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Expert Opinion

Dose adjustment of the non-nucleoside reverse transcriptase inhibitors during concurrent rifampicin-containing tuberculosis therapy: one size does not fit all

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Importance of the field: HIV/tuberculosis (TB) co-infection is common and associated with high mortality. Simultaneous highly active antiretroviral therapy during TB treatment is associated with substantial survival benefit but drug–drug interactions complicate NNRTI dosing.
Areas covered in this review: We reviewed the impact of rifampicin-containing TB therapy on the NNRTIs pharmacokinetics and clinical outcome. PubMed database was searched from 1966 to July 2009 using the terms efavirenz, rifampicin, nevirapine, pharmacokinetics, pharmacogenetics, HIV, TB, CYP2B6, CYP3A4 and metabolism. References from identified articles and abstracts from meetings were also reviewed.
What the reader will gain: A comprehensive review of the literature on this subject including pharmacokinetic and clinical studies. Most studies were small, observational or underpowered to detect the true effect of rifampicin on NNRTI-based therapy. None of the studies were controlled for genetic factors and there were limited data on children.
Take home message: There were insufficient data to make definitive recommendations about dose adjustment of the NNRTIs during rifampin-containing therapy. Current data suggest that the standard dose of efavirenz or nevirapine is adequate in most HIV/TB co-infected adults. However, more research is needed in pediatric populations as well as to define role of drug–gene interactions.

Keywords: drug interactions, efavirenz, HIV, nevirapine, rifampicin, tuberculosis

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1. Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality in people with HIV infection. Of the estimated 9.27 million incident TB cases in 2007, an estimated 1.37 million (15%) were HIV-infected [1] During the period, 456,000 deaths occurred among those who were HIV-infected with TB, which represented 33% of the HIV-positive cases of TB and 23% of the estimated 1.8 million TB deaths in 2007 [1]. Several observational studies have found that simultaneous highly active antiretroviral therapy (HAART) during TB treatment is associated with substantial reduction in mortality [2-4]. However, challenges to simultaneous therapy including high pill burden, overlapping drug toxicities, drug–drug interactions and

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Article highlights.

- Concurrent antiretroviral therapy during TB treatment is associated with substantial survival benefit but the appropriate dose of the NNRTI components is unresolved.
- Rifampin induces the metabolism of efavirenz resulting in decreased plasma concentrations but the influence of rifampicin appears to be highly variable from one individual to another.
- CYP2B6 516G>T genotype is strongly associated with efavirenz disposition irrespective of rifampicin-containing therapy.
- Most pharmacokinetic and clinical studies that evaluated the interactions between efavirenz and rifampicin-containing TB therapy are small and inconclusive and do not take into account the highly inter-individual variability in the rifampin effect.
- A marked decrease in nevirapine concentrations during co-administration with rifampicin is consistently observed in most pharmacokinetics studies but the clinical significance is unclear.
- The drug–drug interactions between nevirapine and rifampicin may also be confounded by host genetics.
- There are very limited data on the interactions between the NNRTIs and rifampicin containing TB therapy in pediatric populations.

This box summarises key points contained in the article.

concerns about immune reconstitution inflammatory syndrome have often been cited as reasons to delay or defer HAART during TB treatment [5,6].

Antiretroviral therapy (ART) programs have been rapidly scaled up in resource-limited countries and WHO estimates that 4 million people were on treatment at the end of 2007 (UNAIDS). TB is the most commonly associated infection and is often the entry point for a significant proportion of HIV-infected patients into care and treatment [7]. While TB can occur at any stage of HIV disease, the incidence increases as immunodeficiency advances. Thus, a significant proportion of HIV-infected patients eligible for HAART also require concomitant TB requiring treatment [8]. Although early initiation of HAART is associated with reduced mortality in patients with concurrent HIV/TB co-infection [9], immune reconstitution due to HAART does not eliminate the higher risk of developing TB in HIV-infected individuals compared to the general population [10]. Thus, it is evident that the treatment of HIV/TB co-infected patients is a major challenge facing many programs, especially those with a limited repertoire of antiretroviral drugs.

Rifampicin, a key component of short-course chemotherapy for TB, is a potent inducer of the CYP enzyme system that metabolizes several drugs including non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral agents. The interactions between rifampicin and the antiretroviral drugs can be complex and occur at different sites including the intestine and the liver (**Figure 1**). Prototypical inducers such as rifampicin increases the expression of CYP3A4 and CYP2B6 by interacting with the nuclear receptors, pregnane X receptor (PXR) or constitutive androstane receptor (CAR), which forms a heterodimer with the retinoid X receptor. The heterodimer then binds to the regulatory region of CYP3A4 or CYP2B6 resulting in upregulation of enzyme synthesis and increased metabolic activity [11,12]. The nuclear receptors PXR and CAR have been linked to the function and activity of drug transporters in the liver, intestines and kidney and play a vital role in drug absorption, distribution and excretion [11,12]. The HIV protease inhibitors and the NNTRIs are themselves potent inhibitors and/or inducers of CYP enzymes, which may complicate prediction of the net effect of drug–drug interactions. The NNRTIs are recommended as components of initial combination HAART regimens in the public health approach recommended by the WHO [13]. Among the NNRTIs, nevirapine is widely used in resource-constrained countries because of its availability as generic fixed-drug combination tablets and lower cost. Unlike efavirenz, the preferred NNRTI in the setting of TB treatment, nevirapine, is suitable for women of child bearing potential, because it is not a known teratogen. In many countries, it is the only available NNRTI.

There are currently > 20 approved antiretroviral drugs in six different classes from which combination HAART regimens can be constructed. However, in sub-Saharan Africa or Asia where > 90% of the HIV/TB co-infected patients in the world live, treatment options are severely limited. The recommended first-line HAART regimen in resource-limited settings is either efavirenz or nevirapine with two nucleoside/nucleotide reverse transcriptase inhibitors, though in the setting of concurrent TB therapy, efavirenz is preferred [13]. The implications of potential pharmacokinetic drug–drug interactions between rifampin and the NNRTIs, efavirenz and nevirapine are not well understood. Consequently, there is no consensus about the appropriate doses of efavirenz or nevirapine when used in the setting of rifampicin-containing TB treatment. Further, pharmacokinetic variability can be due to differences in drug absorption, distribution, metabolism, protein binding and drug–drug interactions. Increased hepatic clearance found in patients of caucasian origin versus African, Asian or Hispanic patients, and reports of differences in treatment response and adverse effects among various ethnic groups suggest that genetic polymorphisms which alter the expression of drug membrane transporter proteins or metabolizing enzymes could influence drug pharmacokinetics.

We performed a literature search to find published articles that evaluated drug–drug interactions between rifampicin or rifampicin-containing TB treatment and the NNRTIs or NNRTI-based HAART. A PubMed database was searched from 1966 to July 2009 using the terms efavirenz, rifampicin, nevirapine, pharmacokinetics, pharmacogenetics, HIV, TB, CYP2B6, CYP3A4 and metabolism. References from identified articles were also reviewed and abstracts from recent meetings were included. Studies were included if they evaluated the influence of rifampicin-containing therapy

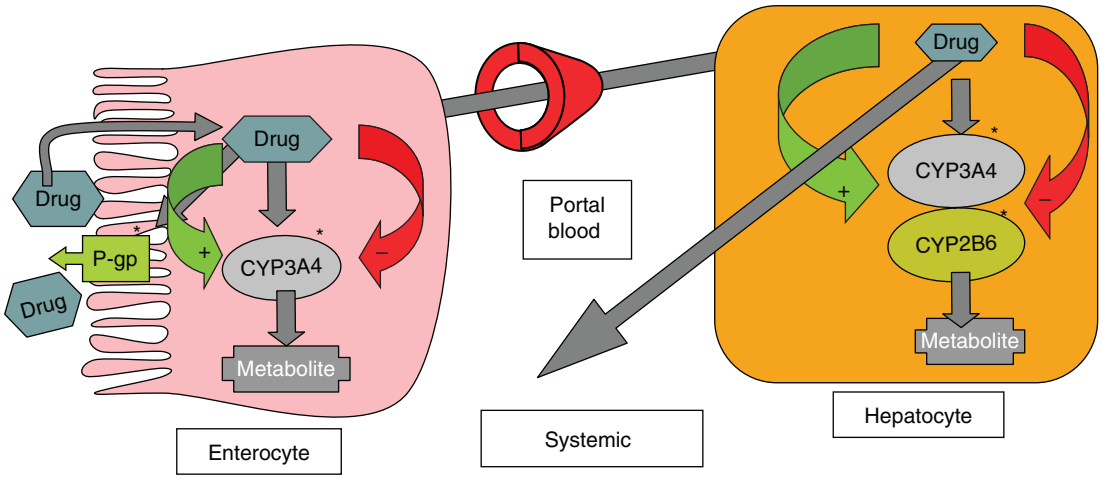

Figure 1. Disposition of CYP substrates such the PIs or the NNRTIs and potential influence of induction or inhibition of enzymes or transporters on systemic drug exposure.

*Rifampin is a potent inducer and the NNRTIs and PIs are themselves inducers and/or inhibitors of CYP enzymes or P-glycoprotein transporter. Modulation of these systems may cause altered metabolism and drug concentrations when inducers and/or inhibitors are used concurrently with enzyme substrates.

NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor.

on pharmacokinetics or clinical effects of efavirenz or nevirapine. Studies were also included if they evaluated the pharmacogenetics of efavirenz or nevirapine metabolism in the presence or absence of concurrent TB therapy. The primary objective of this review is to address the influence of drug–drug interactions as well as biological or genetic factors on the pharmacokinetics and treatment responses to efavirenz and nevirapine-based HAART in the setting of rifampicin-containing TB treatment. Our opinions on the factors that should be considered in deciding appropriate dose adjustment of the NNRTIs and the direction of future research are discussed.

2. Efavirenz

Efavirenz is an NNRTI and is a key component of one of the preferred regimens in the initial treatment of HIV infection. It is also available in generic form in developing countries, making efavirenz-based therapy a major option for HIV-infected person requiring HAART in resource poor settings. The standard dose is 600 mg daily and often taken at night to reduce the effects of CNS side effects. Efavirenz was approved by the FDA for HIV treatment in 1998 and in July 2006 a fixed-dose combination tablet containing efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200 mg was approved by the FDA under the brand name Atripla®.

2.1 Metabolism

Efavirenz is metabolized primarily by hydroxylation through hepatic CYP2B6, with minor contributions from CYP3A4/5 and CYP2A6 to form inactive metabolites 8-hydroxy efavirenz and 7-hydroxy efavirenz [14,15]. The main metabolite, 8-hydroxy efavirenz is further hydroxylated primarily by CYP2B6 to form 8,14-hydroxy efavirenz. The oxidative metabolites undergo conjugation by UDP-glucuronyltransferase (UGT) pathway and are excreted in the urine as glucuronides [15]. Efavirenz also undergoes direct conjugation by UGT to form N-glucuronide, but until recently the enzyme isoform was unknown [15,16]. UGT2B7 has recently been implicated in the direct glucuronidation of efavirenz [17]. The 8-hydroxylation pathway represents the major route of metabolism of efavirenz accounting for > 90% of efavirenz oxidation [15], and alternate pathways such as 7–hydroxylation and N-glucuronidation may be important in individuals with loss-of-function of CYP2B6 [18].

2.2 Influence of TB therapy on efavirenz pharmacokinetics

Rifampicin induces the function and activity of CYP2B6, the main metabolic enzyme for efavirenz. In primary human hepatocytes, the increase in CYP2B6 activity due to rifampicin varies widely from 2.5- to 13-fold [19-21]. However, *in vivo*, co-administration of efavirenz with rifampicin led to only a modest (22 – 26%) reduction in efavirenz plasma exposure [22,23]. In one of these pharmacokinetic studies, the change in efavirenz exposure with concomitant rifampicin ranged from a decrease of 65% to an increase of 37% [23], suggesting inter-individual differences in the inducibility of the drug metabolizing enzymes. Another example of wide inter-individual variability in rifampin effect is illustrated in **Figure 2**, in which healthy volunteers treated with efavirenz in the presence or absence of rifampicin showed a change in efavirenz exposure that ranged from a decrease of 100% to an increase of -56% during rifampicin coadministration (unpublished data). The variability in efavirenz concentrations was found to be greater in the presence of rifampicin than without

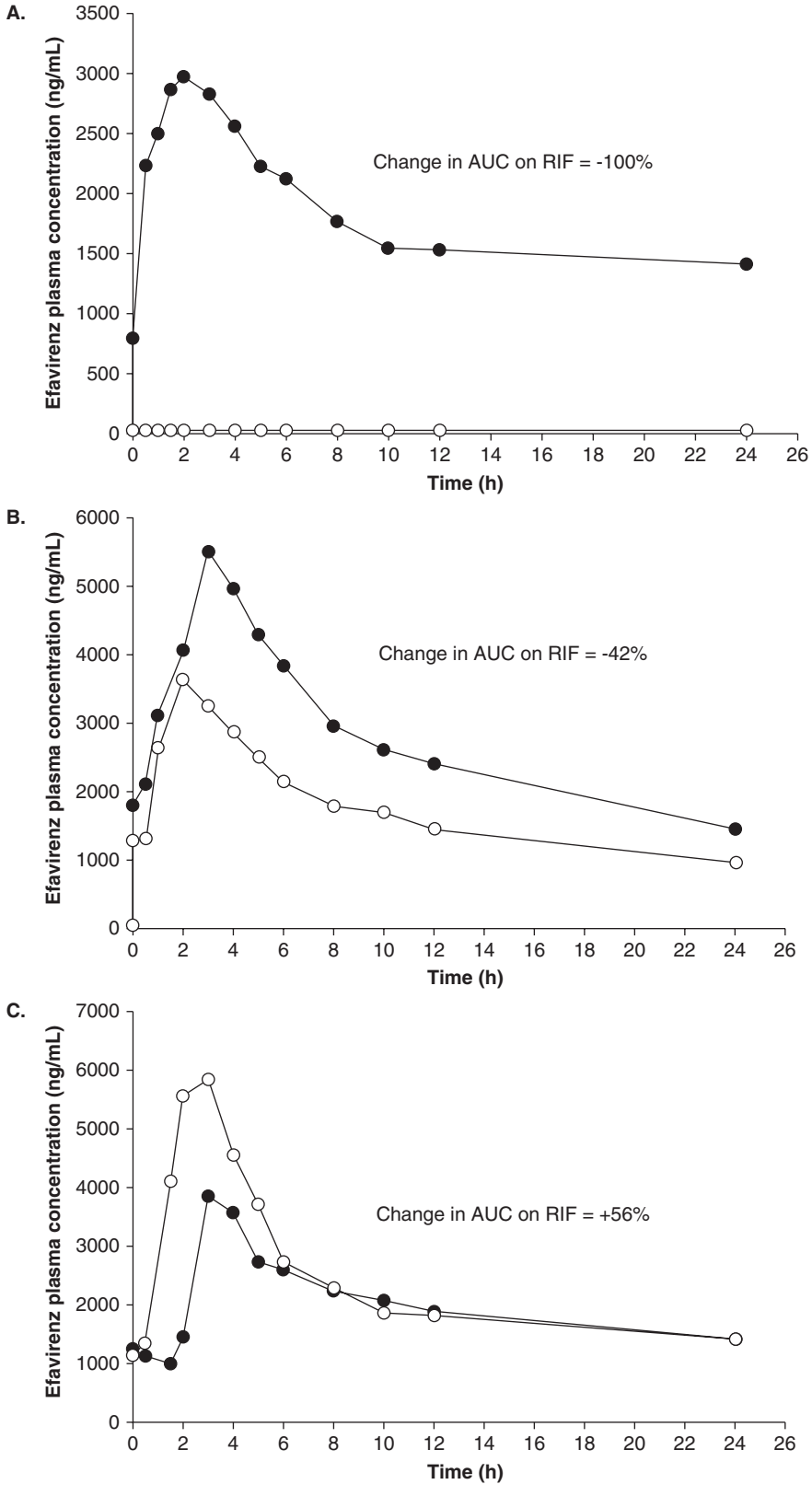

Figure 2. Efavirenz concentration-time profile in three healthy volunteers in the absence (close circles) and presence of rifampin (open circles). The effect of rifampin co-administration varied from a reduction in efavirenz AUC by100% (A) to an intermediate of a reduction by 42% (B) to an increase by 56% (C).

rifampicin [24,25], which is probably a manifestation of inherent differences in the inducibility of *CYP2B6* variants. The possible inter-individual differences in enzyme induction on the clearance of efavirenz when co-administered with rifampicin further complicate decisions about dose adjustments of efavirenz in the setting of concurrent rifampin-containing TB therapy.

2.3 Clinical studies of concurrent efavirenz and rifampicin-containing therapy

The concern about the drug–drug interactions between rifampicin and efavirenz is that reduction in efavirenz concentrations due to induction of metabolism by rifampin could lead to HIV treatment failure and development of drug resistance. Concurrent HIV and TB therapy is necessary as it is associated with reduced mortality but clinicians are often faced with the challenges of managing the drug–drug interactions when multiple drugs are used in a regimen. The 22 – 26% reduction in mean efavirenz plasma exposure due to induction effect of rifampicin on efavirenz clearance has led some experts to recommend an increased efavirenz dose to 800 mg/day when co-administered with rifampin [26-28]. The fixed daily dose of 600 mg for adults is known to be associated with significant inter-individual variability in plasma concentrations as well as some clinical effects [29-31]. Mid-dose or trough efavirenz plasma concentrations below 1000 ng/ml has been associated with increased risk of virologic failure in HIV-infected patients not receiving concurrent rifampicin-containing therapy [30-32], while concentrations above 4000 ng/ml have been associated with risk of CNS side effects [30,31].

Thus, the goal of efavirenz dose adjustment when co-administered with rifampicin is to avoid sub-therapeutic concentrations. However, it must be balanced with the need to avoid supra-therapeutic efavirenz plasma concentrations in individuals who are genetically predisposed to impaired enzyme activity. Recent studies have shown that individuals with *CYP2B6* 516 TT genotypes are at risk of high efavirenz plasma exposures even in the presence of rifampicin-containing therapy [33,34]. Thus, increase in efavirenz dose during rifampin-containing therapy may not be necessary in individuals with a slow metabolizing phenotype. Clinically, efavirenz 800 mg/day has been used in some patients with TB/HIV co-infection on rifampicin-containing therapy but the increased dose has not been shown to result in superior virologic suppression rates [35-37]. Rather, the increased dose was associated with a high frequency of CNS and hepatic toxicities associated with high efavirenz plasma concentrations in one study that predominantly enrolled native Africans [35]. In contrast, another study in which 50% of the participants were Caucasian did not report a higher frequency of supra-therapeutic concentrations and/or increased toxicity in individuals treated with efavirenz 800 mg daily [25]. There are case reports of the need for higher efavirenz doses up to 1600 mg daily to achieve desired plasma concentrations, as well as virologic suppression in two patients with no identifiable slow-metabolizing phenotype mutation who were also treated rifampin [38]. However, in most published studies, efavirenz 600 mg/day appears to be adequate in the setting of TB therapy in most patients [24,37,39]. In addition, the only randomized study of efavirenz 600 or 800 mg daily was conducted in Thai patients and found no difference in virological outcome between the two groups [37]. However, this study was limited by the small size of the study population, which could have missed a small but clinically meaningful effect of the increased dose. Overall, a review of available literature of clinical studies that used efavirenz 600 or 800 mg daily in HIV/TB co-infected patients undertaken by the FDA did not find sufficient evidence to support an increase in dose to 800 mg/day [40].

2.4 Pediatric studies of efavirenz and rifampin interactions

There are very limited data on the pharmacokinetic interactions between rifampin-containing TB treatment and efavirenz in children. Our literature review revealed only one published study to date [41]. Among 15 HIV/TB co-infected children treated with standard efavirenz-based HAART and rifampin-containing TB treatment, a wide inter-patient variability in efavirenz concentration as well as a bimodal distribution of efavirenz trough concentrations was observed [41]. Overall, TB therapy had no significant influence on mean change in efavirenz concentration in the children but 60 and 53% of them had efavirenz trough concentration < 1000 ng/ml during and after antitubercular therapy, respectively. Contrary to expectations, four children with slow metabolizing phenotype had higher efavirenz concentrations during antitubercular therapy than when they were off the rifampin-containing TB treatment [41]. Viral load data were available in 13/15 children, 11 of whom had full suppression of HIV RNA at 6 months of HAART. Of the two children who had detectable viral load, both had efavirenz concentration < 1000 ng/ml. These data suggest that current dosing of efavirenz may be suboptimal in most children irrespective of antitubercular therapy.

2.5 Pharmacogenetics of efavirenz therapy

There is substantial inter-individual variability in the pharmacokinetics of efavirenz. Population pharmacokinetic studies have found the coefficient variation in apparent oral clearance of efavirenz to range from 40 to 55% [29,42,43]. The variability in plasma concentrations in response to the fixed adult dose of 600 mg is up to 120% [30]. The variability in efavirenz pharmacokinetics is probably due to a combination of factors including biologic, exogenous and genetic factors. Unlike the strong and consistent association between CYP2B6 516G>T single nucleotide polymorphism (SNP) and efavirenz exposure [44,45], there is no conclusive evidence to suggest that biological factors such as gender and body weight significantly influence efavirenz plasma concentrations. While some authors found higher efavirenz concentrations in women compared to men [46], others have found no sex-related differences in efavirenz concentrations [29,47-49].

Likewise, some studies found body weight to be associated with efavirenz plasma concentrations or clearance [44,49], while others have not [34,46,50]. On the other hand, ethnicity or race (probably a reflection of host genetics) has been consistently associated with efavirenz concentrations such that Blacks or Asians tend to have higher efavirenz concentrations than Whites [29,34,46,48,49,51].

CYP2B6, the main metabolic enzyme for efavirenz, is highly polymorphic and is subject to pronounced inter-individual variability in expression and activity [52], and genotyping for functional SNPs has proven to be useful in the prediction of efavirenz concentrations in pharmacokinetic studies [53,54]. In particular, the *CYP2B6* c.516G>T is a common polymorphism (21 – 38% allele frequency) [55] that has been consistently associated with reduced enzyme activity and higher efavirenz exposure in studies of different populations with varied racial and ethnic backgrounds [51,53,56-58]. The influence of *CYP2B6* 516G>T SNP on efavirenz disposition has also been observed in children [59,60], as well as during co-administration with rifampicin-containing TB therapy [33,34]. The more recently described *CYP2B6* c.983T>C variant with up to 10% allele frequency is also associated with lower enzyme activity and higher efavirenz concentrations but appears to be exclusively found in populations of African descent [54,61,62]. Other *CYP2B6* polymorphisms that have been identified have either minimal impact on efavirenz metabolism, or are relatively rare (i.e., < 5% allele frequency) [55], and recently, *CYP2A6* genetic polymorphisms [18,44,50], *CYP3A4*1B* and *CYP3A4*_rs4646437 [44], have been also found to influence efavirenz plasma concentrations or clearance.

3. Nevirapine

Nevirapine is the other NNRTI that is widely available for HIV treatment in resource-limited settings. Nevirapine was one of the earlier drugs to be developed and introduced into treatment regimens for HIV-infected patients in 1996.

3.1 Metabolism

Like efavirenz, nevirapine is extensively biotransformed via oxidative metabolism by the CYP pathway to form several hydroxylated metabolites *in vivo* and *in vitro*. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by CYP3A4 and CYP2B6 enzymes. Hence, substances that induce or inhibit the CYP enzyme system could have a profound effect on the metabolism of nevirapine, by decreasing or increasing blood levels of nevirapine, respectively. For example, rifampicin and corticosteroids are inducers and would decrease blood levels while fluconazole is an inhibitor of the CYP enzyme system and could thus increase plasma levels of nevirapine during concurrent administration [21].

Nevirapine biotransformation involves extensive hydroxylation and glucuronidation of hydroxylated metabolites. The metabolites are then largely excreted into the urine, where 2-hydroxy, 3-hydroxy and 12-hydroxy nevirapine glucuronides account for 68% of the total. Thus, CYP metabolism, glucuronide conjugation and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans [63]. Formation of 2- and 12-hydroxy nevirapine is mediated by CYP3A4/5, while that of 3- and 8-hydroxy nevirapine by CYP2B6.

In clinical studies, nevirapine is readily (> 90%) absorbed after oral administration in healthy volunteers and in patients with HIV infection [64]. After a single 200 mg dose, plasma nevirapine concentrations reach a maximum of 2 μg/ml by 4 h post-dose and decline log linearly thereafter, resulting in a terminal phase half-life of ~ 45 h; steady-state plasma concentrations of nevirapine would be higher. Nevirapine is an inducer of CYP metabolism, thereby, auto inducing its own metabolism and reducing its half-life from 45 to 30 h after 2 weeks of dosing with 200 mg/day compared with a single dose [65]. In adults, nevirapine metabolism does not change substantially with age (range 18 – 68 years) and a review of the literature failed to find a significant association between sex and nevirapine pharmacokinetics [66].

3.2 Influence of TB therapy on nevirapine pharmacokinetics

Rifampicin induces the expression and activity of the CYP metabolic enzymes in the liver [67,68], thereby, greatly reducing plasma concentration and exposure to nevirapine during concomitant treatment with both drugs [69]. Cohen *et al.* observed a significant decrease in the ratio between the exposure to nevirapine and its inactive 12-hydroxy metabolite (produced primarily by CYP3A4) in the presence of rifampin-containing TB treatment indicating enhanced metabolism of nevirapine by CYP3A4 [70]. The therapeutic range of nevirapine is generally considered to be 3.4 – 12 μg/ml and several studies (in patients without TB) have found an association between low nevirapine trough levels and suboptimal response to treatment [71-74]. Hence, some treatment guidelines recommend therapeutic drug monitoring and maintaining nevirapine levels within this range by appropriate dose adjustment [75]. The interaction between nevirapine and rifampicin has been studied using three different approaches (pharmacokinetic studies, observational cohort studies and clinical trials), all providing different perspectives on the issue.

3.3 Pharmacokinetic studies

Pharmacokinetic studies in patients on concurrent rifampicin treatment have shown variable reductions in nevirapine blood concentrations ranging from 10 to 68% [49,70,76-79]. Studies done in Indian [78] and African [70] HIV co-infected TB patients found a significant proportion with sub-therapeutic plasma nevirapine concentrations. Ramachandran *et al.* found that 8/13 patients studied had nevirapine C_{min} < 3 μg/ml [78]. Unlike the interaction with efavirenz where some patients paradoxically have increases in efavirenz concentrations during

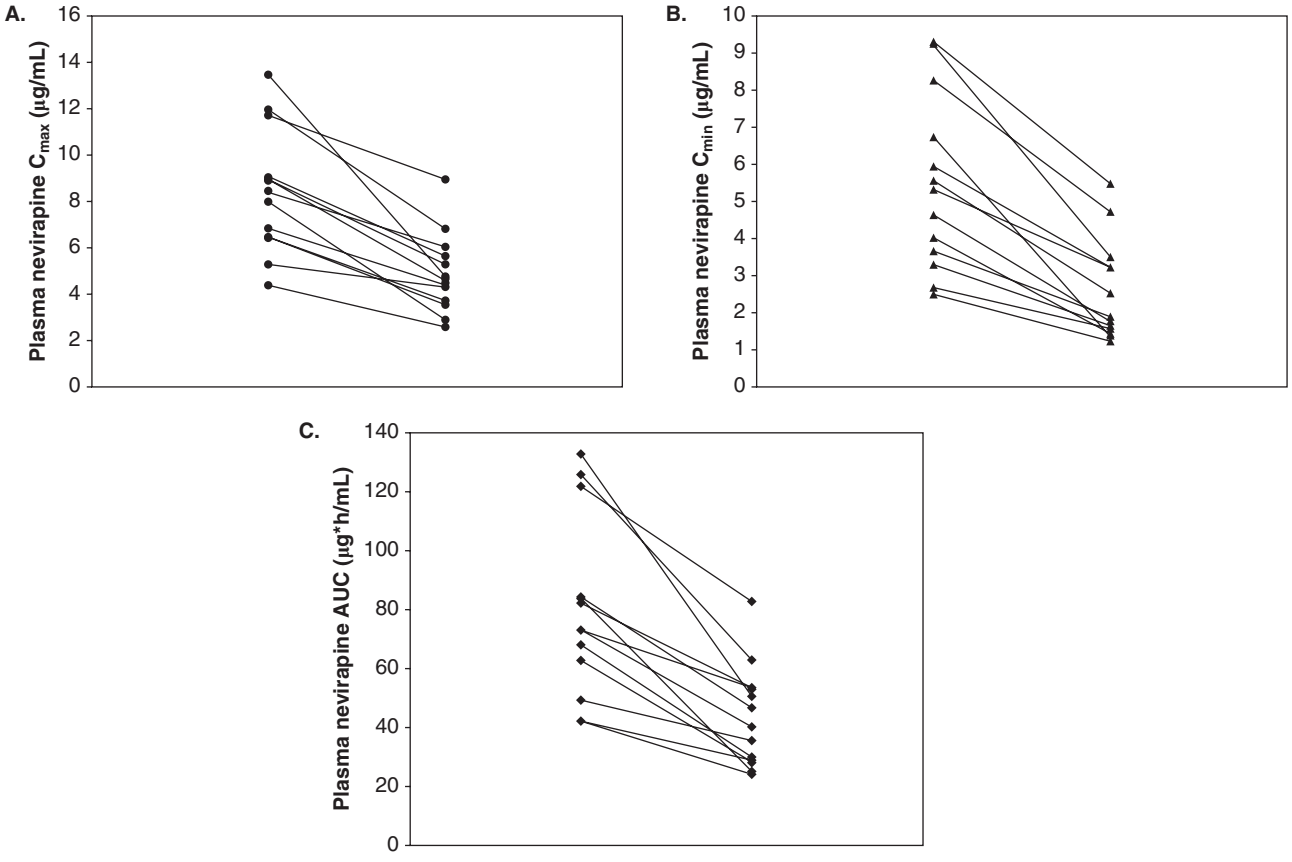

Figure 3. Nevirapine C_{max} (A), C_{min} (B) and AUC (C) in 13 patients with HIV and tuberculosis in the absence and presence of rifampicin. Nevirapine and rifampicin were administered at standard dosage and patients were in steady-state. Rifampicin co-administration caused a mean reduction in C_{max} by 42%, C_{min} by 53% and AUC by 46%.

co-administration with rifampin [24,41], as shown in **Figure 3**, all 13 patients who received nevirapine in the presence of rifampin showed significant reductions in C_{max} (**A**), C_{min} (**B**) and AUC (**C**) in the presence of rifampicin compared to values in the absence of rifampicin. An attempt was made to overcome this interaction by increasing the dose of nevirapine from 200 to 300 mg twice daily in patients with trough nevirapine levels < 3 µg/ml [78]. While this resulted in therapeutic blood levels in the seven patients who had sub-therapeutic concentrations and no adverse events, the study was limited by a small sample size and the short (2 weeks) duration of treatment with the higher dose. In a population pharmacokinetic study of nevirapine in South African patients, the simulations suggested that an increased dose of 300 mg twice daily would achieve adequate nevirapine concentrations in most patients during rifampicin-containing anti-TB treatment [77].

3.4 Observational studies

In a retrospective analysis of a large cohort of HIV-infected patients in south Africa, Boulle *et al.* showed that the probability of virological failure was higher when patients initiated nevirapine-based HAART while on rifampicin but not when they initiated efavirenz-based HAART (adjusted odds ratio 1.7, 95% CI 1.2 – 2.6) (36) [80]. However, if TB developed while patients were stable on nevirapine-based treatment, the failure rates were similar to those on efavirenz. Several studies have shown that despite expected reductions in serum levels of nevirapine, values remained above the inhibitory concentrations of most wild-type strains with satisfactory immunological and virological responses [76,79,81,82]. Among 74 Thai patients, Autar *et al.* reported that 86% had nevirapine plasma concentrations within the therapeutic range during rifampicin co-administration [82]. A retrospective Spanish study of 32 patients reported that 74% of patients with concomitant nevirapine and rifampicin attained undetectable viral loads [81]. A Thai cohort study of 70 patients on concomitant nevirapine and rifampicin found that virological suppression at 60 weeks was similar to a control group without rifampicin treatment [83,84]. Although these data are reassuring and suggest that the majority of patients respond well to treatment in spite of the drug–drug interaction, it is difficult to generalize these findings to other populations due to differences in nutritional status, genetics and the retrospective nature of the studies.

3.5 Clinical trials

The key question of whether nevirapine (in the standard or higher dose) when administered along with rifampicin results in an increased risk of virological failure can only be answered through clinical trials with simultaneous therapeutic drug monitoring and determination of virological outcomes at set time points. In a small clinical trial conducted in Thailand in HIV co-infected TB patients, it was observed that the 48-week efficacy of antiretroviral treatment (based on immunologic and virologic responses) was similar in patients treated with 400 or 600 mg/day of nevirapine [85]. A high percentage of suboptimal levels were found during the 200 mg/day lead-in period whereas the 200 mg twice a day lead-in was associated with more drug hypersensitivity. The authors concluded that nevirapine 200 mg twice a day should be sufficient for most Thai HIV-infected patients receiving rifampicin. Manosuthi *et al.* conducted another randomized clinical trial (the N2R study) comparing the efficacy and plasma drug concentrations of nevirapine and efavirenz in combination with TB treatment. Blood levels of the NNRTIs were correlated with the proportion of patients with undetectable plasma viral load at 48 weeks of ART. This study showed that low drug exposure and low body weight were important predictors for treatment failure and also found a significant correlation between treatment failure and reduced nevirapine trough levels [86]. Swaminathan *et al.* compared the efficacy of once-daily nevirapine (400 mg) versus efavirenz (600 mg) in combination with a dual NRTI backbone among HIV-infected TB patients on antitubercular therapy and found that virological suppression was significantly worse with the nevirapine regimen; 50/59 in the efavirenz arm and 38/57 patients in the nevirapine arm had VL < 400 copies/ml at 24 weeks [87]. In this study and many others, the patients were already on rifampicin when ART was initiated and nevirapine was given at a lead-in dose of 200 mg for the first 2 weeks of therapy, potentially resulting in low blood levels and the development of resistance mutations during that period leading to poor outcomes.

3.6 Pediatric studies

Nevirapine is the backbone of first-line HAART, usually in combination with two NRTIs as part of a three-drug fixed-dose combination (FDC) in resource-limited settings. Pharmacokinetics of many antiretroviral drugs is highly variable in children with absorption, distribution, hepatic metabolism and renal function all changing with age [88]. Given that maturation of the hepatic CYP enzymes is generally not complete till 2 – 5 years of age, younger children require higher doses/kilogram body weight of drugs metabolized by this system [89]. Several generic pediatric FDCs are now available that contain nevirapine in a higher ratio to the other drugs (stavudine and lamivudine) and simplified dosing recommendations have been made by the WHO for use by healthcare personnel in the field. Studies performed in Thailand, Africa and India using these pediatric FDCs have generally shown adequate nevirapine exposure and satisfactory short-term clinical and immunological outcomes [90-92]. However, long-term data are lacking and in view of the sub-therapeutic blood levels observed in a significant proportion of children, especially younger ones, more studies are required.

Apart from age, the factors known to influence nevirapine drug levels include co-administered drugs and pharmacogenetic variability, as in adults [93,94]. Saitoh *et al.* studied HIV-infected children who received nevirapine as a component of HAART and examined the association between *CYP2B6* (G516T) and *ABCB1* (C3435T) gene polymorphisms on the one hand and plasma concentrations of nevirapine and clinical responses to ART on the other [94]. This study demonstrated that children with the *CYP2B6* 516TT genotype may have a better response to therapy due to a favorable pharmacokinetic profile. In a study in Indian children on nevirapine-based HAART, this polymorphism was found to be one of the factors significantly influencing drug levels (Swaminathan, pers. commun., unpublished data).

One factor that has not been given much attention is the impact of malnutrition on nevirapine levels. A study conducted in Malawi and Zambia suggested that stunting (low height for age, suggestive of chronic malnutrition) may be associated with lower blood levels of nevirapine, while wasting (low weight for height) was associated with higher levels [91]. Findings in Indian children are very similar; factors significantly impacting (lowering) nevirapine levels included age < 3 years and stunting (Swaminathan, unpublished data). The impact of malnutrition on antiretroviral drug levels and its role in drug metabolism, pharmacokinetics and response to treatment deserves further study, because the majority of children initiating treatment in resource-poor settings, especially those with TB, are malnourished.

Data on the influence of concomitant rifampicin on nevirapine blood levels in HIV-infected children are limited. Kamateeka *et al.* observed that the clinical, immunological and virological outcomes in 26 Ugandan children receiving Triomune® (NVP/3TC/d4T)-based HAART with concomitant anti-TB therapy was similar to 101 children without TB receiving the same HAART regimen [95]. Oudijk *et al.* conducted a pharmacokinetic study in 21 Zambian children < 3 years co-treated with Triomune FDC and rifampicin-based TB therapy and reported substantial reductions in nevirapine concentrations in young children receiving concurrent rifampicin which led them to suggest that an increase in dose may be required [96].

3.7 Genetic determinants of nevirapine pharmacokinetics

The majority of pharmacogenetic studies to date have focused on efavirenz; however, a few recent studies have investigated the influence of genetic polymorphisms on nevirapine. Patients with the 516TT polymorphism in the CYP2B6 enzyme were observed to have a 1.7-fold increase in plasma AUC of nevirapine compared with 516GG patients [58].

Similar findings from Uganda [97] and India [98] confirmed the prominent role of CYP2B6 in nevirapine elimination; however, the difference in blood levels between patients with the homozygous mutant and wild forms of the allele were less pronounced than in the case of efavirenz. Other CYP polymorphisms such as *CYP2B6* C1459T and *CYP3A4* A392G as well as polymorphisms in the MDR gene (*ABCB1* C3435T) have not been shown to have much impact on nevirapine pharmacokinetics [94,99]. Overall, these findings suggest that pharmacogenetics has the potential to be used as a useful tool in the management of HIV-infected patients and could help design regimens and drug dosages with minimal toxicity and maximum effectiveness.

4. Conclusions

The NNRTIs, efavirenz and nevirapine are essential components of life-saving regimens for the treatment of HIV in resource-limited settings. These NNRTIs in combination with two nucleoside reverse transcriptase inhibitors are often the only options available to patients with HIV/TB co-infection requiring rifampicin-containing therapy in areas devastated by the HIV and TB epidemics as rifabutin is not available to allow the use of protease inhibitors in alternate regimens. However, one unresolved issue for the effective use of these NNRTIs in the setting of rifampicin-containing therapy is the appropriate effective dose. Most of the published pharmacokinetic studies that evaluated drug–drug interactions between these drugs and rifampicin were small, underpowered and often did not control for genetic factors that influence efavirenz and nevirapine metabolism. A majority of the clinical studies were observational in nature and were also underpowered to detect the true effect of rifampicin on NNRTI-based therapy. In addition, there were very limited pharmacokinetic and clinical data in children. Overall, we did not find sufficient data in the literature that could be used to support definitive recommendations on dose adjustment of the NNRTIs during rifampicin-containing TB therapy. However, it does appear that one dose adjustment will not be appropriate for all people because of wide inter-individual differences in the disposition of these NNRTIs in the presence of rifampin-containing TB therapy.

5. Expert opinion

5.1 Efavirenz

While the minimum effective efavirenz plasma concentration and the degree of the effect of rifampin-containing TB therapy on efavirenz pharmacokinetics and clinical effect is debatable, the well-known substantial inter-individual variability (> 100% coefficient of variation) in efavirenz plasma concentrations after fixed standard dosing has the potential to place some individuals at risk of supra-therapeutic or sub-therapeutic concentrations. The ultimate goal of efavirenz dose adjustment during rifampicin-containing therapy is to avoid sub-therapeutic concentrations while minimizing unnecessary increase in efavirenz plasma exposure that will lead to increase frequency of treatment side effects in some individuals. Therefore, one would expect that increasing efavirenz dose by 200 mg/day will probably not be appropriate for all patients, as it does not take into consideration the variability due to genetic factors. The frequency of the slow metabolizing genotype, *CYP2B6* 516TT genotype, is about 25% of African and Indian populations [33,34,56]. Consequently, dosage adjustment of efavirenz during co-administration with rifampin based on a Spanish study may not be applicable to other populations such as Africans or Indians. To our knowledge, no published studies in which efavirenz concentration was measured on and off rifampin-containing TB treatment in the same patient at different times has shown a statistically significant difference with $p < 0.05$ [23,24]. Because efavirenz itself induces *CYP2B6* (i.e., autoinduction), it is possible that rifampicin cannot increase CYP2B6 expression beyond that resulting from chronic efavirenz exposure. Efavirenz dose adjustment during rifampicin-containing TB therapy will need to be individualized-based genetic polymorphisms of *CYP2B6* enzyme, the one single important predictor of efavirenz disposition to date, or based on a combination of clinical and genetic factors. Increased understanding of the interactions between rifampicin and functional variants of efavirenz metabolizing enzymes is urgently needed to guide the management of efavirenz–rifampin pharmacokinetic interactions. In addition, future pharmacokinetic and clinical trials must include children as there is a dearth of data in this population.

5.2 Nevirapine

Current evidence suggests that nevirapine is inferior to efavirenz when given to patients on rifampicin-containing TB therapy, using standard methods of administration and in standard doses. The difference in rates of virological suppression between nevirapine and efavirenz when used along with rifampicin has ranged from 0 to 18% in different studies [87-89]. Most studies have used nevirapine in the conventional dose of 200 mg for the first 2 weeks before dose escalation. When administered in this fashion in the presence of enzyme induction, the levels achieved in the first 2 weeks have been very low, probably overcoming the low genetic barrier to resistance of HIV-1 and leading to the development of resistance mutations. The one small trial that did use nevirapine during the lead-in phase in the higher dose of 200 mg twice a day did not report better efficacy; on the other hand, adverse events were more frequent [88]. The safety and efficacy of initiating nevirapine at the higher lead-in dose is currently being tested in the CARINE 12146 trial in Mozambique [100]. Hence, there is insufficient evidence at this time to recommend a higher dose of nevirapine for patients on rifampicin, though there is a much better rationale to start with the full dose, under close monitoring. It is possible that host genetics may influence the decision to dose

adjust nevirapine during co-administration with rifampicin and this needs to be investigated in future studies.

While nevirapine may be inferior to efavirenz for patients taking rifampicin, it should still be considered the alternate drug in situations where efavirenz cannot be administered (e.g., pregnancy, adverse reactions or intolerance to efavirenz). It would be effective in a majority of patients (> 75%) and hence a life-saving intervention in the absence of other alternatives. An important point to consider is the sequence of the two treatments. For patients who are stable on nevirapine-based therapy (presumably with low or undetectable viral loads), the addition of rifampicin-containing TB treatment does not appear to result in any therapeutic penalty. Future research should examine these different scenarios in which patients get treated in order to recommend appropriate case management strategies. Studies in young children with TB and HIV should address the question of whether higher doses of nevirapine would be required in order to overcome the effect of both age and rifampicin on its metabolism. As efavirenz is contra-indicated in children under 3 years, nevirapine is the only NNRTI that can be used and safety and efficacy in this setting need to be established.

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Declaration of interest

A Kwara has previously received a research grant not related to this work and had been on the speaker's bureau of Bristol-Myers Squibb Co. G Ramachandran and S Swaminathan declare no conflict of interest.

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