

## Nevirapine pharmacokinetics when initiated at 200 mg or 400 mg daily in HIV-1 and tuberculosis co-infected Ugandan adults on rifampicin

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**Background:** Rifampicin lowers nevirapine plasma concentrations by inducing cytochrome P450. However, few data are available on this interaction during the lead-in period of nevirapine treatment.

**Methods:** Eighteen HIV-1/tuberculosis co-infected adults receiving rifampicin daily as part of anti-tuberculosis therapy were evenly randomized to nevirapine initiation by dose escalation (NVP200) or nevirapine initiation at 200 mg twice daily (NVP400). Subjects underwent 12 h intensive pharmacokinetic sampling on Days 7, 14 and 21 of nevirapine treatment. A minimum effective concentration (MEC) of 3000 ng/mL was used to interpret nevirapine concentrations 12 h after dosing ( $C_{12}$ ). Trial registration number: NCT00617643 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

**Results:** Day 7 geometric mean nevirapine  $C_{12}$  [90% confidence interval (CI)] was 1504 (1127–2115) ng/mL and 3148 (2451–4687) ng/mL in the NVP200 and NVP400 arms, respectively ( $P < 0.01$ ). Nevirapine  $C_{12}$  on Days 14 and 21 was similar. On Day 21, nevirapine concentration in 64% of patients was below the MEC. On Day 7, geometric mean area under the curve ( $AUC_{0-12}$ ) was lower in the NVP200 arm, 25223 (90% CI, 21978–29695) ng·h/mL versus 43195 (35607–57035) ng·h/mL in the NVP400 arm ( $P < 0.01$ ). Similarly, on Day 14, nevirapine  $AUC_{0-12}$  was lower in the NVP200 arm 23668 (18253–32218) ng·h/mL versus the NVP400 arm 44918 (36264–62769) ng·h/mL ( $P = 0.03$ ).

**Conclusions:** In co-treated patients, nevirapine concentrations were below the MEC during initiation with dose escalation. Nevirapine initiation at the maintenance dose of 200 mg twice daily is preferred. Sub-therapeutic nevirapine concentrations were common at Day 21 with either regimen. Evaluation of higher nevirapine maintenance doses may be considered.

**Keywords:** PK, antimycobacterial agents, HIV antiviral pharmacology

### Background

In resource-poor countries, HIV and tuberculosis (TB) co-infection results in significant morbidity and mortality. Co-treatment is recommended by the WHO;<sup>1</sup> however, drug interactions are common between anti-TB regimens containing rifampicin and antiretroviral drugs. In these settings, rifampicin is a key drug for TB treatment because alternative rifamycins

are more expensive and usually not available in public TB control programmes. Similarly, for HIV treatment, only a limited number of antiretroviral drugs are routinely used. The problems arising from limited drug options are compounded by the wide use of fixed-dose combination (FDC) formulations for both diseases. When these formulations are used, drug substitutions are not possible and dose adjustments are usually difficult.

In Uganda, nevirapine is widely used as a component of first-line regimens for HIV-1 infection. Nevirapine undergoes hepatic metabolism by cytochrome P450 (CYP) predominantly by the 3A4 and 2B6 isoforms.<sup>2</sup> Importantly, nevirapine enhances its own metabolism (autoinduction) and the maximal effect of this induction is established after 2 weeks. At initiation, nevirapine concentrations in plasma increase and subsequently decline to steady-state levels as a result of increased hepatic metabolism. In clinical practice, half the dose of nevirapine is administered during the initial 2 weeks of treatment with an increase to the full maintenance dose from the 15th day (dose escalation). This strategy reduces the frequency of rash; elevated nevirapine concentrations in plasma have been associated with rash.<sup>2</sup>

Rifampicin potently induces CYP3A4 and CYP2B6 resulting in reduced nevirapine concentrations in plasma. Of concern, two studies reported sub-therapeutic nevirapine concentrations during dose escalation in co-treated patients.<sup>3,4</sup> This study compared nevirapine plasma concentrations when nevirapine was initiated by dose escalation (NVP200) or with the full maintenance dose (NVP400) in HIV-1/TB co-infected Ugandan patients on rifampicin.

## Methods

### Ethics

Ethical approval was granted by the National HIV/AIDS Research Committee, Kampala (ARC 055). The study was registered on www.clinicaltrials.gov (NCT00617643). Written informed consent was obtained from all participants prior to enrolment.

### Participants

The study enrolled HIV-1/TB co-infected patients receiving daily treatment with rifampicin, pyrazinamide, ethambutol plus isoniazid. Patients were excluded if they were anaemic (haemoglobin <8 g/dL), had hepatic or renal impairment, or used medicines known or suspected to interfere with CYP metabolism.

### Study design

This was a two-arm longitudinal intensive pharmacokinetic study. Eighteen patients were randomized to two study arms (nine each) using computer-generated numbers. In the NVP200 arm, patients commenced nevirapine by dose escalation. In the first 14 days of nevirapine treatment, patients received one tablet of an FDC containing nevirapine 200 mg, lamivudine 150 mg plus stavudine 30 mg (Triomune-30; Cipla Limited, Mumbai, India) in the morning and one tablet of lamivudine 150 mg and one capsule of stavudine 30 mg in the evenings, with morning and evening doses administered 12 h apart. From Day 15, patients received one tablet of Triomune-30 twice daily. Patients in the NVP400 arm were initiated and maintained on one tablet of Triomune-30 twice daily.

Adverse events were evaluated using the National Institutes of Health Division of AIDS table (2004) for grading the severity of adverse events. Haematology, liver transaminases and serum biochemistry were performed at screening, and Days 7, 14 and 21. Patients were discharged a minimum of 2 weeks after completing pharmacokinetic sampling.

### Pharmacokinetics

Patients were admitted to Mulago Hospital, Kampala for intensive pharmacokinetic sampling on the 7th, 14th and 21st days of nevirapine treatment (Days 7, 14 and 21). On the morning of each sampling visit,

Triomune-30 was administered under the supervision of study staff. Dosing times for anti-TB treatment were not changed. Samples of venous blood (4 mL) were obtained pre-dose and at 2, 4, 6, 8, 10 and 12 h post-nevirapine dosing. Blood samples were centrifuged without delay and plasma aliquots frozen at  $-70^{\circ}\text{C}$ .

Nevirapine concentrations were estimated by reversed-phase HPLC with ultraviolet detection at Makerere University–Johns Hopkins University Core Research Laboratory, Kampala, based on a validated method developed at the University of Liverpool.<sup>5</sup> The lower limit of quantification for nevirapine was 450 ng/mL. Inter-assay and intra-assay coefficients of variation were 8.2% and 6.1%, respectively.

### Data analysis

Maximum plasma concentration ( $C_{\text{max}}$ ) and nevirapine concentrations 12 h post-dose ( $C_{12}$ ) were obtained by direct inspection of the data. A minimum effective concentration (MEC) of 3000 ng/mL was used to interpret nevirapine  $C_{12}$ .<sup>6,7</sup> Area under the concentration–time curve from 0 to 12 h ( $\text{AUC}_{0-12}$ ) was calculated with STATA<sup>®</sup> version 9.2 (Stata Corp) using non-compartmental methods. Geometric mean ratios and 90% confidence intervals (CIs) were calculated for nevirapine pharmacokinetic parameters (Day 21 nevirapine parameters used as reference). Statistical calculations were performed with STATA<sup>®</sup>. Comparisons between arms were performed using the Mann–Whitney *U*-test.

## Results

### Participants

Eighteen patients were enrolled (NVP200, three females; NVP400, five females). All participants received rifampicin daily for a minimum of 16 days prior to nevirapine initiation. All patients received oral co-trimoxazole daily for *Pneumocystis jirovecii* pneumonia prophylaxis. On Days 7, 14 and 21, seven versus nine, six versus nine and five versus nine patients underwent pharmacokinetic sampling in the NVP200 and NVP400 arms, respectively. In the NVP200 arm, two patients were discontinued for toxicity and two others for non-compliance with study procedures. Two of these patients were discontinued before completing Day 7 sampling and had no pharmacokinetic data. For the remaining 16 participants, demographic parameters at screening are shown in Table 1.

**Table 1.** Demographic parameters [median (interquartile range)] at screening for NVP200 and NVP400 arms

Parameter	NVP200 (n=7)	NVP400 (n=9)
Age (years)	34 (32–40)	36 (35–38)
Weight (kg)	57 (49–59)	51 (47–54)
BMI (kg/m <sup>2</sup> )	21 (20–23)	18 (18–20)
CD4 (cells/ $\mu\text{L}$ )	158 (76–256)	195 (41–269)
ALT (IU/L)	16 (14–19)	16 (13–26)
AST (IU/L)	25 (22–27)	34 (27–40)
Creatinine (mmol/L)	0.7 (0.6–0.8)	0.5 (0.6–0.8)
Duration on rifampicin (days)	23 (20–28)	22 (20–28)

BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase.

## Pharmacokinetics

The  $C_{12}$  blood sample for one patient (NVP400) was not collected on Day 7 and his Day 7 pre-dose nevirapine concentration was used as the  $C_{12}$ . Nevirapine pharmacokinetic parameters and comparisons are shown in Table 2. For nevirapine,  $C_{12}$  on Day 7 and  $AUC_{0-12}$  on Days 7 and 14 were lower in the NVP200 arm compared with the NVP400 arm. In the NVP200 arm,  $C_{12}$  and  $AUC_{0-12}$  on Days 7 and 14 were significantly lower (27%–40%) than the corresponding Day 21 values. The proportions of patients with  $C_{12}$  3000 ng/mL in the NVP200 arm were five of seven on Day 7, five of six on Day 14 and four of five on Day 21. In the NVP400 arm five of nine patients had nevirapine  $C_{12}$  <3000 ng/mL at each sampling visit.

## Toxicity

The two toxicity-related discontinuations (both NVP200 arm) were for rash (grade 3) on Day 7, and vomiting and aspartate transaminase elevation (grade 3, nevirapine  $C_{max}$  on Day 14, 4575 ng/mL). For both patients, symptoms resolved after nevirapine discontinuation. Two other patients reported rash (grade  $\leq 2$ ) in the NVP200 arm. Laboratory adverse events were more common in the NVP400 arm but were generally mild (grade  $\leq 2$ ). One patient (NVP400) was hospitalized with grade 4 anaemia and probable immune reconstitution inflammatory syndrome.

## Discussion

In this study, initiation by dose escalation resulted in lower concentrations and a higher frequency of sub-therapeutic nevirapine

levels in the first few weeks of treatment. Starting nevirapine at 400 mg daily resulted in more consistent concentrations during the study and this approach is preferred from a pharmacokinetic standpoint. From a public health standpoint, starting at the maintenance dose using FDCs results in a low pill burden for co-treated patients. Furthermore, this strategy simplifies prescribing in countries where it may be necessary to shift tasks of HIV care to less-skilled health workers.

The low nevirapine concentrations in this study may be due to a rifampicin effect; however, it is possible that other less well-known factors (e.g. diet) could have played a role in Ugandan patients. By Day 21, most patients (9/14, 64%) had sub-therapeutic nevirapine concentrations. This is worrying because patients with low nevirapine concentrations may be at increased risk of treatment failure with their first-line regimen. Although nevirapine maintenance at 400 mg daily appears adequate in some rifampicin-treated populations,<sup>4</sup> a South African pharmacokinetic model suggests that higher doses (e.g. 600 mg daily) may be appropriate in some populations, if well tolerated.<sup>8</sup> The differences in nevirapine pharmacokinetics in different studies may arise from variations in the prevalence of CYP polymorphisms with altered metabolic activity for nevirapine.<sup>9</sup> However, most known polymorphisms would tend to decrease rather than increase nevirapine clearance.

Our study is limited by the absence of pharmacodynamic data (virological response) during nevirapine initiation. Clinical studies in predominantly pre-treated patients have suggested a cut-off of 3000 ng/mL for nevirapine.<sup>6</sup> In contrast, initial dose-escalation studies for nevirapine suggested that lower concentrations than those reported in this study would be adequate

**Table 2.** Nevirapine pharmacokinetic parameters

Parameter	GM (90% CI)			GM ratios (90% CI)	
	Day 7	Day 14	Day 21	Day 7/Day 21	Day 14/Day 21
$C_{12}$ (ng/mL)					
NVP200	1504 (1127–2115)	1763 (1352–2453)	2401 (1981–3011)	0.60 (0.47–0.76)	0.60 (0.42–0.86)
NVP400	3148 (2451–4687)	2920 (2273–4469)	2702 (2172–3804)	1.16 (1.02–1.32)	1.08 (0.93–1.25)
<i>P</i> value	<0.01	0.08	0.74		
$C_{max}$ (ng/mL)					
NVP200	3255 (2654–4202)	2547 (2004–3333)	3351 (2861–4027)	0.93 (0.43–0.76)	0.60 (0.50–0.71)
NVP400	4496 (3673–6090)	4691 (3855–6349)	4589 (3819–6107)	0.98 (0.92–1.04)	1.02 (0.94–1.11)
<i>P</i> value	0.08	0.01	0.16		
$AUC_{0-12}$ (ng·h/mL)					
NVP200	25 223 (21 987–29 695)	23 668 (18 253–32 218)	32 606 (27 151–40 517)	0.72 (0.55–0.94)	0.57 (0.43–0.76)
NVP400	43 195 (35 607–57 035)	44 918 (36 264–62 769)	41 997 (34 098–58 289)	1.03 (0.94–1.12)	1.07 (0.99–1.14)
<i>P</i> value	<0.01	0.03	0.54		
$T_{max}$ (h)					
NVP200	3.81	3.30	3.29		
NVP400	4.39	3.36	3.63		

GM, geometric mean;  $T_{max}$ , time of  $C_{max}$ .

For the NVP200 arm,  $n=7$ , 6 and 5 subjects on Days 7, 14 and 21, respectively. For the NVP400 arm,  $n=9$  on each visit. *P* comparisons were performed using the Mann–Whitney *U*-test.

for suppression of wild-type HIV-1.<sup>10</sup> It is therefore necessary to confirm the MEC of nevirapine in African patients.

Counter-intuitively, nevirapine initiation with maintenance dosing appeared better tolerated than dose escalation. However, the sample size was inadequate to make inferences on safety outcomes. Furthermore, concentrations in the NVP400 arm appear to be lower than those reported in the Asian study that raised concerns about increased toxicity with nevirapine initiation at 400 mg.<sup>4</sup>

In conclusion, nevirapine initiation by dose escalation resulted in sub-therapeutic concentrations and this strategy should be avoided in rifampicin co-treated patients. Sub-therapeutic concentrations were also common at Day 21 with either regimen. Evaluation of the pharmacokinetics and safety of higher nevirapine maintenance doses (e.g. 600 mg daily) in rifampicin co-treated patients may be considered.

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## Transparency declarations

None to declare.

## Author contributions

M. L., P. B., V. O., F. K. and C. M. participated in the recruitment of patients and reporting of data. S. K., D. B., R. N., P. C., M. B. and M. R. contributed to the design, conduct and analysis of the study. All authors were involved

in the interpretation of the data, reviewed and revised the manuscript for intellectual content, and approved the final version for submission.

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