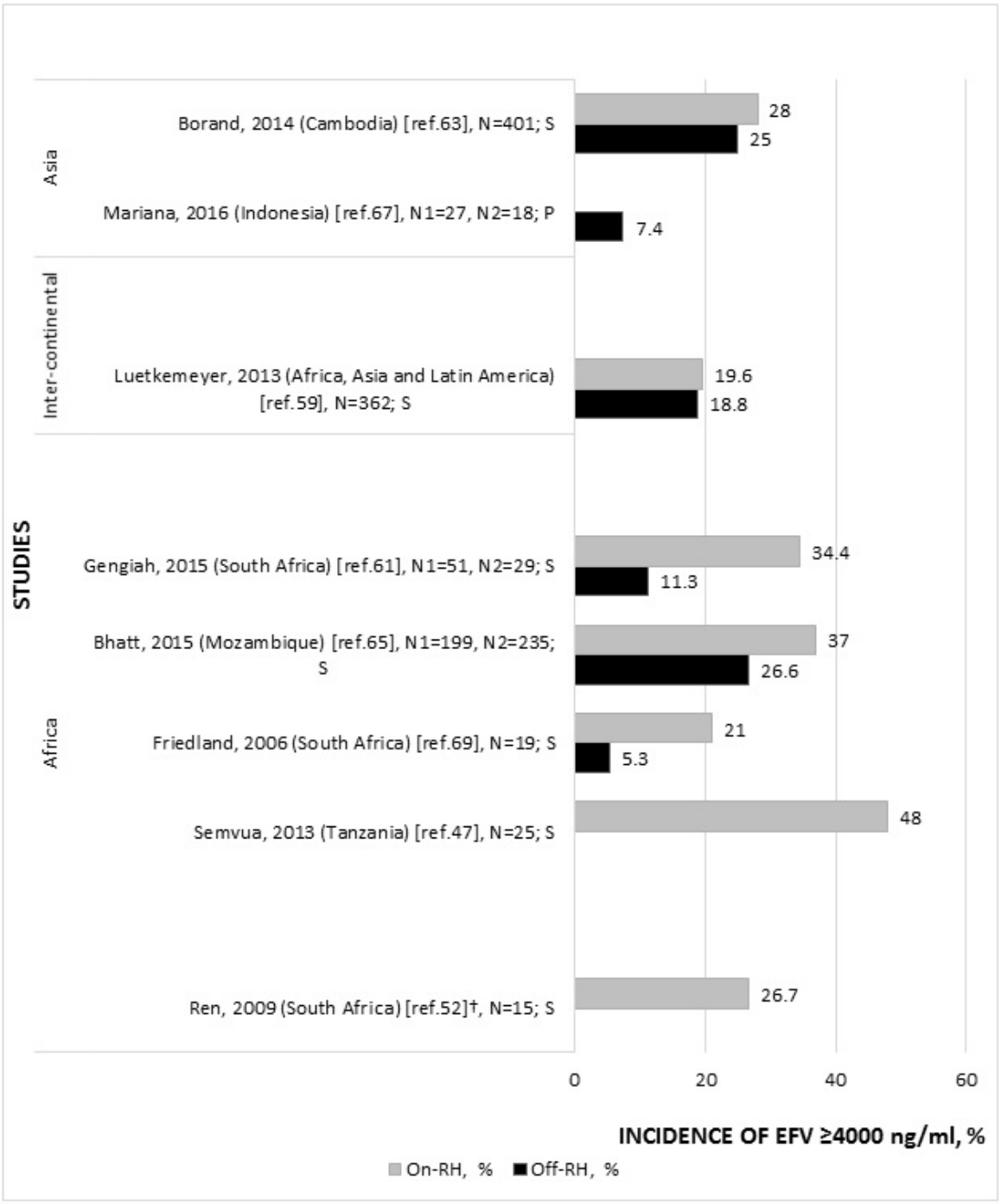

Fig 3. Proportion of patients with supra-therapeutic efavirenz plasma concentration.

†Children studies; EFV= Efavirenz; RH= Rifampicin and Isoniazid; S= on and off RH sub-therapeutic EFV concentrations assessed in the same patient; P = on and off RH sub-therapeutic EFV concentrations assessed in different patient groups (HIV-TB co-infected Versus HIV only). N= Sample size on which the EFV sub-therapeutic frequencies either with or without RH co-administration is based; N1= Sample size on which the EFV sub-therapeutic frequencies during ART without RH co-administration is based; N2= Sample size on which the EFV sub-therapeutic frequencies during ART with RH co-administration is based; ref= reference number.

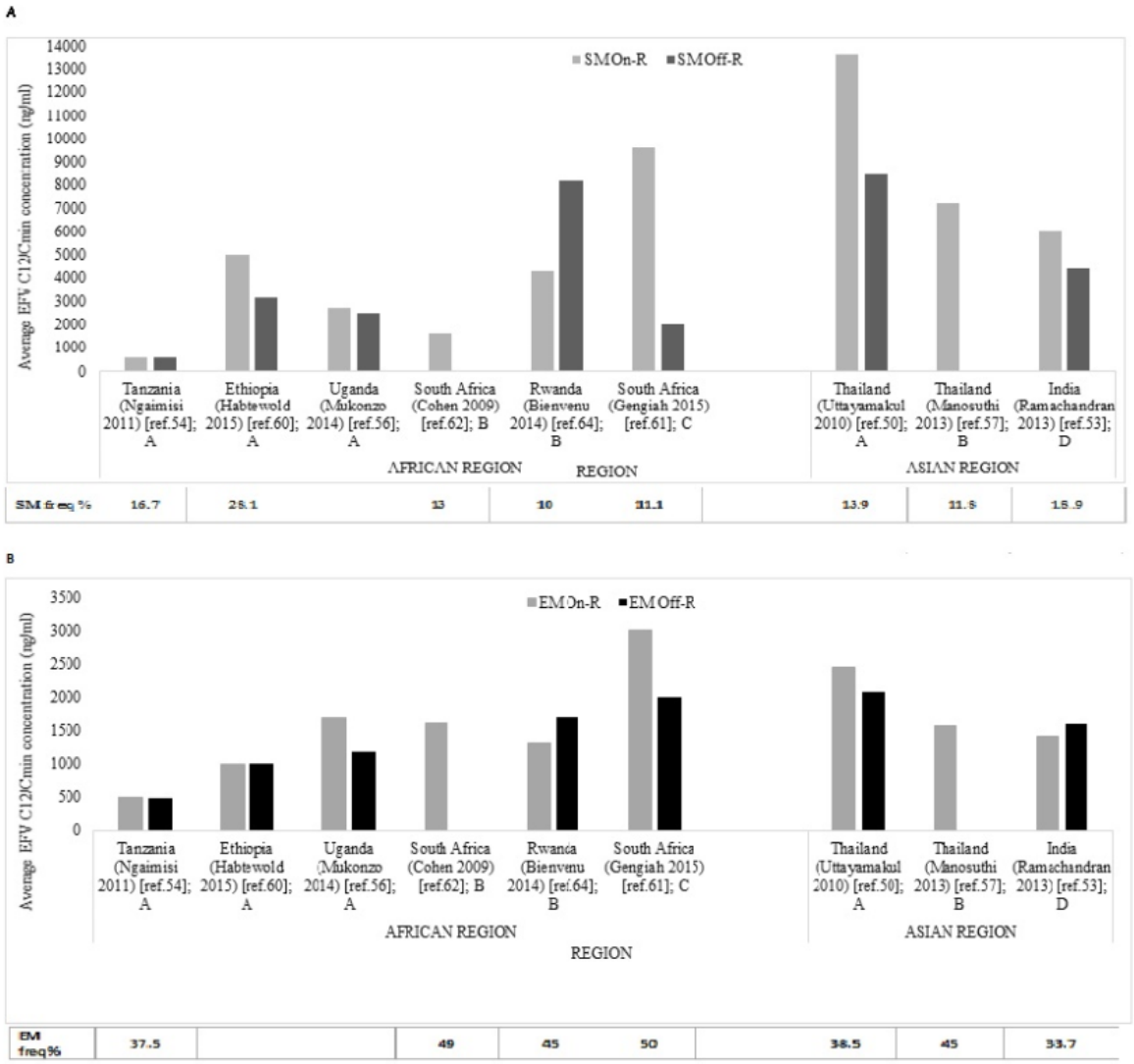

Fig 4. Efavirenz plasma concentrations on and off rifampicin co-administration among patients with CYP2B6 homozygous slow and extensive metabolizer genetic polymorphism, *CYP2B6 G516T*.

Panel A. Slow metabolizer genetic polymorphism

Panel B. Extensive metabolizer genetic polymorphism

On-R: on rifampicin. Off-R: off rifampicin. SM: Slow metabolizer. EM: Extensive metabolizer. EFV: Efavirenz. . Ref: reference number
C12: efavirenz mid-dose concentrations. Cmin: minimum efavirenz concentration. A: C12, mean, B: C12, median, C: Cmin, median, D: Cmin, Mean

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

Appendix 1. DATA EXTRACTION FORM

SECTION A. IN-DEPTH FULL TEXT REVIEW OF ELIGIBLE ARTICLES

1. Date of screening: |__|__|/|__|__|/|__|__|__|__|			This column is for comments
2. Surname of first author, Year			
3. Study title			
4. Reviewer ID (D-A, M-B)	|__|__|__|		
5. Author's email address			
6. Was author contacted?	☐ Yes	☐ No	
7. Language	☐ English	☐ Other	(If other, Exclude study)
Type of publication			
8. Journal article	☐ Yes	☐ No	
9. Conference abstract	☐ Yes	☐ No	
10. Other	☐ Yes	☐ No	(Decide after consultation)
11. If other, specify;	|_____|		
Study Design			
12. Single country RCT	☐ Yes	☐ No	
13. International Multicentre RCT (All sites in WHO high-burden countries)	☐ Yes	☐ No	
14. International Multicentre RCT (Some sites not in WHO high-burden countries)	☐ Yes	☐ No	
15. Cohort	☐ Yes	☐ No	
16. Case-control	☐ Yes	☐ No	
17. Cross-sectional	☐ Yes	☐ No	
18. Systematic review/meta-analysis	☐ Yes	☐ No	(If Yes, Exclude study)
19. Unclear design	☐ Yes	☐ No	(Exclude after consultation)
20. Other designs	☐ Yes	☐ No	(Decide after consultation)
21. If other design, specify:	|_____|		
22. Involved WHO listed high-burden countries.	1._____ 2._____ 3._____ 4._____ 5._____ 6._____ 7._____ 8._____ 9._____ 10._____ 11._____ 12._____		
23. Involved WHO listed Low-burden countries.	1._____ 2._____ 3._____ 4._____ 5._____ 6._____		
24. Was the pharmacokinetics of EFV with R co-administration evaluated?	☐ Yes	☐ No	(If No Exclude study)
25. If studies compare PK of EFV without R	☐ Yes	☐ No	(If Yes, Exclude study)
26. If Multicentric study with low and high-burden countries, are the PK parameters reported per country?	☐ Yes	☐ No	(If No, include but discuss with MB/AM)
27. Are PK results reported separately?	☐ Yes	☐ No	
If No above, Whether PK results are reported separately according to:			

Systematic review: Data extraction form. Version 3.0_14th 2016
INVESTIGATOR: Dr. ATWINE DANIEL

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

28. Age	☐ Yes	☐ No	
29. Region/country	☐ Yes	☐ No	
30. Gender	☐ Yes	☐ No	
31. Race	☐ Yes	☐ No	
32. Body weight	☐ Yes	☐ No	
33. Drug dosage	☐ Yes	☐ No	
34. Safety Outcomes evaluated	☐ Yes	☐ No	
35. Relationship between interaction between EFV and R with Hepatic events evaluated?	☐ Yes	☐ No	(If No, still include and use in Objective1)
36. Relationship between interaction between EFV and R with Neuropsychiatric events evaluated?	☐ Yes	☐ No	(If No, still include and use in Objective1)
35. Efficacy outcomes evaluated	☐ Yes	☐ No	
37. Relationship between interaction between EFV and R with TB treatment efficacy Outcomes evaluated?	☐ Yes	☐ No	(If No, still include and use in Objective1)
38. Relationship between interaction between EFV and R with HIV treatment efficacy R evaluated?	☐ Yes	☐ No	
Type of participants			
39. HIV/TB co-infected	☐ Yes	☐ No	(Exclude if No)
40. Age range of study participants (Years)	|__|__| to |__|__| years		
41. Patients on first-line R-based TB treatment	☐ Yes	☐ No	(Exclude if No)
42. Patients under EFV-based HIV treatment	☐ Yes	☐ No	(Exclude if No)
Type of health system			
43. Included Atleast one WHO TB/HIV-high burden country?	☐ Yes	☐ No	(Exclude if No)
44. Study Eligible	☐ Yes	☐ No	
IF STUDY IS INCLUDED, PROCEED TO FORM B.			

IF NOT INCLUDED, GIVE REASONS FOR EXCLUSION	*(Tick box to reflect your answer)*	
	0=No	1=Yes
1. Abstract only	☐	☐
2. Review opinion	☐	☐
3. Systematic review	☐	☐
4. Case-report	☐	☐
5. Switch studies	☐	☐
6. Missing information	☐	☐
7. Studies enrolled patients with comorbidities	☐	☐
8. Anti-TB prophylaxis	☐	☐
9. Used other Rifamycins besides rifampicin	☐	☐
10. Countries not on the WHO high burden list	☐	☐
11. Multi-centric study with low and high-burden countries and not reporting PK per country	☐	☐
12. Studies not using Rifampicin	☐	☐

Study screening ID: |__|__|__|__|__| Study ID: |__|__|__|__|

13. Duplicated studies	☐	☐
14. Failed participant Criteria	☐	☐
15. Other	☐	☐
16. If other, specify		

SECTION B. ADDITIONAL STUDY CHARACTERISTICS

GENERAL INFORMATION		
1. Beginning and ending date of recruitment	|__|__|/|__|__|__|__| to |__|__|/|__|__|__|__| (mm/yyyy)	
2. Study type: prospective or retrospective study?	☐ Prospective	☐ Retrospective
3. Total overall Sample size?	|__|__|__|__|__| participants	
4. Explain how patients were selected	☐ Consecutive ☐ Random ☐ Stratified ☐ Systematic ☐ Cluster ☐ Convenience	
Treatment dosages		
5. Different EFV doses used	☐ Yes	☐ No
6. Different R doses used	☐ Yes	☐ No
7. Different H doses used	☐ Yes	☐ No
8. Exact EFV doses used	|_____|mg, |_____|mg, |_____|mg,	
9. Exact R doses used	|_____|mg/kg, |_____|mg/kg, |_____|mg/kg, OR |_____|mg, |_____|mg, |_____|mg,	
10. Exact H doses used	|_____|mg/kg, |_____|mg/kg, |_____|mg/kg, OR |_____|mg, |_____|mg, |_____|mg,	
Drug Combinations Used		
11. TB treatment Regimen types used? (Write exactly)	Intensive Phase i. |_____| ii. |_____|	Continuation Phase |_____| |_____|
12. ART Regimen types used? (Write exactly)	EFV + |_____/_____| EFV/_____/_____	EFV + |_____| +|_____|
13. Companion drugs	☐ Pyridoxine ☐ Cotrimoxazole ☐ Other..... ☐ No information	
PHARMACOKINETIC DATA		
14. EFV intake time	☐ Morning ☐ Evening ☐ Not specified	
15. No. of patients included in PK analysis	|__|__|__|__|__| participants	

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

16. Selection of patients for PK ANALYSIS	☐ All pts exposed and sampled ☐ Pre-selected, give detail |_____| ☐ Adherence based ☐ Comorbidity based ☐ Other, specify: |_____|	
17. Pk type conducted (e.g population, etc)	☐ Population ☐ Full Pk sampling ☐ Cthrough	
18. Number of PK sampling times per day	|__|__| times	
19. Number of PK sampling days during co-admin EFV&R	|__|days	
20. PK time from beginning of EFV/R co-administration	|__|__| weeks (if same time consistently) (NB: in case of more than one Pk sampling done) Time 1. |__|__| weeks Time 2. |__|__| weeks Time 3. |__|__| weeks Time 4. |__|__| weeks	
21. Timing of PK EFV without R co-administration.	☐ NA ☐ Post TB treatment completion: |__|__| weeks ☐ Others, specify:_____:|__|__| weeks	
22. Methods PK analysis?	☐ HPLC ☐ Other, Specify: _____	
23. Patient group types in which PK comparisons were made?	☐ Two different groups ☐ Same group	
PK parameters used for EFV, R and H		
24. AUC0-24	☐ Yes	☐ No
25. AUC0-12	☐ Yes	☐ No
26. Cmax	☐ Yes	☐ No
27. Cmin	☐ Yes	☐ No
28. C12	☐ Yes	☐ No
29. Cthrough	☐ Yes	☐ No
Safety parameters Used		
30. Hepatitis (ALT, AST, etc)	☐ Yes	☐ No
31. Neuro-psychiatric effects	☐ Yes	☐ No
	32. If yes, use of qualitative assessment scales? ☐ Yes, specify the scale used: _____ ☐ No	
33. Use of severity grading	☐ Yes,	☐ No
	34. If Yes, specify : _____	
TB Efficacy indicators Used		
34. Month-2 culture conversion	☐ Yes	☐ No
35. End of treatment outcome	☐ Yes	☐ No
36. Post-treatment follow-up	☐ Yes	☐ No
HIV Efficacy indicators Used		
37. 6-months virological response	☐ 6-months virological response	☐ >6months virological response ☐ Both

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

38. If >6months, What exact time	|__|__|__| weeks	
39. Virological failure threshold used	☐ |_____|	☐ NA
40. Use of resistance mutation	☐ No	☐ Yes, at baseline ☐ Yes, for failures
41. Immunological response	☐ Yes	☐ No
42. If yes, at what time of follow-up?	|__|__|__| Months	
43. Drug susceptibility (R and/or H) evaluated at baseline?	☐ Yes	☐ No
44. Baseline virological resistance done?	☐ Yes	☐ No

Forms C & D can be duplicated for each treatment regimen based on WHO regions, age groups (adults or children), gender, race, geographical region/country and drug dosage of R, H and EFV)

SECTION C. PATIENT CHARACTERISTICS

Presentation of study patient characteristics

☐ No stratification (*results generally for all patients*)
☐ Stratified (*results given per strata*)

Specify field of stratification (if applicable)

☐ Region/Country: |_____|
☐ Age category: |_____|years.
☐ Race: |_____| (specify if applicable)
☐ EFV dose: |__|__|mg/kg or |__|__|__|mg.
☐ R dose: |__|__|mg/kg or |__|__|__|mg.
☐ Body weight: |__|__|__|kg.
☐ Gender : ☐ Males ☐ Females

					Comment
Analyzed sample size, N	|____|____|____|____|				
	Mean	SD	Median	IQR	
Age					
Weight (kg)					
Baseline CD4 count, cells/mm³					
Baseline Viral Load					
In: log_{10}/ml					
In: copies/mm³					
	n	%			
Sex,					
Male					
Female					
Type of TB					
Pulmonary					
Extra-pulmonary					
Both					
Non-specified					
Bacillary population					

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

Low (<2+)					
High (>2+)					

SECTION D. END-POINTS

Presentation of study patient characteristics

☐ No stratification (*results generally for all patients*)
☐ Stratified (*results given per strata*)

Specify field of stratification (if applicable)

☐ Region/Country: |_____|
☐ Age category: |_____|years.
☐ Race: |_____| (specify if applicable)
☐ EFV dose: |__|__|mg/kg or |__|__|__|mg.
☐ R dose: |__|__|mg/kg or |__|__|__|mg.
☐ Body weight: |__|__|__|kg.
☐ Gender ☐ Males ☐ Females

PK parameters for:			Overall		EFV alone (off-RIF)		EFV (on-rif)		Difference, N=|____|____|____|				P value
	Threshold LL	Threshold UL	Mean or Median	SD or IQR	Mean or Median	SD or IQR	Mean or Median	SD or IQR	Mean diff	SD	Median diff	IQR	
AUC0-24, ng.h/mL													
AUC0-12, ng.h/mL													
Cmax ng/mL													
Cmin, ng/mL													
C12, ng/mL													
Cthrough, ng/mL													
Time between drug-intake and PK sampling (mins)													

	During co-admin		During off RIF		P value
	n/N	%	n/N	%	
% of patients with EFV below LL					
% of patients with EFV above UL					

	Off-RIF		On-rif		Difference. N= |___|___|___|		P value
	n	%	n	%	n	%	
SAFETY PARAMETERS							
Raised ALT							

Study screening ID: |__|__|__|__| Study ID: |__|__|__|__|

Grade 3&4	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	
Grade 1&2	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	
Raised AST									
Grade 3&4	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	
Grade 1&2	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	
Neuropsychiatric adverse effects									
Grade 3&4	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	
Grade 1&2	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	

TB TREATMENT EFFICACY INDICATORS

	Overall N= |__|__|__|		Patients with EFV/R interaction, N= |__|__|__|		Patients without EFV/R Interaction, N= |__|__|__|		% Difference	P value
TB outcomes rates, %	n	%	n	%	n	%		
Month-2 culture conversion	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Cured	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Completed	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Treatment failure	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Death	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Defaulter/Loss-to-follow-up	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
Transfer-out	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	
TB Relapse	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|·|__|	

HIV TREATMENT EFFICACY OUTCOMES

% Virological reduction [At: |__|__| months]	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	
% CD4 reduction [At: |__|__| months]	|__|__|__|	|__|__|·|__|	|__|__|__|	|__|__|·|__|	|__|__|__|	

Appendix 2. Study specific characteristics, N=22

Study ID	Study design	Ref. no	N	PK sample	Patients' groups	Hepatic toxicity assessed	CNS toxicity assessed	Virological f-up month	Male (%)	Age, median/mean (years)	Body weight, median/mean (Kg)
Adult Studies, N=20											
Mariana, 2016 (Indonesia)[a]	Prospective non randomized comparative study	(67)	45	C12	A	Yes	Yes	6	81.5	32	54
Habtewold, 2015 (Ethiopia)	Prospective non randomized comparative study	(60)	493	C12	A	Yes	No	6	52.6	35	50
Mukonzo, 2014 (Uganda)	Prospective non randomized comparative study	(56)	263	C12	A	No	No		50	37	50
Borand, 2014 (Cambodia)	Cohort from a randomized clinical trial	(63)	540	C12	B	No	Yes	6, 12	65	35	45
Bienvenu, 2014 (Rwanda)	Prospective cohort	(64)	21	C12	B	No	No	1.5	51.3	38	
Mukonzo, 2013 (Uganda)	Prospective non randomized comparative study	(55)	197	C12	A	No	Yes		44.7	33.8	53.6
Luetkemeyer, 2013; (Botswana, Brazil, Haiti, Kenya, Malawi, South Africa, Thailand, Uganda, Zimbabwe, Peru, USA)	Cohort from a randomized clinical trial	(59)	543	Cmin	B	No	Yes	12	63	34	52.8
Manosuthi, 2013 Thailand	Prospective non randomized comparative study	(57)	139	C12	A	No	No		78	37	54
Borand, 2013 (Cambodia)	Cohort from a randomized clinical trial	[61]	482	C12	C	No	No		93		
Semvua, 2013 (Tanzania)[b]	Prospective cohort	[47]	25	Cmin[a]	B	Yes	No		56	32	48.4
Orrell, 2011* (South Africa)	Prospective cohort	(35)	72	C12[a]	B	Yes	Yes	12	35		60
Cohen, 2009 (South Africa)	Cross-sectional study	(62)	142	C12	A	No	Yes	6	72.5	40.3	65.2
Friedland, 2006 (South Africa)[b]	Prospective cohort	(69)	20	Cmin	B	Yes	Yes	6	25	31	59.4
Ramachandran, 2013 (India) [b, c]	Cohort from a randomized control trial	(53)	55	Cmin	B	No	No	6	46	34.8	
Uttayamakul, 2010 (Thailand)	Cohort from a randomized control trial	(50)	124	C12	B	No	No	6-12	64.6	35.9	53.3

Manosuthi, 2009 (Thailand)	Cohort from a randomized control trial	(58)	71	C12	C	No	No	12	64.8	35.7	52.9
Bhatt, 2015 (Mozambique)	Cohort from a randomized control trial	(65)	270	C12	B	Yes	Yes	3-12	59.3	33	52.3
Yimer, 2011 (Ethiopia)	Case-control: liver toxicity vs no liver toxicity	(49)	353	C12	B	No	No		58.6		
Ngaimisi, 2011 (Tanzania)	Prospective non randomized comparative study	(54)	182	C12	A	No	No		36.6	40.5	
Gengiah, 2015 (South Africa) [b]	Cohort from a randomized control trial	(61)	58	Cmin	B	Yes	No		53.6	32	57.4
Children studies , N= 2											
Ren, 2009 (South Africa)	Prospective cohort	(52)	15	Cmin	B	No	No	6	60	6.3	18
McIlleron, 2013 (South Africa)	Prospective cohort	(38)	40	C12	B	Yes	No	6	38	8.5	23.4

[a] On and off RH values of PK not reported. [b]Efavirenz intake in the morning. [c]ATT given thrice a week throughout the 6 months of treatment.
Note: Same R-dose of 10mg/kg used, *Average C12 was calculated as an average of the 3 medians provided for the different SNPs (41, 54 and 67 for GG, GT and TT respectively). C12: mid-dose concentration; Cmin: Ctrough, pre-dose concentration; Ref.no: reference number corresponding to the cited study. PK: Pharmacokinetics CNS; central nervous system
A: 2 different groups: HIV-TB co-infected and HIV infected without TB
B: HIV-TB co-infected patients on and off antituberculosis drugs
C: One group of HIV-TB co-infected patients on antituberculosis drugs
D: Two groups of HIV-TB co-infected patients on antituberculosis drugs with two different dose of efavirenz