Journal of Antimicrobial Chemotherapy

Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship

Nilesh B. Bhatt[1,2]*, Elisabeth Baudin[3], Bindiya Meggi[1], Carlota da Silva[3], Aurélie Barrail-Tran[4,5],
Valérie Furlan[4], Beatriz Grinsztejn[2], Maryline Bonnet[3] and Anne-Marie Taburet[4]
on behalf of the ANRS 12146/12214-CARINEMO Study Group†

[1]Instituto Nacional de Saúde, Ministry of Health, Maputo, Mozambique; [2]Instituto de Pesquisa Clínica Evandro Chagas,
Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; [3]Epicentre, Paris, France; [4]Assistance Publique Hôpitaux de Paris, Bicêtre Hospital, Hôpitaux
Universitaires Paris Sud, Clinical Pharmacy, Paris, France; [5]EA4123, Faculty of Pharmacy, University Paris Sud, Paris, France

*Corresponding author. Tel: +2588221311038; Fax: +25821311038; E-mail: nbhatt.mz@gmail.com
†Other members are listed in the Acknowledgements section.

Objectives: We describe nevirapine and efavirenz exposure on and off tuberculosis treatment and consequences for virological efficacy and tolerance in patients included in the ANRS 12146/12214-CARINEMO trial.

Methods: Participants were randomly selected to receive either nevirapine at 200 mg twice daily ($n=256$) or efavirenz at 600 mg daily ($n=270$), both combined with two nucleoside analogues. Blood samples were drawn 12 h after nevirapine or efavirenz administration, while on tuberculosis treatment and after tuberculosis treatment discontinuation. In 62 participants, samples taken 12 h after drug administration were drawn weekly for the first month of ART. Sixteen participants participated in an extensive pharmacokinetic study of nevirapine. Concentrations were compared with the therapeutic ranges of 3000–8000 ng/mL for nevirapine and 1000–4000 ng/mL for efavirenz.

Results: Nevirapine concentrations at the end of the first week of treatment (on antituberculosis drugs) did not differ from concentrations off tuberculosis treatment, but declined thereafter. Concentrations at steady-state were 4111 ng/mL at week 12 versus 6095 ng/mL at week 48 ($P<0.0001$). Nevirapine concentrations <3000 ng/mL were found to be a risk factor for virological failure. Efavirenz concentrations were higher on than off tuberculosis treatment (2700 versus 2450 ng/mL, $P<0.0001$).

Conclusions: The omission of the 2 week lead-in dose of nevirapine prevented low concentrations at treatment initiation but did not prevent the risk of virological failure. Results support the WHO recommendation to use efavirenz at 600 mg daily in patients on rifampicin-based antituberculosis therapy.

Keywords: TB/HIV coinfection, nevirapine, efavirenz, drug–drug interactions

Introduction

Tuberculosis is a leading opportunistic infection and a major cause of mortality among individuals infected with HIV. Substantial reduction of tuberculosis-related morbidity and mortality among individuals with HIV can be achieved with early initiation of ART.[1–3] Efavirenz is an NNRTI drug recommended by the WHO as a first-line ART for individuals coinfected with HIV and tuberculosis.[4] Nevirapine has been widely used in resource-limited countries with a high burden of HIV due to the convenience and affordability of generic fixed-dose combinations.

Nevirapine could be an alternative NNRTI for HIV/tuberculosis-infected individuals and may be preferred to efavirenz in some cases where efavirenz presents CNS toxicity that requires discontinuation of early treatment.[5] However, nevirapine has other risks, and studies have found that clearance of nevirapine is more sensitive than efavirenz to the potent enzyme induction caused by rifampicin; as a result nevirapine-based regimens carry greater risk of sub-therapeutic NNRTI concentrations.[6–8] This is related to differences in their biotransformation pathways, as nevirapine is metabolized by several P450 cytochromes (CYPs) (CYP2B6, CYP3A and CYP2C) and efavirenz is metabolized mainly by CYP2B6.[9,10] Reduction in nevirapine levels when combined with rifampicin-based antituberculosis therapy is more pronounced during the first 2 weeks of ART, when nevirapine is typically prescribed at half dose (200 mg) (lead-in dose) as a way of

preventing hypersensitivity.[11] There is debate over the optimal dose of efavirenz when combined with rifampicin-based antituberculosis therapy.[12] Therefore, the best dose regimen of both NNRTIs remains a subject of discussion.

The ANRS 12146-CARINEMO trial was a multicentre, open-label, randomized, non-inferiority clinical trial conducted at three health-centres in Maputo. It was the first trial conducted in Mozambique, Africa, comparing the efficacy and safety of nevirapine and efavirenz ARTs in HIV/tuberculosis-coinfected patients. In patients who were on antituberculosis therapy, nevirapine was initiated at the full dose of 200 mg twice daily and efavirenz at 600 mg daily. Although the non-inferiority of the nevirapine regimen was not shown, the results led investigators to conclude that nevirapine at full dose could be a safe alternative for patients unable to tolerate efavirenz.[13] The present analysis used data from the ANRS 12146-CARINEMO trial to describe nevirapine and efavirenz plasma concentrations during and after rifampicin-based tuberculosis treatment from early treatment initiation to the end of the first year of ART and to analyse whether these concentrations could be related to virological failure or the occurrence of side effects.

Methods

Study design and participants

Study design, eligibility criteria and study procedures for the ANRS 12146-CARINEMO trial are described elsewhere.[13] The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The research protocol was approved by two ethics committees: the Comité Nacional de Bioética para a Saúde, Mozambique (228/CNBS/2007), and the Médecins Sans Frontières Ethics Review Board, Zurich, Switzerland (approval letter dated 2 May 2007). All participants provided a signed informed consent form. In brief, 573 HIV/tuberculosis-coinfected patients were enrolled ~4–6 weeks after initiation of tuberculosis treatment to receive either nevirapine (200 mg twice daily) without a lead-in dose or efavirenz (600 mg once daily). All participants received stavudine (30 mg twice daily) and lamivudine (150 mg twice daily), and once-daily tuberculosis treatment consisting of an initial 2 month intensive phase of fixed-dose combination treatment containing 150 mg of rifampicin, 75 mg of isoniazid, 275 mg of ethambutol and 400 mg of pyrazinamide, followed by a 4 month maintenance phase of fixed-dose combination treatment containing rifampicin and isoniazid. Dosage was adjusted based on body weight in both the intensive and maintenance phases: rifampicin (10 mg/kg), isoniazid (5 mg/kg), ethambutol (15 mg/kg) and pyrazinamide (25 mg/kg).

Clinical examination and laboratory analysis were performed at enrolment, on a weekly basis during the first 8 weeks and every 4 weeks thereafter until study completion at 48 weeks. CD4+ T cell counts were obtained at screening and at weeks 24 and 48. HIV-1 RNA was determined in plasma (limit of quantification 50 copies/mL) at enrolment and at weeks 12, 24, 36 and 48. Adverse events were coded according to MedDRA and graded according to the ANRS scale (www.anrs.fr) as previously described.[13]

Pharmacokinetic studies

Pre-dose concentrations of nevirapine and morning concentrations 12 h after evening intake (C_{12}) of efavirenz were measured at week 12 (while participants were on tuberculosis drugs) and at weeks 36 and 48 (when participants were off tuberculosis drugs). C_{12} was measured at the end of week 2 of ART to monitor drug exposure in the first 100 participants enrolled in the nevirapine treatment arm. A sub-group of participants were selected to be in the early sample group for additional blood samples drawn on days 7 (week 1), 14 (week 2), 21 (week 3) and 28 (week 4) of ART to assess nevirapine and efavirenz concentrations.

An additional sub-group of participants being treated with nevirapine were selected to be in a pharmacokinetic study group. They participated in an extensive nevirapine pharmacokinetic study and had blood samples collected during a dosing interval at steady-state 4 weeks after initiation of ART (while on antituberculosis drugs) and 4 weeks after completion of antituberculosis treatment (while off antituberculosis drugs). Blood was drawn before drug intake (time 0) and after drug intake (0.5, 1, 1.5, 2, 4, 6, 8, 10 and 12 h). Plasma concentrations of nevirapine and efavirenz were assayed by validated HPLC methods with a lower limit of quantification (LLOQ) of 25 and 50 ng/mL, respectively.[14,15] Plasma concentrations were compared with previously described therapeutic ranges, which are between 3000 and 8000 ng/mL for nevirapine[16] and between 1000 and 4000 ng/mL for efavirenz.[17]

A non-compartmental method was used to estimate nevirapine pharmacokinetic parameters (WinNonlin software, Pharsight Corporation, Mountain View, CA, USA). Plasma C_{max}, time to plasma peak concentration (T_{max}) and plasma C_{min} were the observed values. The AUC during the 12 h dosing intervals at steady-state (AUC_{0-12}) was estimated using the linear up–log down trapezoidal method. Two-sided 90% CIs were constructed for the ratios of the geometric mean values (GMR parameters) with versus without tuberculosis treatment of AUC_{0-12}, C_{min} and C_{max}.

Statistical analysis

Unless otherwise indicated, descriptive data were reported using the median and IQR. Nevirapine or efavirenz plasma concentrations were excluded from analysis in the following cases: treatment switch in patients with adverse event or pregnancy; patients still on antituberculosis drugs at weeks 36 and 48; and blood samples collected outside the range of 11.5–15.5 h after the last drug intake. Concentrations below the LLOQ were included as LLOQ/2 for analysis. As normality of drug concentrations was not achieved after log transformation, plasma concentrations of NNRTIs on and off antituberculosis therapy were compared by the Wilcoxon signed-rank test. Mixed models were used to analyse the change in log-transformed concentrations, with time being a fixed effect in the model. Logistic regression was used to identify predictors of virological failure (HIV1 RNA ≥50 copies/mL) at week 48 and binary safety outcomes of interest (occurrence of central neurological adverse event and hepatitis grade 2 or higher). Factors with an association with a P value <0.2 were used for multivariate analyses.

A sensitivity analysis was performed for predictors of virological failure after excluding NNRTI plasma concentration below the LLOQ used as a surrogate marker of poor treatment adherence. All statistical analyses were conducted with StataSE™ software (2005, Release 12.1; StataCorp, College Station, TX, USA). The level of statistical significance was set at 0.05.

Results

Participant characteristics

Of 573 patients enrolled in the ANRS 12146-CARINEMO trial, 526 had at least one 12 h (13.5 ± 2 h) post-dose concentration measurement available for nevirapine or efavirenz at weeks 12, 36 and 48 of study follow-up. One hundred and fourteen participants on nevirapine had an available concentration measure at week 2. Sixty-two patients were enrolled in the nevirapine and efavirenz early sample group. Sixteen patients (eight males) participated in the two periods of the extensive nevirapine pharmacokinetic study. Baseline characteristics of these patients are shown in Table 1. Participant age and weight at enrolment were 33 years and 52.1 kg, and 57% were male. CD4+ T cell count was 92/mm^3 and HIV-1 RNA was 5.6 $\log_{10}$ copies/mL.

Table 1. Demographic, clinical and laboratory characteristics of patients at baseline[a]

| Characteristic | Entire study population[b] | | Early samples group | | Extensive PK group |
	NVP group ($n=256$)	EFV group ($n=270$)	NVP group ($n=32$)	EFV group ($n=30$)	NVP group ($n=16$)
Age, years	33 (29–41)	33 (28–40)	36 (31–42)	34 (29–38)	36 (31–47)
Sex, male	142 (55.5)	160 (59.3)	20 (62.5)	17 (56.7)	8/16 (50.0)
Weight, kg	52.0 (46.6–57.5)	52.3 (47.2–58.7)	51.9 (46.0–58.9)	50.9 (47.2–55.1)	52.6 (46.6–55.6)
BMI, kg/m^2	18.7 (17.2–20.3)	18.9 (17.6–20.3)	19.1 (16.9–20.4)	18.5 (16.9–20.1)	18.3 (17.0–19.5)
Haemoglobin, g/dL	9.4 (8.5–10.3)	9.4 (8.3–10.4)	9.0 (8.1–9.8)	9.4 (8.3–10.4)	9.4 (7.9–10.3)
ALT, IU/L	22.6 (14.7–36.8)	23.0 (15.6–37.7)	26.4 (12.8–44.4)	28.7 (22.1–38.3)	13.0 (9.0–20.0)
Total bilirubin, mg/dL	0.4 (0.3–0.6)	0.5 (0.3–0.6)	0.4 (0.3–0.5)	0.5 (0.3–0.7)	0.8 (0.7–0.9)
CD4+ T cell count, cells/mm^3	94 (44–152)	86 (44–144)	106 (47–153)	91 (69–127)	86 (57–169)
HIV-1 RNA, $\log_{10}$ copies/mL	5.7 (5.1–6.0)	5.5 (5.2–6.1)	5.7 (5.3–5.9)	5.4 (5.2–6.0)	5.5 (5.2–5.7)
HBsAg, reactive	53/255 (20.8)	57/266 (21.4)	1/32 (3.1)	4/30 (13.3)	1 (6.3)
HCV antibody, reactive	4 (1.6)	5 (1.9)	1 (3.1)	1 (3.3)	1 (6.3)
Pulmonary tuberculosis	202 (78.9)	203 (75.2)	29 (90.6)	20 (66.7)	11 (68.8)
Smear-positive pulmonary tuberculosis	93/202 (46.0)	111/203 (54.7)	7/29 (24.1)	16/20 (80.0)	9/11 (81.8)

NVP, nevirapine; EFV, efavirenz; HCV, hepatitis C virus; PK, pharmacokinetic.
[a]Data are median (IQR), n (%) or n/N (%).
[b]At least one 12 h post-dosing concentration available for nevirapine or efavirenz at weeks 12, 36 and 48 of study follow-up.
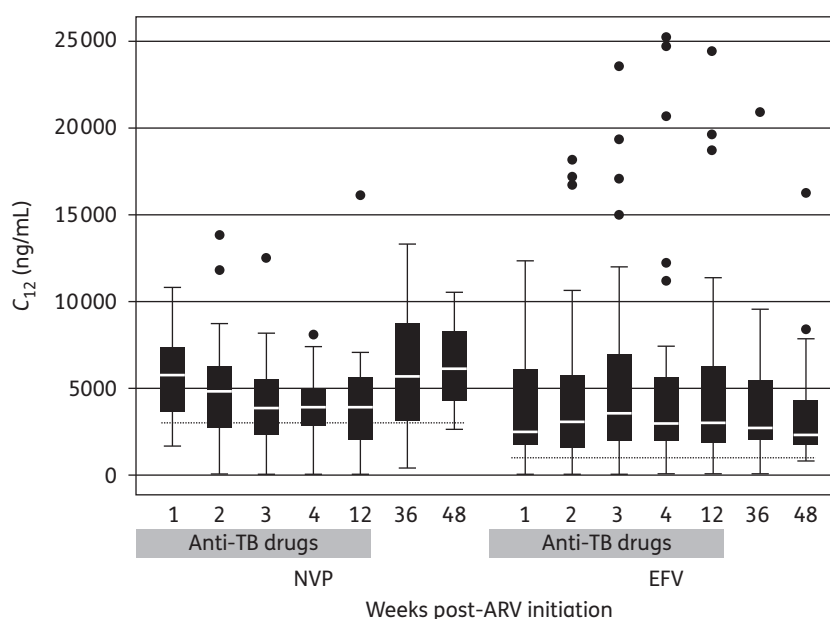

Figure 1. Plasma trough concentrations 12 h after dosing (C_{12}) of nevirapine in 32 patients and efavirenz in 30 patients during 48 weeks of ART. The white horizontal line shows the median; IQRs are shown by boxes; the whiskers show minimum and maximum without outliers; outliers are indicated by circles. Dotted lines are the lower targets of the therapeutic ranges (3000 and 1000 ng/mL for nevirapine and efavirenz, respectively). EFV, efavirenz; NVP, nevirapine; ARV, antiretroviral; TB, tuberculosis.

The baseline characteristics of participants in each subgroup were similar to the characteristics of all participants.

Nevirapine and efavirenz exposure at treatment initiation (early sample group)

Thirty-two patients were on nevirapine and 30 patients were on efavirenz. During co-administration, nevirapine concentrations decreased over time from week 1 (5721 ng/mL) to week 12 (4003 ng/mL) ($P=0.001$) and increased after completion of antituberculosis therapy (6271 ng/mL) ($P<0.001$) (Figure 1). Nevirapine concentrations remained steady from week 3 (3844 ng/mL) to week 12 when combined with antituberculosis therapy. Conversely, there was a non-significant increase in efavirenz concentration from week 1 (2509 ng/mL) to week 3 (3555 ng/mL) and week 12 (2994 ng/mL), then a significant

decrease after antituberculosis therapy discontinuation at week 48 (2329 ng/mL) when compared with week 12 ($P < 0.001$). Importantly, when nevirapine was initiated at full dose, plasma concentrations 1 week after starting nevirapine during co-administration with antituberculosis therapy were not significantly different from those after completion of antituberculosis therapy at week 48. Similar findings were obtained with efavirenz.

Nevirapine and efavirenz exposure on and off antituberculosis therapy

Concentrations on and off antituberculosis therapy in the whole population are presented in Table 2. Nevirapine and efavirenz concentrations were not different when measured at weeks 36 and 48 after tuberculosis therapy discontinuation, and concentrations at week 48 were therefore considered for further comparisons. Nevirapine plasma concentrations at weeks 2 and 12 were significantly lower than at week 48 ($P = 0.0003$ and $P < 0.0001$, respectively). Importantly, 22% and 25% of patients had concentrations <3000 ng/mL at weeks 2 and 12 versus 11% at week 48. In the 16 patients who participated in the extensive nevirapine pharmacokinetic study, nevirapine concentrations were lower while on antituberculosis drugs than after discontinuation of antituberculosis drugs (Figure S1, available as Supplementary data at *JAC* Online). Nevirapine AUC_{0-12} and C_{min} were reduced by 13% and 17% respectively, but the 90% CIs of GMR parameters failed to lie within the 0.80–1.25 bioequivalence range, as indicated in Table 3. Efavirenz concentrations decreased slightly but significantly after tuberculosis drug discontinuation between weeks 12 and 48 ($P < 0.0001$). Efavirenz concentrations were <1000 ng/mL

in 9% of participants at weeks 12 and 48. At week 12, 5.1% of the patients had efavirenz concentrations <50 ng/mL (limit of detection) and were possibly not fully adherent, and only 3.8% had concentrations ≥50 and <1000 ng/mL. Notably, ~25% of the participants had concentrations of efavirenz and nevirapine above the therapeutic range when off antituberculosis drugs, and the proportion was as high as 37% when efavirenz was combined with antituberculosis drugs.

Concentration–efficacy relationship

Plasma HIV-1 RNA was <50 copies/mL at weeks 12, 24 and 48 in 77.2% (156/202), 78.3% (155/198) and 77.3% (157/203) of the participants on nevirapine and 85.0% (170/200), 85.5% (171/200) and 88.2% (164/186) of the participants on efavirenz, respectively. Analysis within each treatment arm demonstrated that, in the nevirapine arm, having reactive hepatitis B surface antigen (HBsAg), being a male and having C_{12} <3000 ng/mL at week 12 were independently associated with the risk of virological failure, as shown in Table 4. Interestingly, such association was unchanged when concentrations below the LLOQ were removed. The only predictor of virological failure in the efavirenz arm was having concentrations <1000 ng/mL at week 12 (Table 4). The association was no longer significant after excluding concentrations below the LLOQ.

Safety issues related to concentrations

Fourteen participants on nevirapine and two participants on efavirenz switched treatment because of adverse events. There were 11 cases of hepatitis (for 7 participants concentrations ranged

Table 2. Concentrations of nevirapine and efavirenz at weeks 2 and 12 (on tuberculosis drugs) and at weeks 36 and 48 (off tuberculosis drugs) measured 12 h after dosing (trough concentrations for nevirapine and mid-dose concentrations for efavirenz)

	Time (weeks)			
	2	12	36	48
Nevirapine				
no. of patients	114	225	218	205
plasma concentration, ng/mL				
median (IQR)	4759 (3201–7327)	4111 (2970–5534)	5970 (4261–7898)	6095 (4521–8504)*,**
trough				
<25	3 (2.6)	6 (2.7)	6 (2.8)	3 (1.5)
≥25 to <3000	22 (19.3)	51 (22.7)	15 (6.9)	20 (9.8)
≥3000 to <8000	68 (59.6)	148 (65.8)	144 (66.1)	125 (61.0)
≥8000	21 (18.4)	20 (8.9)	53 (24.3)	57 (27.8)
Efavirenz				
no. of patients	—	235	199	189
plasma concentration, ng/mL				
median (IQR)	—	2700 (1701–6965)	2604 (1742–4412)	2450 (1742–4086)**
trough				
<50	—	12 (5.1)	6 (3.0)	5 (2.6)
≥50 to <1000	—	9 (3.8)	9 (4.5)	12 (6.3)
≥1000 to <4000	—	127 (54.0)	131 (65.8)	122 (64.6)
≥4000	—	87 (37.0)	53 (26.6)	50 (26.5)

*Week 2 versus week 48, $P = 0.0003$.
**Week 12 versus week 48, $P < 0.0001$.

Table 3. Nevirapine pharmacokinetic parameters (16 patients in the nevirapine treatment group)[a]

Time	C_{min} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-12} (ng·h/mL)
With antituberculosis drugs	4513 (2527–8797)	6561 (4744–10311)	2.0 (1.5–4.2)	66743 (46817–114072)
Alone	5025 (3557–10662)	7283 (5246–13637)	1.5 (1.0–4.0)	71332 (53440–146908)
GMR[b] (90% CI)	0.83 (0.71–0.97)	0.89 (0.79–1.00)		0.87 (0.77–0.99)

[a]Data are expressed as median (range).
[b]Ratio of geometric means for parameters with rifampicin to those without rifampicin.

Table 4. Factors associated with virological failure after 48 weeks of ART among participants in the nevirapine and efavirenz treatment groups

	Treatment outcome at week 48, proportion of patients (%)		Univariate analysis		Multivariate analysis	
Possible risk factors	success	failure	OR (95% CI)	P value	OR (95% CI)	P value
Nevirapine						
C_{12} <3000 ng/mL at week 12	30/156 (19.2)	20/46 (43.5)	3.23 (1.59–6.54)	0.001	3.44 (1.65–7.17)	0.001
male	87/175 (49.7)	37/53 (69.8)	2.34 (1.21–4.51)	0.011	2.18 (1.03–4.61)	0.036
weight ≤50 kg	70/175 (40.0)	20/53 (37.7)	0.92 (0.95–3.29)	0.767	—	—
HBsAg, reactive	33/175 (18.9)	15/53 (28.3)	1.69 (0.83–3.42)	0.148	2.51 (1.15–5.51)	0.035
baseline CD4+ cell count <50 cells/mm³	48/175 (27.4)	13/53 (24.5)	0.86 (0.42–1.75)	0.674	—	—
HIV-1 RNA viral load at baseline ≥5.5 log	77/175 (44.0)	17/53 (32.1)	1.66 (0.87–3.19)	0.118	—	NS
Efavirenz						
C_{12} <1000 ng/mL at week 12	7/170 (4.1)	5/30 (16.7)	4.70 (1.37–15.81)	0.020	4.70 (1.37–15.81)	0.020
male	109/198 (55.1)	18/33 (54.6)	0.98 (0.47–2.05)	0.957	—	—
weight ≤50 kg	77/198 (38.9)	21/33 (63.6)	0.90 (0.42–1.93)	0.782	—	—
HBsAg, reactive	46/198 (23.2)	4/33 (12.1)	0.44 (0.15–1.33)	0.116	—	NS
baseline CD4+ cell count <50 cells/mm³	51/198 (25.8)	12/33 (36.4)	1.65 (0.76–3.58)	0.216	—	—
HIV-1 RNA viral load at baseline ≥5.5 log	101/198 (51.0)	11/33 (33.3)	2.08 (0.96–4.52)	0.058	—	NS

NS, not significant.

from 3417 to 30321 ng/mL) and 3 of rashes (concentrations not available) in the nevirapine arm and two acute psychiatric disorders in the efavirenz arm (786 and 5863 ng/mL). There was no significant association between the occurrence of grade 2 or higher CNS adverse events reported within the first 12 weeks of ART in six participants on efavirenz and efavirenz concentrations >4000 ng/mL at week 12 ($P=0.293$). Among the factors analysed for association with the occurrence of hepatitis (increase in ALT) of grade 2 or higher, which occurred in 32 patients, only efavirenz concentration during the same time period (OR 5.25, 95% CI 2.1–13.2, $P=0.0002$) was significant.

Discussion

In this study we describe nevirapine and efavirenz exposure from initiation of ART in patients coinfected with HIV and tuberculosis on antituberculosis therapy until 6 months after completion of antituberculosis treatment in a large cohort of participants. We have demonstrated marked differences in exposure to two NNRTIs when combined with rifampicin/isoniazid-based antituberculosis therapy in an African population. Metabolism of nevirapine, but not of efavirenz, is induced by this concomitant treatment. However, plasma concentrations of both nevirapine (omitting the lead-in dose) and efavirenz at the end of the first week of ART were in the same range as they were after discontinuation of antituberculosis drugs, which is of importance for optimal antiretroviral efficacy at ART initiation. Nevirapine concentrations declined thereafter, reaching a steady-state from week 3 to the end of antituberculosis therapy. Our extensive pharmacokinetic study supports these pre-dose concentration findings. Despite such a moderate decrease, 25% of the participants on nevirapine-based ART had concentrations <3000 ng/mL on antituberculosis therapy (week 12) versus 11% after antituberculosis therapy discontinuation. Such a decrease was a predictor of virological failure.

Nevirapine concentrations reported here differ from those in previous studies, in which all participants received the standard lead-in dose and as many as 59%–79% of HIV/tuberculosis-coinfected patients had low pre-dose concentrations during the first 2 weeks of rifampicin-based antituberculosis therapy.[18,19] Our results support our study design, in which a full dose of nevirapine was given at initiation of treatment to avoid the first 2 week period of treatment with low nevirapine concentrations. Concentrations measured at the end of the first 2 weeks of nevirapine treatment at 200 mg twice daily were slightly lower

(4759 ng/mL) than that reported in the study of Avihingsanon *et al.*[18] (5300 ng/mL), in which 16 Thai patients included in the 600 mg nevirapine daily dose group received a lead-in dose of 200 mg twice daily, but higher than that reported by Lamorde *et al.*[20] in 9 Ugandan adults (2920 ng/mL). Those two studies are limited by the small number of patients included and the absence of a relationship with virological response. The study conducted in Thai patients was prematurely discontinued because the lead-in strategy with nevirapine at 200 mg twice daily was associated with a high rate of nevirapine hypersensitivity.[18] In our study, treatment tolerance was good and did not differ between the nevirapine and efavirenz groups.[13] The nevirapine concentrations that we observed at steady-state of induction were similar to those reported in one study conducted in Africa[21] but lower than those in other studies conducted in different countries.[19,22] Differences in patients' weight and pharmacogenetics could explain the differences in nevirapine exposure between African and South-East Asian populations. This decrease in nevirapine concentrations is surprising as it is generally accepted that the enzyme induction process is maximal after 10–15 days of drug-inducer administration. Nevirapine metabolism involves different CYP enzymes, which may be induced differently by rifampicin and nevirapine. Interestingly, the autoinduction process of efavirenz was demonstrated to continue up to 16 weeks of therapy; whether such a mechanism could occur for nevirapine combined with rifampicin remains to be investigated.[23]

Recent studies, mainly conducted in sub-Saharan Africa, showed that, at least in some sub-groups of patients, efavirenz concentrations were higher on than off antituberculosis therapy.[24,25] Bertrand *et al.*[26] recently demonstrated that the efavirenz–antituberculosis drug interaction depends on *CYP2B6* and *NAT2* genetic polymorphism, suggesting that isoniazid, which has inhibiting properties with respect to some non-CYP2B6 biotransformation pathways, could play a role, counterbalancing the inducing properties of rifampicin. There was no significant association between the occurrence of grade 2 or higher CNS adverse events reported within the first 12 weeks of ART in six participants on efavirenz and efavirenz concentrations >4000 ng/mL at week 12 ($P = 0.293$). Among the factors analysed for association with the occurrence of hepatitis (increase in ALT) of grade 2 or higher, which occurred in 32 patients, only efavirenz concentration >4000 ng/mL during the same time period (OR 5.25, 95% CI 2.1–13.2, $P = 0.0002$) was significant.

Importantly, the association between low nevirapine concentrations at week 12 and virological failure at 48 weeks was not affected by the exclusion of concentrations below the LLOQ (used as surrogate marker of poor adherence) from the analysis, which was not the case for efavirenz. This finding supports the main results of the CARINEMO trial, which failed to show the non-inferiority of nevirapine compared with efavirenz, and demonstrates the different drug–drug interaction mechanism, which explains, at least in part, the difference in virological response between the two antiretroviral regimens.[13]

Liver injury due to drug usage was reported in African patients with high efavirenz concentrations when efavirenz was combined with antituberculosis therapy.[27,28] In contrast to some studies,[17,29] other studies and our study failed to correlate the few recorded CNS adverse effects with high efavirenz concentrations.[25]

Our study had some limitations. First, C_{12} and not pre-dose trough concentrations were collected as a surrogate of efavirenz exposure. However, such approximation is acceptable as efavirenz has an elimination half-life longer than the 24 h dosing interval, which would minimize fluctuations between peak and trough concentrations.[30] Second, it is now well demonstrated that nevirapine and efavirenz concentrations are highly dependent on *CYP2B6* genetic polymorphism.[6,31–35] Indeed, the frequency of the *CYP2B6* loss-of-function variants was reported to be higher in people of African than in those of European descent.[6,26,32,33] The frequency of the *CYP2B6516T* loss-of-function allele in the Mozambican population is as high as 40%[36] and explains, at least in part, the high concentrations observed in our study. The exact mechanism of the nevirapine–antituberculosis drug interaction warrants further study, and pharmacogenetics could be a useful tool. Third, none of the metabolites of nevirapine or efavirenz was quantified. Several nevirapine metabolites involving different CYP pathways were identified. 8-Hydroxy efavirenz is the main CYP2B6-mediated metabolite of efavirenz. Metabolite concentrations in plasma were found to be below those of the parent drug and therefore their contribution to nevirapine or efavirenz efficacy is unlikely.[23,37]

In conclusion, this pharmacokinetic study conducted in 526 HIV/tuberculosis-coinfected patients adds new evidence on nevirapine or efavirenz exposure and drug–drug interaction when combined with rifampicin- and isoniazid-based antituberculosis treatments. Our efavirenz data are in agreement with most recent studies and support the WHO recommendation. Omitting the 200 mg once daily dosage for the first 2 weeks of nevirapine treatment allows concentrations to be within the therapeutic range at initiation of treatment when combined with antituberculosis drugs, and this drug regimen was well tolerated. However, such a strategy does not avoid a decrease in nevirapine concentrations after the first 2 weeks of treatment and supports the results of the main trial, which recommends using efavirenz whenever possible.

Other members of the ANRS 12146/12214-CARINEMO Study Group

Ilesh V. Jani MD PhD, Nádia Sitoe BSc, Adolfo Vubil BSc MSc, Maria Nhadzombo, Fernando Sitoe, Delário Nhumaio, Odete Bule and Kátia Cossa (Instituto Nacional de Saúde, Mozambique); Rui Bastos MD

and Elizabete Nunes MD (Hospital Central, Maputo, Mozambique); Paula Samo Gudo MD MPH (National Tuberculosis Control Program, Mozambique); Josué Lima MD and Mie Okamura (International Center for AIDS Care and Treatment Programs, Mozambique); Laura Ciaffi MD, Agnès Sobry MD, Mariano Lugli and Bruno Lab (Médecins Sans Frontières– Switzerland, Mozambique); Avertino Barreto MD (Mozambique National AIDS Service Organisation, Mozambique); Christophe Michon MD (Regional Hospital, Annecy, France); Alexandra Calmy MD PhD (Médecins Sans Frontières; Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland); Alpha Diallo (ANRS pharmacovigilance unit, France); and Christine Rouzioux PharmD PhD (Paris-Descartes University, EA3620, Sorbonne Paris Cite, APHP, Necker Hospital, Paris, France).

Funding

Transparency declarations

None to declare.

Author contributions

M. B. and A.-M. T. conceived and designed the study. N. B. B. and M. B. implemented and led the study. E. B. coordinated data management and performed the statistical analysis. E. B., C. da S., B. M., V. F., A. B.-T. and B. G. critically revised the study design and contributed to the interpretation of results. C. da S., B. M., V. F. and A. B.-T. coordinated the laboratory analyses and supervised efavirenz and nevirapine assays in accordance with good laboratory practice. C. da S. supported the implementation and running of the study. N. B. B. and A.-M. T. wrote and prepared the manuscript. All authors reviewed and approved the final version of the manuscript.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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