Non AIDS complications and treatment optimizations for HIV-1 infected Thai adult patients with and without TB or hepatitis

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CHAPTER 10

Pharmacokinetics and 48 weeks efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis co-infection receiving highly active antiretroviral therapy and rifampicin

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Background: We aim here to determine the appropriate dose of nevirapine (NVP) in Thai HIV–tuberculosis (TB) coinfected patients receiving rifampicin.

Methods: Thirty-two HIV-infected adults with CD4+ T-cell counts <200 cells/mm$^3$ and active TB, receiving rifampicin for 2–6 weeks were randomized to receive either NVP 400 mg (NVP 400) or 600 mg (NVP 600) per day plus two nucleoside reverse transcriptase inhibitors; a 2-week NVP lead-in was performed at 200 mg once daily (OD) and 200 mg twice daily, respectively. Plasma NVP levels were determined at weeks 2, 4 and 12. Twelve-hour pharmacokinetics (PK) were obtained ($n=20$) at week 4.

Results: Baseline body weight was comparable. There were more patients with NVP plasma concentration at 12 h (C$^{12h}$) <3.1 mg/l at week 2 in NVP$^{400}$ than in NVP$^{600}$ (79% versus 19%, respectively; $P=0.002$). However, the proportions were comparable at weeks 4 and 12. From week 4, 12 h PK studies showed that NVP$^{400}$ had lower median NVP area under the plasma concentration-0–12 h (AUC$^{0–12}$), maximum concentration in plasma (C$^{max}$) and C$^{12h}$ than NVP$^{600}$ ($P<0.05$). Four patients in NVP$^{600}$ developed NVP hypersensitivity. At week 48, the median CD4+ T-cell count rise and proportion with viral load <50 copies/ml (intention-to-treat analysis 56% versus 50% and as-treated analysis 75% versus 89%) were comparable. Conclusions: In rifampicin-treated patients, 200 mg NVP OD lead-in led to a significant short-term suboptimal NVP C$^{12h}$ level, while NVP 400 mg lead-in then 600 mg/day was associated with a high rate of NVP hypersensitivity. Forty-eight week efficacy was comparable. Thus, NVP 600 mg/day in rifampicin–treated patients is not recommended.

Introduction

Coinfection with tuberculosis (TB) and human immunodeficiency virus (HIV) is common, particularly in developing countries. Despite the availability of effective therapy for both diseases, simultaneous treatment is still problematic due to drug interactions, high pill burden, paradoxical reactions and overlapping toxicities [1]. These problems potentially affect drug adherence and may lead to treatment failure. Moreover, Thai HIV–TB-coinfected patients usually present with more advanced HIV infection: in one study, the median CD4+ T-cell count was 29 cells/mm$^3$ (interquartile range [IQR] 14–79 cells/μl) and 90% of
patients had a CD4+ T-cell count <200 cells/mm³ [2]. It might not therefore be safe to delay highly active antiretroviral therapy (HAART) until the completion of TB treatment, as TB could accelerate HIV disease progression [3]. While awaiting the results of current research studies, the World Health Organization recommends that in persons with CD4+ T-cell counts <200 cells/mm³, antiretroviral therapy (ART) should be started between 2 and 8 weeks after anti-TB therapy when the patient has stabilized on TB treatment [4].

Rifampicin, the backbone anti-TB drug, is a strong inducer of the family of cytochrome P450 (CYP450) isoenzymes, of which both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates [5,6]. Rifampicin can therefore decrease plasma concentrations of the antiretroviral drugs while rifabutin, a less potent inducer for cytochrome CYP450, has less effect on antiretroviral drug levels. However, rifabutin is more expensive and not available in most developing countries where there is a high burden of TB.

Efavirenz-based HAART is preferred in HIV–TB-coinfected patients receiving rifamycin because of its improved safety and limited drug interaction [4,7]. However, efavirenz has central nervous system side effects, teratogenicity in pregnant women and is more expensive. Nevirapine (NVP)-based HAART has shown effective antiretroviral efficacy [8] and has been widely used in resource-limited settings because of its fixed-dose combination (FDC) with other nucleoside reverse transcriptase inhibitors (NRTIs). FDCs are easily accessible, convenient, have a low pill burden [9] and provide an attractive option for combining NVP with anti-TB therapy. Rifampicin has been demonstrated to reduce the NVP area under the plasma concentration-time curve (AUC) and both the maximum (Cmax) and minimum (Cmin) concentration of drug by 31%, 36% and 21%, respectively, with no significant effect of NVP on rifampicin concentrations [10]. Previous studies have shown that a dosage of 400 mg/day NVP may be optimal to treat HIV-hepatic patients receiving rifampicin [11,12]. However, 15% of patients taking NVP concomitantly with rifampicin had subtherapeutic levels of NVP [13], which can be overcome by an increase in the NVP dosage from 400 mg/day to 600 mg/day [14]. A large study of Thai HIV-infected patients receiving NVP 400 mg/day with or without rifampicin, showed that patients receiving rifampicin had lower plasma NVP concentrations, while maintaining long-term acceptable CD4+ T-cell levels and viral loads [2,15]. It remains unclear whether an increased dose of NVP is required during treatment with rifampicin as hepatotoxic risk may be increased. This is the first randomized, controlled study comparing treatment outcomes and NVP pharmacokinetic (PK) profiles in patients with advanced HIV infection also receiving rifampicin and treated with either NVP 400 mg/day (NVP_{400}) or 600 mg/day (NVP_{600}).

Methods

Study design

The study was designed to evaluate the effect of rifampicin on the PK of NVP_{400} and NVP_{600}. This study is an ongoing, prospective, randomized, controlled, open-label, two-group study with Thai HIV–TB-coinfected patients in one site in Bangkok (HIV Research collaboration Netherlands-Australia-Thailand [HIV-NAT], Thai Red Cross AIDS Research Centre, Bangkok, Thailand), two sites in Nonthaburi (Bamrasnaradura Infectious Diseases Institute and Chest disease Institute, Nonthaburi, Thailand) and three sites in Chiangrai (Chiangrai hospital, Phan Hospital and Mae-Chan Hospital, Chiangrai, Thailand).

Study patients

Between November 2005 and August 2006, 32 Thai HIV–TB-coinfected patients were enrolled. Inclusion criteria for both groups were HIV-infected individuals ≥18 years old, a CD4+ T-cell count of ≤200 cells/mm³, a diagnosis of smear positive, active TB, receipt of a rifampicin-containing anti-TB regimen 2–6 weeks prior to enrolment and a willingness to participate and provide a consent form. Exclusion criteria for both groups were receipt of previous HAART, receipt of a medication that has drug–drug interactions with NVP or rifampicin, aspartate aminotransferase/serum glutamic-oxalacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) levels >5 times the upper limit of the normal range, a haemoglobin level <8 g/dl and neutrophil counts <700 cells/μl, and being pregnant or breast feeding. The study was approved by the ethic committee of human research of each institute and the Thai Ministry of Public Health.

Patients were randomized to receive NVP_{400} or NVP_{600}. No stratification was done for any parameters. FDC (GPOvir-z®, Government Pharmaceutical Organization, Bangkok, Thailand) of zidovudine 250 mg, lamivudine 150 mg and NVP 200 mg per tablet were used for both groups. During the first 2 weeks, all patients received a lead-in dosage of 200 mg of NVP once daily (GPOvir-z® one tablet in the morning and zidovudine/lamivudine in the evening) for the NVP_{400} group and 200 mg of NVP twice daily (GPOvir-z® one tablet oral every 12 h) for the NVP_{600} group. After the 2 week lead-in, both groups received a single tablet of GPOvir-z® twice a day with an additional tablet of NVP (200 mg) in the morning for the NVP_{600} group. The anti-TB regimen consisted of isoniazid, rifampicin,
ethambutol and pyrazinamide administered during the first 2 months of therapy, followed by isoniazid and rifampicin for the subsequent 4–7 months. The dosage of rifampicin was 450 mg/day for patients with a body weight ≤50 kg and 600 mg/day for patients with a body weight >50 kg. The general characteristics (for example, gender, age, body weight, body mass index, previous opportunistic infections and site of TB infection) were recorded. After baseline assessment, patients had follow-up visits at 2, 4, 8, 12, 20, 24 and then every 12 weeks until week 48 after initiation of NVP-based HAART as per main protocol. The CD4+ T-cell count and HIV RNA levels were monitored every 12 weeks by flow cytometry and Roche Amplicor Ultrasensitive assay, (Roche Molecular Diagnostics, Basel, Switzerland), respectively; ALT/AST testing was carried out at weeks 2, 4, 8, 12, 20, 24 and then every 12 weeks. Blood samples were obtained for NVP C_{min} at week 2, 4 and 12 with a window of 1 h (11–13 h post-ingestion). A 12 h PK study of NVP and rifampicin was performed in 20 patients (10 per dose group) at week 4 at the HIV-NAT center. All 20 patients were instructed to take TB therapy and antiretroviral drugs at 8.00 am before breakfast. After taking their medication they were told to have a standard breakfast. In addition, they were instructed to take their antiretroviral drugs again at 8.00 pm. This was done starting daily from 2 weeks before the day of the intensive PK study.

Pharmacokinetic studies at week 4
Samples (5 ml) of heparinized blood were collected at pre-dosing, 1, 2, 3, 4, 6, 8 and 12 h after antiretroviral drug intake for the NVP PK study. Samples were centrifuged at 1,500 g for 10 min at 4°C and stored at -20°C until analysis at the HIV-NAT laboratory. Another 2 ml of heparinized blood were collected at pre-dosing, 1, 2, 4, 6 and 8 h after rifampicin intake for assessment of rifampicin levels. Samples were centrifuged at 1,800 g for 10 min at 4°C and stored at -80°C until analysis [18]. Rifampicin bioanalysis was performed with HPLC at the Research Institute of Tuberculosis (Tokyo, Japan). The detection limit was 0.2 μg/ml.

On the day of blood sampling, the patients were directly observed taking their drugs with a standardized breakfast of 550 kcal. The medication was administered immediately after breakfast with 100 ml of water. All other meals and snacks in the PK study days were also standardized. The NVP plasma levels were measured by HPLC assay [19]. The NVP calibration curve was linear over the range of 0.15–15.0 mg/l. Recovery after extraction from plasma was 101.8 ±4.6%. Accuracy in plasma ranged from 91.5–102.6%. The within-day precision ranged from 1.3–3.9% and between-day precisions ranged from 1.9–3.0%. The HIV-NAT PK laboratory participates in the international interlaboratory quality control program for therapeutic drug monitoring in HIV infection (www.ikkkt.org). PK parameters were calculated by noncompartmental methods using the WinNonlin software package (version 5.0.1; Pharsight Corporation, Mountain View, CA, USA) and the log/linear trapezoidal rule. On the basis of the individual plasma concentration-time data, the PK parameters determined were the AUC from time zero to 12 h (AUC_{0-12}), the C_{max}, the time to reach C_{max} (T_{max}) in h, the plasma concentration at 12 h (C_{12}) in mg/l, the apparent elimination half-life (t_{1/2}) in h, and the apparent oral clearance (CL/F) in l/h.

Statistical analyses
Initially, this study was powered to detect differences in viral efficacy (42 patients per group), however, this study was prematurely discontinued by the Data and Safety Monitoring Board (DSMB) due to the high rate of hypersensitivity. Therefore, this study was underpowered for most of the endpoints and must be considered as a pilot study. Statistical analyses were performed with SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). The AUC_{0-12}, C_{max} and C_{12} of NVP and rifampicin were reported for study week 4. The median, interquartile range (IQR; 25–75%) and 90% confidence intervals for AUC_{0-12}, C_{max} and C_{12} were calculated.

Median (IQR) and frequency (%) were used to describe patient characteristics for continuous and categorical data, respectively. A Mann–Whitney test was used to compare plasma NVP levels between groups. A Fisher’s exact test or χ² test was used to compare the number of patients with plasma NVP levels (C_{12} <3.1 mg/l at week 2, 4 and 12. A P-value <0.05 was considered statistically significant.

Results
Demographics
Thirty-two HIV–TB-coinfected patients were enrolled to receive GPOvir-z® (zidovudine 250 mg+lamivudine 150 mg+NVP 200 mg) 1 tablet twice daily (NVP_{400} group) or GPOvir-z® 1 tablet twice daily plus extra NVP 200 mg once daily (NVP_{600} group). The baseline characteristics of the patients, including body weight, CD4+ T-cell count, HIV RNA, liver function test and haemoglobin results, did not differ among both groups (Table 1). The median duration of rifampicin received by the patients was 5.8 and 4.7 weeks in the NVP_{400} and NVP_{600} group, respectively. Eighty-one percent of patients in the NVP_{400} group took rifampicin 450 mg/day, whereas only 31% of patients in the NVP_{600} group took rifampicin 450 mg/day.
Both study groups had very low median CD4+ T-cell counts (45 and 40 cells/mm³ in NVP 400 and NVP 600 mg groups, respectively) and very high HIV RNA (over 100,000 copies/ml). Eleven (34%) patients discontinued the study before week 24: five due to NVP hypersensitivity (four from the NVP600 group and one from NVP 400; three developed during the 2-week lead-in and two developed after 2 weeks), three from rifampicin-induced cholestatic jaundice (two from the NVP400 group), two deaths (one each), and one non-TB mycobacterium (in the NVP 400 group). The two deaths resulted from cardiomyopathy with heart failure (NVP600 group) and disseminated Mycobacterium avium complex with bloody pleural effusion (NVP 400 group). DSMB decided that these two cases were associated with immune reconstitution syndrome and were not study drug-related.

Therapeutic drug monitoring
Individual NVP plasma concentrations (C₁₂) between the two treatment groups at weeks 2, 4 and 12 are listed in Figure 1. At week 2, (median [IQR]) NVP levels of NVP₄₀₀ (1.9 [0.7–3.0] mg/l) were significantly lower than NVP₆₀₀ (5.3 [3.3–7.8] mg/l; P=0.001). Then at week 4, the levels of NVP significantly differed between the two groups (3.9 [2.9–4.8] mg/l and 5.7 [4.5–7.1] mg/l; P=0.03 for NVP₄₀₀ and NVP₆₀₀, respectively). However, the NVP levels at week 12 did not differ significantly (3.83 [2.6–5.9] and 5.9 [4.4–7.7]; P=0.16). The proportion of patients who had C₁₂ <3.1 mg/l at week 2, 4 and 12 are shown in Figure 2. There were more patients with NVP C₁₂ <3.1 mg/l at week 2 in the NVP₄₀₀ group (79% versus 19%; P=0.002). However, the proportions were comparable among the groups at week 4 and 12.

Pharmacokinetics at week 4
There were 20 patients that completed the 12 h PK study of NVP. The results of steady-state PK parameters calculated on the basis of plasma NVP concentrations obtained at different time points for both groups are shown in Figure 3 and Table 2. The NVP AUC₀–₁₂, C_max and C₁₂ of NVP 400 were significantly lower than for NVP 600. The median AUC₀–₁₂ (IQR) of NVP 400 and NVP₆₀₀ was 64.8 (54–78.3) and 87.5 (72.8–106.1) mg/h/l (P=0.03), C_max was 6.6 (6.1–8.0) and 8.9 (7.5–11.0) mg/l (P=0.03) and C₁₂ was 4.1 (3.6–4.6) and 5.9 (5.02–7.4) mg/l (P=0.01), respectively. The NVP T_max, half-life and clearance were comparable among the two groups.

Ten patients from each group participated in an 8 h PK study of rifampicin. There were nine patients for rifampicin 450 mg and 11 patients for rifampicin 600 mg; eight patients on rifampicin 450 mg were in the NVP₄₀₀ group and nine patients on rifampicin 600 mg were in the NVP₆₀₀ group. The rifampicin AUC₀–₈, C_max and plasma concentration at 8 h (C₈) were comparable between the two groups. The median AUC₀–₈ (IQR) of rifampicin in NVP₄₀₀ and NVP₆₀₀ was 30.6 (16.5–40.6) and 25.2 (15.4–37.8) mg·h/ml (P=0.65), C_max was 7.1 (3.4–9.7) and 6.6 (3.2–9.9) mg/l (P=0.76), and C₈ were 2.6 (1.8–3.3) and 1.7 (0.95–2.7)

### Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NVP 400 mg/day (n=16)</th>
<th>NVP 600 mg/day (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female), n (%)</td>
<td>10:6 (62.5/37.5)</td>
<td>12:4 (75/25)</td>
<td>0.7</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>34 (28–40)</td>
<td>34 (30–39)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median weight, kg (IQR)</td>
<td>46 (43–51)</td>
<td>54 (46–58)</td>
<td>0.1</td>
</tr>
<tr>
<td>Median interval TB ARV (IQR), week</td>
<td>5.8 (4.8–6.3)</td>
<td>4.7 (4.1–5.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Median CD4+ T-cell count, cells/mm³ (IQR)</td>
<td>45 (31–114)</td>
<td>40 (19–68)</td>
<td>0.3</td>
</tr>
<tr>
<td>Median log₁₀ HIV RNA (IQR), copies/ml</td>
<td>5.6 (5.3–5.7)</td>
<td>5.2 (4.9–5.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Viral hepatitis C coinfection*</td>
<td>1 (6)</td>
<td>3 (19)</td>
<td>0.6</td>
</tr>
<tr>
<td>Route of transmission</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Heterosexual, n (%)</td>
<td>11 (69)</td>
<td>10 (63)</td>
<td></td>
</tr>
<tr>
<td>Intravenous drug use, n (%)</td>
<td>2 (13)</td>
<td>6 (38)</td>
<td></td>
</tr>
<tr>
<td>Prior AIDS defining illness, n (%)</td>
<td>1 (6)*</td>
<td>3 (19)*</td>
<td>0.6</td>
</tr>
<tr>
<td>Site of TB</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Pulmonary, n (%)</td>
<td>7 (44)</td>
<td>6 (38)</td>
<td></td>
</tr>
<tr>
<td>Disseminated, n (%)</td>
<td>7 (44)</td>
<td>8 (50)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes/ abscess at forehead, n (%)</td>
<td>2 (13)</td>
<td>2(13)</td>
<td></td>
</tr>
<tr>
<td>Median haemoglobin, g/dl (IQR)</td>
<td>10.1 (8.9–11.8)</td>
<td>10.9 (10.4–11.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Median ALT/SGPT, U/l (IQR)</td>
<td>21 (14–27)</td>
<td>20.5 (14.3–26.8)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Hepatitis B virus and hepatitis C virus testing was available in a few patients. †Pneumocystis jiroveci pneumonia (PCP). PCP, two patients and Cryptococcal meningitis, one patient. ALT/SGPT, alanine aminotransferase/serum glutamic-pyruvic transaminase; ARV, antiretroviral drug; IQR, interquartile range; NVP, nevirapine; TB, tuberculosis.
mg/l (P=0.13). Comparing between rifampicin 450 mg (nine patients) and 600 mg (11 patients), the median (IQR) of AUC0–8, Cmax and C8 was 25.4 (16.3–36.8) and 28.2 (16.4–42.9) mg/h/l (P=0.79), 6.3 (3.2–9.2) and 7.7 (3.2–10.2) mg/l (P=0.73), and 2.6 (1.8–2.9) and 1.7 (0.99–3.2) mg/l (P=0.27), respectively. All patients had rifampicin <0.1 mg/l (plasma concentration at 0 h) prior to taking the next dose of rifampicin. There was no correlation between AUC of rifampicin and AUC of NVP (P=0.58).

**Adverse events**

All patients had at least one episode of adverse events during the study. TB-related immune recovery syndrome occurred in 31% (5:5 each group). Zidovudine induced severe anaemia in 25% of patients (4:4 each group). Grade 2 ALT elevation occurred in one patient with hepatitis C virus (HCV) coinfection from NVP600 and one hepatitis B virus (HBV)-coinfected patient from NVP400. Fever and rashes from drug hypersensitivity occurred in four patients (25%) of NVP600, which was associated with high C12 at week 2. Two out of four patients in this group developed NVP hypersensitivity during the first 2 weeks of NVP 200 mg twice daily lead-in and three out of four patients were female. Another one patient (6%) from the NVP400 group developed NVP hypersensitivity.

**Figure 1.** Nevirapine plasma concentrations versus minimum effective concentration (3.1 mg/l) at weeks 2, 4 and 12

**Figure 2.** The percentage of patients with nevirapine C12 <3.1 mg/l
Median (range) NVP $C_{12}$ at time of NVP hypersensitivity was 7.3 (5.6–10.2) mg/l with median (range) body weight of 49.5 (35–58) kg. Cholestatic hepatitis from rifampicin was seen in three patients (two from NVP$_{400}$). There was no significant difference in plasma ALT levels at 12, 24 and 48 weeks.

Week 48 efficacy results
At week 48, there were no differences in the median increase in CD4+ T-cell count between the NVP$_{400}$ and NVP$_{600}$ groups (154 [78–203] versus 114 [82–198] cells/mm$^3$; $P$=0.91) or in the proportion of patients with plasma HIV-1 RNA <50 copies/ml (intention-to-treat analysis 56% versus 50%, $P$=1 and on-treatment analysis 75% versus 89%, $P$=0.6). Only one patient from the NVP$_{400}$ group had HIV RNA >400 copies/ml by week 48 due to poor adherence, and subsequently developed M184V and G190A mutations. This case had NVP levels of 10.53 mg/l at week 4.

Discussion
Treatment of TB and HIV coinfection is complex with drug interactions being a key hurdle. Maintaining maximum plasma HIV-1 RNA suppression essentially delays the emergence of resistant viral strains and lead to long-term efficacy of antiretroviral drugs. The 2NN study demonstrated that the risk of virological failure was increased when the plasma NVP level fell <3.1 mg/l [16]. Although, some papers defined the cut-off point differently [20,21], when co-administered with rifampicin, the optimal NVP dosage is still debatable because studies comparing different doses of NVP are still lacking. It is known that initiation of NVP requires dose titration (lead-in) because the hepatic isoenzymes are induced over time. However, there is limited data on NVP lead-in treatment for patients on rifampicin. Rifampicin may decrease NVP levels during initiation and lead-in strategy may not be necessary. Therefore, this study was designed to determine the optimal dose of NVP by comparing doses of 400 mg/day and 600 mg/day of NVP. The question of the 200 mg/day of NVP lead-in strategy was also addressed.

In this study, the $C_{12}$ of NVP was significantly lower during the lead-in period of NVP 200 mg/day and 79% of these patients had $C_{12}$ <3.1 mg/l. After increasing the dose to 400 mg/day of NVP, the majority of cases achieved acceptable $C_{12}$ levels. By contrast, a lead-in strategy with NVP 200 mg twice daily was associated with a high incidence of adverse side effects ($P$=0.01). These included fever with severe rashes from drug hypersensitivity that led to NVP discontinuation in several patients. Due to this high rate of hypersensitivity in the NVP$_{600}$ group the DSMB decided to prematurely discontinue the study.

Table 2. Pharmacokinetics of nevirapine at week 4

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nevirapine 400 mg/day</th>
<th>Nevirapine 600 mg/day</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-12}$, mg/h/l</td>
<td>64.8 (54.7–78.3)</td>
<td>87.5 (72.8–106.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>$C_{max}$, mg/l</td>
<td>6.6 (6.1–8.0)</td>
<td>8.9 (7.5–11.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>$C_{12}$, mg/l</td>
<td>4.1 (3.6–4.6)</td>
<td>5.9 (5.0–7.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>$T_{max}$, h</td>
<td>2 (1.75–4)</td>
<td>3 (2–6)</td>
<td>0.2</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>11.8 (10.2–13.7)</td>
<td>17.6 (11.8–20.9)</td>
<td>0.105</td>
</tr>
<tr>
<td>Clearance, l/h</td>
<td>6.19 (5.12–7.45)</td>
<td>6.86 (5.66–8.23)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range). There were 10 patients per group. $AUC$, area under the plasma concentration-time data curve; $C_{max}$, maximum concentration of drug in plasma; $C_{12}$, concentration of drug in plasma at 12 h; $T_{max}$, the time required to reach $C_{max}$; $t_{1/2}$, the elimination of drug half-life.
This study, however, found no difference in median NVP levels during 12 weeks of treatment, that is, 75% of patients in the NVP\textsubscript{400} group achieved an acceptable target of NVP C\textsubscript{12} at week 4. More interestingly, at weeks 24 and 48, the efficacy of viral suppression did not differ between the two doses, whereas the toxicities were increased in the NVP\textsubscript{600} group. A larger trial and a longer term of follow-up of NVP 400 mg/day is necessary to confirm these results.

The decision making for lead-in of NVP during the first 2 weeks in rifampicin-treated patients should balance the risk of toxicity and subtherapeutic levels that could compromise virological efficacy. This study suggests that low NVP levels during the first 2 weeks of treatment could reduce the risk of NVP hypersensitivity without compromising the antiviral efficacy. This was demonstrated by comparable short-term virological and immunological responses. The high inhibitory quotient of NVP may indicate that plasma NVP concentrations in combination with rifampicin are above the adjusted 50% effective inhibitory concentration (IC\textsubscript{50}; 0.025 mg/l) [17] or 95% effective inhibitory concentration (IC\textsubscript{95}; 0.19 mg/l) of the wild-type HIV virus. In the present study, NVP C\textsubscript{12} was clearly above the IC\textsubscript{95}. Thus, increasing NVP dosage when it is given with rifampicin is not needed. The study from Thailand in 70 rifampicin-treated patients compared with rifampicin-untreated patients, showed that the virological and immunological response at week 60 (68.8% by intention-to-treat analysis and 85.7% by on-treatment analysis had HIV RNA <50 copies/ml) still existed for NVP 200 mg twice daily with 200 mg once daily lead-in during the first 2 weeks in rifampicin-treated patients [15]. From that study, the average body weight was 54 kg (as compared with 46 kg in the the NVP\textsubscript{400} of our study) and median plasma NVP at week 4 was 5.4 mg/l (as compared with 3.9 mg/l in the the NVP\textsubscript{400} of our study), but the researches did not show any data of plasma NVP at 2 weeks which could be lower during the lead-in period as our study has shown. However, the incidence (7%) of NVP-associated rash in the NVP\textsubscript{400} rifampicin group from a study by Manosuthi et al. [2] did not differ from the NVP\textsubscript{400} group in our study (6%). In contrast, the rash was much higher in the NVP\textsubscript{600} group (25%). Although the underlying mechanism of NVP is still poorly understood, we noticed that higher NVP levels might contribute to more hypersensitivity (median NVP C\textsubscript{12} at time of NVP hypersensitivity was 7.3 [range 5.6–11.02] mg/l). However, other components, like genetic factors, may contribute to NVP hypersensitivity as well [22].

The 12 h PK study at week 4 showed that C\textsubscript{max}, AUC and C\textsubscript{12} of the NVP\textsubscript{400} group were lower when compared with NVP\textsubscript{600}. Although only two patients in the NVP\textsubscript{400} group and one patient in the NVP\textsubscript{600} group had NVP C\textsubscript{12} <3.1 mg/l, all these patients had HIV RNA <50 copies/ml at week 48. According to the study of Ramachandran et al. [14], their PK parameters (a C\textsubscript{max} of 4.9 mg/l, C\textsubscript{min} 2.59 mg/l and AUC 43.20 mg/l/h) for the NVP\textsubscript{400} group combined with rifampicin were considerably lower than our NVP\textsubscript{400} values. However, our study had a higher proportion of patients with low body weight (46 kg versus 58 kg) and low CD4\textsuperscript{+} T-cell counts (41 versus 315 cells/mm\textsuperscript{3}) and it is possible that the difference in body weight and racial or genetic factors may explain these differences in PK parameters.

In this study, the 8 h PK study of rifampicin did not differ between 450 mg and 600 mg of rifampicin. There was no correlation between the AUC of rifampicin and NVP. However, there are limitations to draw a strong correlation due to small sample size and imbalance between the two groups with regards to rifampicin dosage and body weight. In the NVP\textsubscript{400} group, eight out of 10 patients took rifampicin at 450 mg/day and in the NVP\textsubscript{600} group, nine out of 10 patients took rifampicin at 600 mg/day.

In this present study, elevated ALT levels and NVP-associated skin rashes are not higher among patients taking standard doses of NVP with rifampicin. The sample size was small and, therefore, was not powered to detect adverse events occurring with relatively low incidence in patients with low CD4\textsuperscript{+} T-cell counts (<250 cells/mm\textsuperscript{3}). However, the use of NVP concomitant with anti-TB is associated with a risk of hepatotoxicity, so liver function test (ALT) should be monitored especially during the first 2 months [4].

Although, there were some differences among the body weight between the two groups (NVP\textsubscript{400} versus NVP\textsubscript{600}), it was not statistically significant due to the small sample size. We observed that the NVP\textsubscript{400} group had lower body weight and even more subtherapeutic levels, whereas the NVP\textsubscript{600} group had higher body weight and even more toxicity during or after the lead-in period.

Of note, the small sample size and early study termination have led to an imbalance in mean body weight at baseline. Hence, this study has no sufficient power to draw a definitive conclusion on the basis of the efficacy results in regards to the suitable dosage of NVP.

In conclusion, our study confirms that NVP-based HAART can be used in combination with rifampicin-containing anti-TB. A lead-in strategy with 200 mg/day NVP followed by an increase to 200 mg twice daily NVP can be safely and effectively combined with rifampicin in the Thai population. This may not apply to other ethnic groups that could differ in cytochrome P450 activity, body weight and nutritional status. The evaluation of long-term efficacy and safety is underway.
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Disclosure statement

AA, WM, PK, CC, SM, WS, MG, NY, HY, NI, DB declare no conflicts of interest. KR has received grants, consultancy fees and honoraria from various pharmaceutical companies including Hoffmann-La Roche, Merck, Sharpe & Dohme, Bristol–Myers Squibb and Abbott. DC has received research grants/funding, honoraria or lecture sponsors from, or is a consultant or advisor to, Abbott, Boehringer-Ingelheim, Bristol–Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Merck Sharpe & Dohme, Pfizer and Hoffmann-La Roche. PP has received honoraria from Bristol–Meyers Squibb as a scientific consultant and research grants from Bristol–Myers Squibb, Hoffmann-La Roche, GlaxoSmithKline, Merck, Sharpe & Dohme.

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