Nevirapine or efavirenz for tuberculosis and HIV co-infected patients: exposure and virological failure relationship

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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.4 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 CYP2B6.8,9 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. There is debate over the optimal dose of efavirenz when combined with rifampicin-based antituberculosis therapy. 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 healthcare 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. 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. 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 participants provided a signed informed consent form. In brief, 573 participants were enrolled in the ANRS 12146-CARINEMO trial are described elsewhere. 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 participants were enrolled in the ANRS 12146-CARINEMO trial are described elsewhere. 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.

Participants were on tuberculosis drugs at week 1 of ART and to analyse whether these concentrations could be related to virological failure or the occurrence of side effects.

Pharmacokinetic studies

Pre-dose concentrations of nevirapine and morning concentrations 12 h after evening intake (Cmin) 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). Cmax 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. Plasma concentrations were compared with previously described therapeutic ranges, which are between 3000 and 8000 ng/mL for nevirapine and between 1000 and 4000 ng/mL for efavirenz.

A non-comparative method was used to estimate nevirapine pharmacokinetic parameters (WinNonlin software, Pharsight Corporation, Mountain View, CA, USA). Plasma Cmax time to plasma peak concentration (Tmax) and plasma Cmin were the observed values. The AUC during the 12 h dosing intervals at steady-state (AUC0–12) 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 AUC0–12, Cmin and Cmax.

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/mm³ and HIV-1 RNA was 5.6 log10 copies/mL.
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 over time from week 1 (5721 ng/mL) to week 12 (4003 ng/mL) \((P=0.001)\).

**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.

**Table 1.** Demographic, clinical and laboratory characteristics of patients at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire study populationb</th>
<th>Early samples group</th>
<th>Extensive PK group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NVP group (n=256)</td>
<td>EFV group (n=270)</td>
<td>NVP group (n=32)</td>
</tr>
<tr>
<td>Age, years</td>
<td>33 (29–41)</td>
<td>33 (28–40)</td>
<td>36 (31–42)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>142 (55.5)</td>
<td>160 (59.3)</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>52.0 (46.6–57.5)</td>
<td>52.3 (47.2–58.7)</td>
<td>51.9 (46.0–58.9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.7 (17.2–20.3)</td>
<td>18.9 (17.6–20.3)</td>
<td>19.1 (16.9–20.4)</td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>9.4 (8.5–10.3)</td>
<td>9.4 (8.3–10.4)</td>
<td>9.0 (8.1–9.8)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>22.6 (14.7–36.8)</td>
<td>23.0 (15.6–37.7)</td>
<td>26.4 (12.8–44.4)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.4 (0.3–0.6)</td>
<td>0.5 (0.3–0.6)</td>
<td>0.4 (0.3–0.5)</td>
</tr>
<tr>
<td>CD4+ T cell count, cells/mm³</td>
<td>94 (44–152)</td>
<td>86 (44–144)</td>
<td>106 (47–153)</td>
</tr>
<tr>
<td>HIV-1 RNA, log₁₀ copies/mL</td>
<td>5.7 (5.1–6.0)</td>
<td>5.5 (5.2–6.1)</td>
<td>5.7 (5.3–5.9)</td>
</tr>
<tr>
<td>HBsAg, reactive</td>
<td>53/255 (20.8)</td>
<td>57/266 (21.4)</td>
<td>1/32 (3.1)</td>
</tr>
<tr>
<td>HCV antibody, reactive</td>
<td>4 (1.6)</td>
<td>5 (1.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>202 (78.9)</td>
<td>203 (75.2)</td>
<td>29 (90.6)</td>
</tr>
</tbody>
</table>

NVP, nevirapine; EFV, efavirenz; HCV, hepatitis C virus; PK, pharmacokinetic.

aData are median (IQR), \(n\) (%), or \(n/N\) (%).

bAt least one 12 h post-dosing concentration available for nevirapine or efavirenz at weeks 12, 36 and 48 of study follow-up.
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 0–1 and Cmin 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). Importantly, ~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 C12 ≥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 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 patients 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.

### 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)

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

*Week 2 versus week 48, P = 0.0003.
**Week 12 versus week 48, P < 0.0001.
Nevirapine and efavirenz with TB drugs

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 greater than 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 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 greater than 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.

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

<table>
<thead>
<tr>
<th>Time</th>
<th>$C_{\min}$ (ng/mL)</th>
<th>$C_{\max}$ (ng/mL)</th>
<th>$T_{\max}$ (h)</th>
<th>AUC$_{0-12}$ (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With antituberculosis drugs</td>
<td>4513 (2527–8797)</td>
<td>6561 (4744–10311)</td>
<td>2.0 (1.5–4.2)</td>
<td>66743 (46817–114072)</td>
</tr>
<tr>
<td>Alone</td>
<td>5025 (3557–10662)</td>
<td>7283 (5246–13637)</td>
<td>1.5 (1.0–4.0)</td>
<td>71332 (53440–146908)</td>
</tr>
<tr>
<td>GMR$^b$ (90% CI)</td>
<td>0.83 (0.71–0.97)</td>
<td>0.89 (0.79–1.00)</td>
<td>0.87 (0.77–0.99)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$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

<table>
<thead>
<tr>
<th>Possible risk factors</th>
<th>Treatment outcome at week 48, proportion of patients (%)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>success</td>
<td>failure</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{12}, &lt;3000$ ng/mL at week 12</td>
<td>30/156 (19.2)</td>
<td>20/46 (43.5)</td>
<td>3.23 (1.59–6.54)</td>
</tr>
<tr>
<td>male</td>
<td>87/175 (49.7)</td>
<td>37/53 (69.8)</td>
<td>2.34 (1.21–4.51)</td>
</tr>
<tr>
<td>weight $\leq$50 kg</td>
<td>70/175 (40.0)</td>
<td>20/53 (37.7)</td>
<td>0.92 (0.95–3.29)</td>
</tr>
<tr>
<td>HBsAg, reactive</td>
<td>33/175 (18.9)</td>
<td>15/53 (28.3)</td>
<td>1.69 (0.83–3.42)</td>
</tr>
<tr>
<td>baseline CD4+ cell count $&lt;50$ cells/mm$^3$</td>
<td>48/175 (27.4)</td>
<td>13/53 (24.5)</td>
<td>0.86 (0.42–1.75)</td>
</tr>
<tr>
<td>HIV-1 RNA viral load at baseline $\geq5.5$ log</td>
<td>77/175 (44.0)</td>
<td>17/53 (32.1)</td>
<td>1.66 (0.87–3.19)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{12}, &lt;1000$ ng/mL at week 12</td>
<td>7/170 (4.1)</td>
<td>5/30 (16.7)</td>
<td>4.70 (1.37–15.81)</td>
</tr>
<tr>
<td>male</td>
<td>109/198 (55.1)</td>
<td>18/33 (54.6)</td>
<td>0.98 (0.47–2.05)</td>
</tr>
<tr>
<td>weight $\leq$50 kg</td>
<td>77/198 (38.9)</td>
<td>21/33 (63.6)</td>
<td>0.90 (0.42–1.93)</td>
</tr>
<tr>
<td>HBsAg, reactive</td>
<td>46/198 (23.2)</td>
<td>4/33 (12.1)</td>
<td>0.44 (0.15–1.33)</td>
</tr>
<tr>
<td>baseline CD4+ cell count $&lt;50$ cells/mm$^3$</td>
<td>51/198 (25.8)</td>
<td>12/33 (36.4)</td>
<td>1.65 (0.76–3.58)</td>
</tr>
<tr>
<td>HIV-1 RNA viral load at baseline $\geq5.5$ log</td>
<td>101/198 (51.0)</td>
<td>11/33 (33.3)</td>
<td>2.08 (0.96–4.52)</td>
</tr>
</tbody>
</table>

NS, not significant.
between the two antiretroviral regimens.13
strates the different drug–drug interaction mechanism, which
inferiority of nevirapine compared with efavirenz, and demon-
main results of the CARINEMO trial, which failed to show the non-
which was not the case for efavirenz. This finding supports the
(trations at week 12 and virological failure at 48 weeks was not
concentration
grade 2 or higher, which occurred in 32 patients, only efavirenz
for association with the occurrence of hepatitis (increase in ALT) of
P
5.25, 95% CI 2.1–13.2,
ART in six participants on efavirenz and efavirenz concentrations
higher CNS adverse events reported within the first 12 weeks of
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, counter-
balancing 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 concen-
trations 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 demonstr-
strates 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.22,28 In contrast to some studies,27,29
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, C12 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 nevir-
apine 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 inter-
action warrants further study, and pharmacogenetics could be
a useful tool. Third, none of the metabolites of nevirapine or efa-
virenz 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 efa-
virenz efficacy is unlikely.23,37

In conclusion, this pharmacokinetic study conducted in 526
HIV/tuberculosis-coinfected patients adds new evidence on nevir-
apine 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 treat-
ment 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.

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Bhatt et al.
Nevirapine and efavirenz with TB drugs

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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/).

References


