Original article

Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV–tuberculosis coinfection receiving 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/mm³ 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_{12}) <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 ($AUC_{0-12\ h}$), maximum concentration in plasma (C_{max}) and C_{12} 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_{12} 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/mm³ (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 hepatic 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 rifampicin 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 (C_{max}) and minimum (C_{min}) 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-infected 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 daily starting 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.kkgt.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}) in mg×h/l, the C_{max} in mg/l, 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 χ^2 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.

Table 1. Baseline characteristics of study participants

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

*Hepatitis B virus and hepatitis C virus testing was available in a few patients. †*Pneumocystis jirovecii* pneumonia (PCP). ‡PCP, two patients and Cryptococcal meningitis, one patient. ALT/SGPT, alanine aminotranferase/serum glutamic-pyruvic transaminase; ARV, antiretroviral drug; IQR; interquartile range; NVP, nevirapine; TB, tuberculosis.

Both study groups had very low median CD4$^+$ T-cell counts (45 and 40 cells/mm^3 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 NVP_{600} 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 NVP_{400} group), two deaths (one each), and one non-TB mycobacterium (in the NVP_{400} group). The two deaths resulted from cardiomyopathy with heart failure (NVP_{600} 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

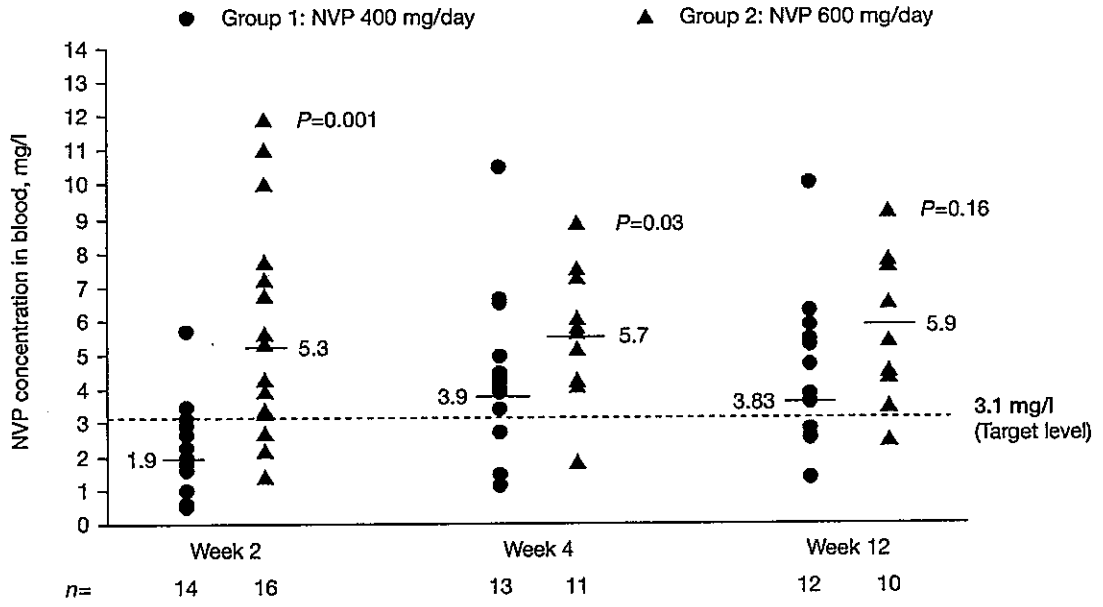
Individual NVP plasma concentrations (C_{12}) between the two treatment groups at weeks 2, 4 and 12 are listed in Figure 1. At week 2, (median [IQR]) NVP levels of NVP_{400} (1.9 [0.7–3.0] mg/l) were significantly lower than NVP_{600} (5.3 [3.3–7.8] mg/l; P=0.001). Then at week 4, the levels of NVP significantly 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 NVP_{400} and NVP_{600}, 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 C_{12} <3.1 mg/l at week 2, 4 and 12 are shown in Figure 2. There were more patients with NVP C_{12} <3.1 mg/l at week 2 in the NVP_{400} 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 AUC_{0-12}, C_{max} and C_{12} of NVP_{400} were significantly lower than for NVP_{600}. The median AUC_{0-12} (IQR) of NVP_{400} and NVP_{600} 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 C_{12} 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 NVP_{400} group and nine patients on rifampicin 600 mg were in the NVP_{600} group. The rifampicin AUC_{0-8}, C_{max} and plasma concentration at 8 h (C_8) were comparable between the two groups. The median AUC_{0-8} (IQR) of rifampicin in NVP_{400} and NVP_{600} was 30.6 (16.5–40.6) and 25.2 (15.4–37.8) mg/h/l (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 C_8 were 2.6 (1.8–3.3) and 1.7 (0.95–2.7)

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



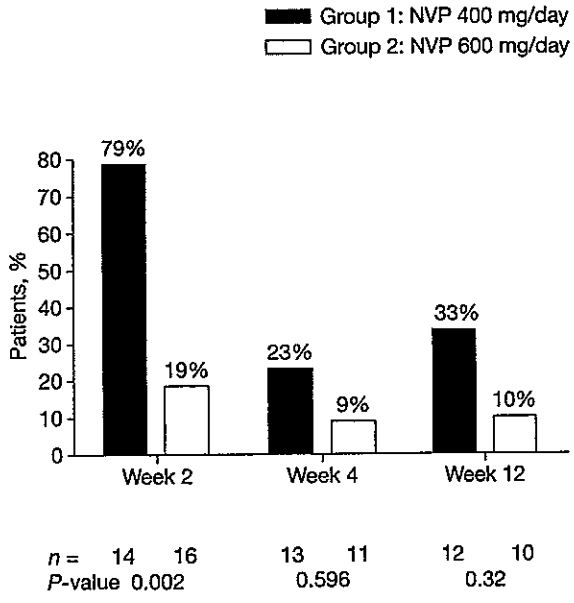
NVP, nevirapine.

mg/l (P=0.13). Comparing between rifampicin 450 mg (nine patients) and 600 mg (11 patients), the median (IQR) of AUC_{0-8}, C_{max} and C_8 was 25.4 (16.3–36.8) and 28.2 (16.–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 NVP_{600} and one hepatitis B virus (HBV)-coinfected patient from NVP_{400}. Fever and rashes from drug hypersensitivity occurred in four patients (25%) of NVP_{600}, which was associated with high C_{12} 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 NVP_{400} group developed NVP hypersensitivity.

Figure 2. The percentage of patients with nevirapine C_{12} <3.1 mg/l



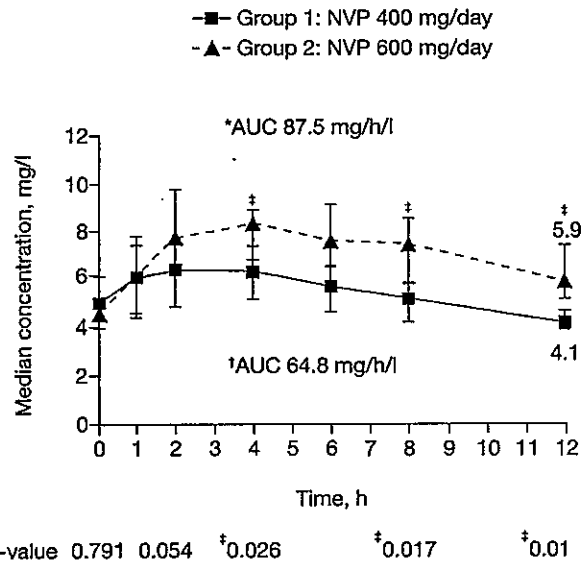
C_{12}, nevirapine plasma concentration at 12 h; NVP, nevirapine.

Median (range) NVP C_{12} at time of NVP hypersensitivity was 7.3 (5.6–1.02) 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.

Figure 3. Median plasma nevirapine concentration versus time curves at week 4



There were 10 patients in each group. *Median area under the plasma concentration-time data curve between 0 and 12 h (AUC_{0-12}) for the NVP_{600} group. †Median AUC_{0-12} for the NVP_{400} group. ‡Significant difference, P<0.05. NVP, nevirapine.

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 hypersensivity 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

Characteristic	Nevirapine 400 mg/day	Nevirapine 600 mg/day	*P*-value
AUC_{0-12}, mg/h/l	64.8 (54–78.3)	87.5 (72.8–106.1)	0.03
C_{max}, mg/l	6.6 (6.1–8.0)	8.9 (7.5–11.0)	0.03
C_{12}, mg/l	4.1 (3.6–4.6)	5.9 (5.02–7.4)	0.01
T_{max}, h	2 (1.75–4)	3 (2–6)	0.2
$t_{1/2}$, h	11.8 (10.2–13.7)	17.6 (11.8–20.9)	0.105
Clearance, l/h	6.19 (5.12–7.45)	6.86 (5.66–8.23)	0.26

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_{400} group achieved an acceptable target of NVP C_{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_{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_{50}; 0.025 mg/l) [17] or 95% effective inhibitory concentration (IC_{95}; 0.19 mg/l) of the wild-type HIV virus. In the present study, NVP C_{12} was clearly above the IC_{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_{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_{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_{400} rifampicin group from a study by Manosuthi *et al.* [2] did not differ from the NVP_{400} group in our study (6%). In contrast, the rash was much higher in the NVP_{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_{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_{max}, AUC and C_{12} of the NVP_{400} group were lower when compared with NVP_{600}. Although only two patients in the NVP_{400} group and one patient in the NVP_{600} group had NVP C_{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_{max} of 4.9 mg/l, C_{min} 2.59 mg/l and AUC 43.20 mg/l/h) for the NVP_{400} group combined with rifampicin were considerably lower than our NVP_{400} values. However, our study had a higher proportion of patients with low body weight (46 kg versus 58 kg) and low $CD4^+$ T-cell counts (41 versus 315 cells/mm^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_{400} group, eight out of 10 patients took rifampicin at 450 mg/day and in the NVP_{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 $CD4^+$ T-cell counts <250 cells/mm^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_{400} versus NVP_{600}), it was not statistically significant due to the small sample size. We observed that the NVP_{400} group had lower body weight and even more subtherapeutic levels, whereas the NVP_{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 sponsorships 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-LaRoche, GlaxoSmithKline, Merck, Sharpe & Dohme.

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A 72-week randomized clinical trial comparing the safety and efficacy of antiretroviral regimens-GPO-VIR S (d4T/3TC/NVP) for 24 weeks followed by GPO-VIR Z (AZT/3TC/NVP) vs GPO-VIR Z vs TDF/FTC/NVP

TITLE: A 72-week randomized clinical trial comparing the efficacy and safety of three initial antiretroviral regimens –GPO-VIR S (d4T/3TC/NVP) for 24 weeks followed by GPO-VIR Z (AZT/3TC/NVP) vs GPO-VIR Z vs TDF/FTC/NVP (SEARCH 003)

ชื่อภาษาไทย: การศึกษาแบบสุ่มกลุ่มเป็นระยะเวลา 72 สัปดาห์ เพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของการใช้ยาต้านไวรัสเอดส์สูตรแรก 3 สูตร คือ ยา จีพีโอเวียร์ เอส ใน 24 สัปดาห์แรก ตามด้วย ยา จีพีโอเวียร์ แซดหรือ การใช้ยาจีพีโอเวียร์ แซด หรือ ยาทรูวาดาร่วมกับเนวิราปีน (เซิร์ช 003)

ABSTRACT

Background:

Due to superior long-term toxicity profile, AZT and TDF are preferred to d4T for first-line regimens. However, short-term d4T use could be beneficial in avoiding AZT-induced anemia.

Method:

Naive Thai HIV-infected adults were randomized (1:1:1) to arm 1: 24-wk d4T 30mg + 3TC 150mg + NVP 200mg followed by 48-wk AZT 250mg + 3TC 150mg + NVP 200mg; arm 2: 72-wk AZT 250mg + 3TC 150mg + NVP 200mg; or arm 3: 72-wk TDF 300mg + FTC 200mg + NVP. During NVP lead-in, AZT was given at 200mg or 300mg BID for weight <60 kg or >60 kg, respectively. Hemoglobin, DEXA, neuropathic signs, serum creatinine, CD4 count, plasma HIV-RNA, and adherence were assessed.

Results:

Among 150 randomized patients, 55% were female, mean (SD) age was 34 (8) years. Baseline mean CD4 count was 161 (94) cells/mm^3, HIV-RNA was $\log_{10}$ 4.87 (0.65) copies/ml, hemoglobin was 12.5 (1.6) g/dL, weight was 57.9 (10.8) kg, and eGFR (MDRD formula) was 82.9 (15.5) mL/min/1.73m^2.

CD4 count increased more in arm 1 than arm 2 and arm 3 from baseline to week 24 (168 vs. 117 and 118 cells/mm^3, p=0.01 and 0.02, respectively) but the increase from baseline to week 72 was similar among arms. At week 72, HIV-RNA was <40 copies/mL in 84%, 92%, and 83% of patients in arms 1, 2, and 3, respectively. Adherence was similar between arms.

At week 24, mean hemoglobin decreased significantly from baseline in arm 2 compared to arm 1 (-0.19 vs. 0.68 g/dL, p=0.001) and arm 3 (0.48 g/dL, p=0.010), and neuropathic signs were significantly more common in arm 2 compared to arm 3 (20.4% vs. 4.2%, p=0.028).

ในบรรดาผู้ติดเชื้อ 150 รายที่ได้รับการสุ่มกลุ่ม เป็นเพศหญิง 55% อายุเฉลี่ย (SD) อยู่ที่ 34 (8) ปี CD4 count เฉลี่ย เท่ากับ 161 (94) cells/mm^3 ปริมาณ HIV-RNA เท่ากับ log_{10} 4.87 (0.65) copies/ml ค่า hemoglobin เฉลี่ย เท่ากับ 12.5 (1.6) g/dL น้ำหนักตัวเฉลี่ย 57.9 (10.8) kg และค่า eGFR (คำนวณโดยสูตร MDRD) เท่ากับ 82.9 (15.5) mL/min/1.73m^2

CD4 count เพิ่มในกลุ่ม 1 จากก่อนเริ่มยาจนถึงสัปดาห์ที่ 24 มากกว่ากลุ่ม 2 และกลุ่ม 3 (168 vs. 117 และ 118 cells/mm^3, p=0.01 และ 0.02 ตามลำดับ) แต่การเพิ่มขึ้นจากก่อนเริ่มยาจนถึงสัปดาห์ที่ 72 ไม่แตกต่างกันระหว่างกลุ่ม ณ สัปดาห์ที่ 72 มีผู้ที่มี HIV-RNA <40 copies/mL 84%, 92% และ 83% ในกลุ่ม 1, กลุ่ม 2 และกลุ่ม 3 ตามลำดับ ไม่พบว่า adherence มีความแตกต่างกันระหว่างกลุ่ม

ณ สัปดาห์ที่ 24 ค่า hemoglobin เฉลี่ยลดลงอย่างมีนัยสำคัญจากก่อนเริ่มยาในกลุ่ม 2 เทียบกับกลุ่ม 1 (-0.19 vs. 0.68 g/dL, p=0.001) และกลุ่ม 3 (0.48 g/dL, p=0.010) และพบ neuropathic signs บ่อยกว่าในกลุ่ม 2 เทียบกับกลุ่ม 3 (20.4% vs. 4.2%, p=0.028) ไม่พบว่าการเปลี่ยนแปลงของ peripheral fat และ eGFR จากก่อนเริ่มยามีความแตกต่างกันระหว่างกลุ่ม

ณ สัปดาห์ที่ 72 ค่า hemoglobin ในกลุ่ม 3 เพิ่มขึ้นอย่างมีนัยสำคัญจากก่อนเริ่มยาเมื่อเทียบกับกลุ่ม 1 (0.90 vs. 0.17 g/dL, p=0.006) กลุ่ม 1 มี peripheral fat ลดลง (-301g) จากก่อนเริ่มยา มากกว่ากลุ่ม 2 (143g) และกลุ่ม 3 (281g) แต่ไม่ได้แตกต่างกันอย่างมีนัยสำคัญทางสถิติ มีผู้ป่วยเพียง 1 รายในกลุ่ม 2 ที่มี clinical lipoatrophy ไม่พบว่าสัดส่วนของผู้ป่วยที่มี neuropathic signs และการเปลี่ยนแปลงของ eGFR จากก่อนเริ่มยามีความแตกต่างกันระหว่างกลุ่ม

บทสรุป:

การใช้ d4T ระยะสั้นก่อนการเริ่มใช้ AZT ทำให้เกิดภาวะซีดน้อยลง และเกิด peripheral neuropathic signs น้อยกว่าเมื่อเทียบกับการเริ่มด้วย AZT ตั้งแต่ต้น การใช้ d4T ทำให้ CD4 count เพิ่มดีที่สุดในช่วงแรก อย่างไรก็ตาม มีการลดลงของ peripheral fat ที่สามารถตรวจพบได้จาก DEXA ที่ 1 ปีหลังหยุด d4T ไปแล้ว แต่ไม่พบอาการทางคลินิกที่เกิดจากการลดลงนี้ ดังนั้น การเริ่มด้วยยาสูตรที่มี d4T เป็นระยะเวลา 6 เดือน ก่อนเปลี่ยนเป็นยาอื่นอาจเป็นทางเลือกหนึ่งสำหรับผู้ป่วยที่มีภาวะซีดหรือมี CD4 count ต่ำก่อนเริ่มยา ข้อมูลที่ได้จากการศึกษานี้สามารถนำไปใช้ประกอบการพิจารณาแนะนำการเริ่มใช้ยาต้านไวรัสทั่วโลกได้ในประเทศที่ยังคงมีการใช้ AZT มากกว่า TDF ในสูตรยาต้านไวรัสสูตรแรกอยู่

Patients underwent a neuropathy examination during the screening process utilizing the AIDS Clinical Trials Group (ACTG)/Neurology and Neurologic AIDS Research Consortium (NARC) methodology [3]. Patients diagnosed to have possible peripheral neuropathy (absent or diminished ankle reflex OR either diminished vibratory, pin or temperature sensation OR contact allodynia) were excluded from the study because of the potential risk of randomization to the d4T containing arm. Hepatitis B co-infection was added to the exclusion criteria in December 2008 to avoid randomization of patients with hepatitis B co-infection to the d4T or AZT containing arms.

Data collection

Clinical assessment including neuropathy examination were performed at baseline, weeks 4, 8, 12, and every 3 months thereafter. Hemoglobin (Hb) and serum alanine aminotransferase (ALT) were measured at baseline, weeks 2, 12 and every 3 months after that. CD4 count, plasma HIV-RNA, and serum creatinine (Cr) were assessed at baseline and every 3 months. Serum lactate, fasting plasma glucose, fasting lipid profiles, and dual energy absorptiometry (DEXA) were performed at baseline and every 6 months. Self-reported adherence using 30-day visual analog scale was assessed at weeks 4, 8, 12, and then every 3 months.

Data analysis

We based our study sample size on the assumption that hemoglobin levels among patients in the arms treated with d4T-based or TDF-based regimens would not fall whereas mean change in hemoglobin would be -1.09 (standard deviation, SD, 1.54) g/dL after 24 weeks of treatment (data derived from HIV-NAT 001 study). A sample size of 44 in each arm would provide the power to detect, at the 5% significant level with a power of 90%, a 1.09 g/dL change in hemoglobin between arms. With the estimation of approximately 10% lost to follow up, a sample size of 50 per arm was used.

The population for both efficacy and safety analyses was intention to treat (ITT), including all patients who were assigned to a particular treatment arm and had some follow-up data, according to their allocated treatment arm at baseline. All hypothesis tests were two-sided, pairwise comparisons of treatment difference between the switch arm and the other treatment arms; statistical significance was taken at a level of 5 percent. P-values were not adjusted for multiple endpoints. Continuous endpoints with missing data had the last observation carried forward. Treatment differences, and 95 percent confidence intervals (95%CI), were calculated in addition to two-sided significance levels. If important imbalances in baseline covariates were apparent, then further adjusted analyses were performed and presented in addition to unadjusted analyses. All primary analyses (ITT) used only available data. Secondary analyses was on an as treated dataset (per protocol, PP), in which randomized patients were censored once they ceased their randomised treatment strategy.

arms; 51 in arm 1 (GPO-VIR S switch arm), 50 in arm 2 (GPO-VIR Z arm), and 49 in arm 3 (Truvada/NVP arm). Two patients did not receive allocated study drugs; 1 in arm 2 who had asymptomatic peripheral neuropathy revealed at the baseline visit and 1 in arm 3 who did not return for the baseline visit.

Among 150 randomized patients, 55% were female and mean (SD) age was 34 (8) years (Table 1). Baseline mean CD4 count was 161 (94) cells/mm^3, plasma HIV-RNA was $\log_{10}$4.87 (0.65) copies/ml, hemoglobin was 12.5 (1.6) g/dL, body weight was 57.9 (10.9) kg, and eGFR was 82.9 (15.5) mL/min/1.73m^2. There was no significant difference between arms in terms of baseline characteristics.

Immunological and virological responses to 3 antiretroviral regimens

From baseline to week 24 and week 72, mean absolute CD4 count increased from 154 to 322 and 361 cells/mm^3 in arm 1, from 174 to 290 and 340 cells/mm^3 in arm 2, and from 157 to 274 and 355 cells/mm^3 in arm 3 (Figure 2). By the ITT analysis, absolute CD4 count increased more in arm 1 than arm 2 and arm 3 from baseline to week 24 (168 vs. 117 and 118 cells/mm^3, p=0.01 and 0.02, respectively) but was similar among arms by week 72.

Absolute changes in $\log_{10}$ plasma HIV-RNA from baseline to week 24 (-3.13 in arm 1 vs. -3.14 in arm 2 vs. -3.05 copies/mL in arm 3) and from baseline to week 72 (-3.12 in arm 1 vs. -3.16 in arm 2 vs. -3.17 in arm 3) were similar among arms. There were no significant differences in the proportion of patients with plasma HIV-RNA <40 copies/mL or <400 copies/mL at weeks 24 and 72 between arms (Figure 3). By the ITT analysis, plasma HIV-RNA <40 copies/mL was detected at week 24 in 75% of patients in arm 1 vs. 78% in arm 2 vs. 71% in arm 3 (not significantly different). At week 72, plasma HIV-RNA was <40 copies/mL in 84% of patients in arm 1 vs. 92% in arm 2 vs. 83% in arm 3 (not significantly different). Virologic efficacy was similar when patients were stratified by baseline CD4 count of <100 or ≥100 cells/mm^3 and proportions of patients who achieved plasma HIV-RNA <40 copies/mL at week 72 were 82.2 and 88.3%, respectively (p=0.3). Plasma HIV-RNA <400 copies/mL was detected at week 24 in 94% of patients in arm 1 vs. 96% in arm 2 vs. 87% in arm 3 (not significantly different). At week 72, plasma HIV-RNA was <400 copies/mL in 88% of patients in arm 1 vs. 92% in arm 2 vs. 87% in arm 3 (not significantly different).

Among patients who received GPO-VIR Z250 in the study, 92% of those who received 72-week of GPO-VIR Z250 treatment and 84% of those who received 24-week GPO-VIR S30 followed by 48-week GPO-VIR Z250 had plasma HIV-RNA <40 copies/mL at week 72.

Proportions of patients who reported <95% adherence were similar among arms at any individual study visit. At week 72, 4.1% of patients in arm 1, 2.1% in arm 2, and 0.0% in arm 3 had <95% adherence measured by 30-day visual analog scale.

Changes in hemoglobin level, body composition, neuropathic signs, and renal function among Thai patients receiving 3 antiretroviral regimens (intention to treat analysis)

Changes from baseline to week 24

significantly lower in arm 3 (4.7 fl) compared to arm 1 (19.6 fl, p<0.001) and arm 2 (20.0 fl, p<0.001).

Arm 1 had larger decrease in peripheral fat (-301 g) than arm 2 (143 g) and arm 3 (281 g) by week 72 but this did not reach statistically significant level (Figure 5). Proportion of patients with >10% decline in peripheral fat mass from baseline was 43.1% in arm 1, 34.7% in arm 2, and 33.3% in arm 3 (not significantly different among arms). Only 1 patient in arm 2 had grade 1 clinical lipoatrophy noted at week 48 and had AZT switched to TDF at week 60. Peripheral fat measured by DEXA in this patient was 8814.1, 7625.2, and 9246.3 at baseline, week 24, and week 72, respectively. Changes in lean body mass, and weight from baseline to week 72 were similar among arms (data not shown)

Proportion of patients with neuropathic signs at week 72 (Figure 6) was 9.8% in arm 1, 24.5% in arm 2, and 12.5% in arm 3. This was not significantly different among arms. Rate of peripheral neuropathy at week 72 was 9.8% in arm 1, 16.3% in arm 2, and 8.3% in arm 3. This was also not significantly different among arms. Among patients who met the peripheral neuropathy definition, only 1 patient in arm 2 had symptoms related to peripheral neuropathy. None of the patients had both diminished sensation and absent or diminished ankle reflexes relative to knees, detected bilaterally in the lower extremity.

Mean CCr was 82.51 mL/min in arm 1, 88.30 mL/min in arm 2, and 80.45 mL/min in arm 3. Mean eGFR was 79.84 mL/min/1.73 m^2 in arm 1, 83.19 mL/min/1.73 m^2 in arm 2, and 74.28 mL/min/1.73 m^2 in arm 3. From baseline to week 72, changes in CCr (-1.86, -1.46, and -6.55 mL/min in arm 1, 2, and 3, respectively) and eGFR (-2.680, -0.15, and -8.72 mL/min/1.73 m^2, respectively) were not different among arms (p=0.066 comparing arm 3 vs. arm 2 changes in eGFR). There was no proteinuria case and 1 glucosuria case was identified in arm 2 at week 72.

Other antiretroviral drugs-associated toxicities

Mean absolute white blood cell (WBC) count decreased significantly more in arm 2 (from 5.59 at baseline to 4.69 at week 24 and to 4.92 x $10^3/mm^3$ at week 72) than in arm 1 (from 5.04 to 5.82 at week 24, p<0.001, and to 5.18 x $10^3/mm^3$ at week 72, p<0021) and in arm 3 (from 4.96 to 5.52 at week 24, p<0.001, and to 5.64 x $10^3/mm^3$ at week 72, p<0.001). Mean absolute neutrophil count (ANC) decreased significantly more from baseline to week 24 in arm 2 (from 2.90 to 2.35 x $10^3/mm^3$) than arm 1 (from 2.61 to 3.24 x $10^3/mm^3$, p<0.001) and arm 3 (from 2.71 to 3.12 x $10^3/mm^3$, p=0.001). From baseline to week 72, ANC decreased significantly more in arm 2 than arm 3 (from 2.90 to 2.61 x $10^3/mm^3$ vs. from 2.71 to 3.24 x $10^3/mm^3$, p=0.004). Changes in platelet count was not different between arms.

Mean total cholesterol increased significantly less from baseline to week 24 in arm 3 than arm 1 (17.3 vs. 36.8 mg/dL, p=0.01) but not than arm 2 (25.1 mg/dL, p=0.3). From baseline to week 72, mean total cholesterol increased significantly less in arm 3 than arm 1 (16.4 vs. 38.4 mg/dL, p=0.005) and arm 2 (32.1 g/dL, p=0.043). Mean high density lipoprotein (HDL) cholesterol in arm 1 increased significantly more from baseline to week 24 than arm 2 (14.7

Grade 2-4 rash related to study drugs was found in 19.6%, 24.5%, and 10.4% of patients in arm 1, arm 2, and arm 3, respectively. Nausea and vomiting of grade 2-4 was found in 7.8%, 10.2%, and 2.1% in arm 1, arm 2, and arm 3, respectively. None of these adverse events were statistically different among arms.

Rates of grade 2-4 hepatotoxicity and rash were similar between 120 patients who had baseline CD4 count <250 cells/mm^3 and 28 patients who had baseline CD4 count between 250-350 cells/mm^3 (p=1.0 and p=0.6, respectively). In addition, there was no significant difference in the occurrence of grade 2-4 anemia, hepatotoxicity, eGFR reduction or rash when patients were stratified by baseline CD4 count of <100 or ≥100 cells/mm^3 (p=0.2, p=0.6, p=0.1, and p=0.6, respectively). Use of folic acid or iron supplement were not found to be confounding factors for anemia endpoint. Similarly, use of isoniazid or vitamin B supplement were not found to be confounding factors for neuropathy endpoint.

Changes in antiretroviral drugs due to toxicities

Antiretroviral drug changes due to drug toxicities occurred in 35 patients. NVP-related toxicities, mostly NVP-associated rash, caused antiretroviral drug changes from NVP to EFV in 28 cases, 6 of these cases subsequently needed change from EFV to lopinavir/ritonavir (LPV/r), and from NVP to LPV/r in 1 case. One case had d4T changed to AZT due to numbness in extremities. AZT-related toxicities led to regimen modification in 5 cases (4 due to anemia and 1 due to lipoatrophy). AZT/3TC was switched to TDF/FTC in 4 cases and AZT dose was reduced to 200 mg BID in 1 anemic case. There was no TDF dose reduction in this study.

DISCUSSION

Our study was the first randomized controlled trial to compare toxicity and efficacy of 3 antiretroviral regimens containing short-term d4T use, AZT use, and TDF use with NVP. Use of AZT or TDF-based regimens are currently recommended in resource-limited settings including Thailand [1, 2] as first-line antiretroviral regimens. However, AZT may still be used more commonly than TDF in some countries due to the higher cost of the latter. Use of d4T was phased out globally to avoid potential long-term risks on peripheral neuropathy and lipoatrophy. No data are available on the potential risks and benefits of short-term d4T use. Nevertheless, certain guidelines currently recommend short-course d4T lead-in use prior to AZT use to avoid anemia, commonly caused by AZT, during the early treatment period [2].

We demonstrated that all 3 study regimens resulted in similar virologic efficacy at 72 weeks of treatment. Among patients who received GPO-VIR Z250 in the study, 92% of those who received 72-week of GPO-VIR Z250 treatment and 84% of those who received 24-week GPO-VIR S30 followed by 48-week GPO-VIR Z250 had plasma HIV-RNA <40 copies/mL at week 72. Plasma HIV-RNA was <40 copies/mL by week 72 in 83% of patients who received Truvada/NVP. Previous studies have provided conflicting data on virologic efficacy

arm, 10.2% in the AZT arm, and 2.1% in the TDF arm at week 24, and was 9.8% in the d4T arm, 16.3% in the AZT arm, and 8.3% in the TDF arm at week 72. Only 1 patients in the AZT arm had symptomatic peripheral neuropathy. Peripheral neuropathy and symptomatic peripheral neuropathy rates found in our study was lower than those recently reported from naive HIV-positive patients starting antiretroviral treatment in the ACTG studies [4]. At 48 weeks after antiretroviral initiation, 29.7% and 10.1% developed peripheral neuropathy and symptomatic peripheral neuropathy, respectively. Unlike our patients, 22.6% and 4.3% of the ACTG patients already had peripheral neuropathy and symptomatic peripheral neuropathy prior to antiretroviral initiation.

We did not identify any significant increase in renal toxicity with TDF use in our study although there was a trend in eGFR reduction at week 72 compared to the AZT arm (-0.15 vs. -8.72 mL/min/1.73 m^2, p=0.066). In a recent systematic review and meta-analysis on renal safety of TDF in HIV-infected patients, there was a significantly greater loss of renal function among the TDF recipients compared to control subjects (mean CCr difference of 3.92 mL/min) [17] as well as a greater risk of acute renal failure. Selection of a relatively healthier group of patients in to most of the studies, including our study, may underestimate the risk of renal toxicity from TDF use in the real world clinical settings. With expanded use of TDF in developing countries, regular and long-term monitoring of renal function will become necessary.

Our study is unique in several ways. This study was the first randomized controlled trial to compare safety and efficacy of 3 antiretroviral regimens containing short-term d4T use, AZT use, and TDF use with NVP. The inclusion of equal proportion of female and male patients helped generalize our study results to HIV-infected population in most developing countries where HIV transmission occurs mainly through heterosexually transmission. Use of DEXA scan to identify any changes in body mass composition also help strengthen the findings of possible adverse effects on peripheral fat from short-term d4T use even though this might be subtle.

A few limitations were identified in our study. First, baseline mean CD4 count of our study population was higher than that in general Thai HIV-infected patients when they accessed antriretroviral treatment in the National Antiretroviral Treatment Program (41 cells/mm^3) [18] and we only included patients with predefined range of safety laboratory values. These might result in bias when interpreting the efficacy and toxicities data of different antiretroviral regimens. Second, we had a small sample size in each study arm and a short follow-up time which might not be enough to identify differences in less common safety parameters or parameters which might occur with longer use of antiretroviral drugs. Most of the major toxicities from the study antiretroviral drugs, however, should have been captured in the study period.

In summary, we demonstrated that short-term d4T use before introducing AZT caused less anemia and peripheral neuropathic signs compared to initiating treatment with AZT. Initial rise in CD4 was greatest with d4T. However, peripheral fat reduction by DEXA could be observed at 1 year after d4T discontinuation. A 6-month d4T lead-in therapy could be

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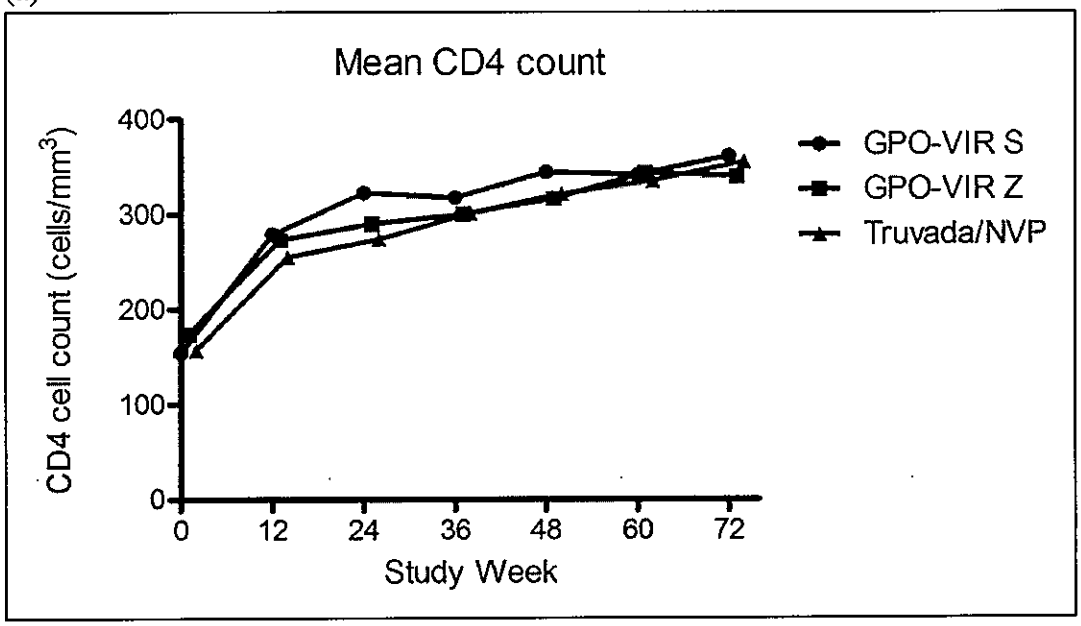
Table 1: Baseline characteristics of SEARCH 003 patients, by study arm.

Parameter	Arm 1 GPO-VIR S (n = 51)	Arm 2 GPO-VIR Z (n = 49)	Arm 3 Truvada/NVP (n = 48)	All arms (n = 148)
Site, n(%)				
Bangkok	29 (57)	29 (59)	29 (60)	87 (59)
Chonburi	22 (43)	20 (41)	19 (40)	61 (41)
CDC classification, n(%)				
A	25(49)	26 (53)	27 (56)	78 (53)
B	23 (45)	21 (43)	21 (44)	65 (44)
C	3 (6)	2 (4)	0 (0)	5 (3)
Female n(%)	28 (55)	28 (57)	25 (52)	81 (55)
Age (years) Mean (SD) Median (IQR)	35 (7) 33 (29 – 40)	34 (8) 24 (28 – 40)	35 (9) 34 (28 – 39)	34 (8) 34 (29 – 40)
Weight (kg) Mean (SD) Median (IQR)	56.7 (12.0) 54.3 (47.9 -60.5)	58.2 (11.2) 57.3 (50 -64.2)	58.9 (9.6) 58.4 (51.4-66)	57.9 (10.9) 56.1 (50-65.2)
Height (cm) Mean (SD)	160.3 (8.6)	161.9 (8.1)	162.6 (8.8)	161.6 (8.5)
CD4 Count (cells/mm^3) Mean (SD)	154 (91)	174 (97)	157 (94)	161 (94)
Plasma HIV-RNA, log_{10} copies/mL Mean (SD)	4.84 (0.67)	4.88 (0.63)	4.88 (0.68)	4.87 (0.65)
Hemoglogin (g/dL) Mean (SD)	12.4 (1.66)	12.43 (1.61)	12.76 (1.61)	12.53 (1.63)
Hemoglobin <10g/dL, n(%)	3 (6)	3 (6)	2 (4)	8 (5)
WBC count Mean (SD)	5 (1.4)	5.6 (1.9)	5 (1.1)	5 (1.5)
Platelets Mean (SD)	210 (66.3)	225 (66.0)	234 (79.7)	222 (71.1)
CCr by Cockcroft--Gault formula (mL/min) mean (SD)	84.37 (21.95)	86.85 (18.11)	86.99 (17.78)	86.04 (19.33)
eGFR by MDRD formula				

(a)



(b)

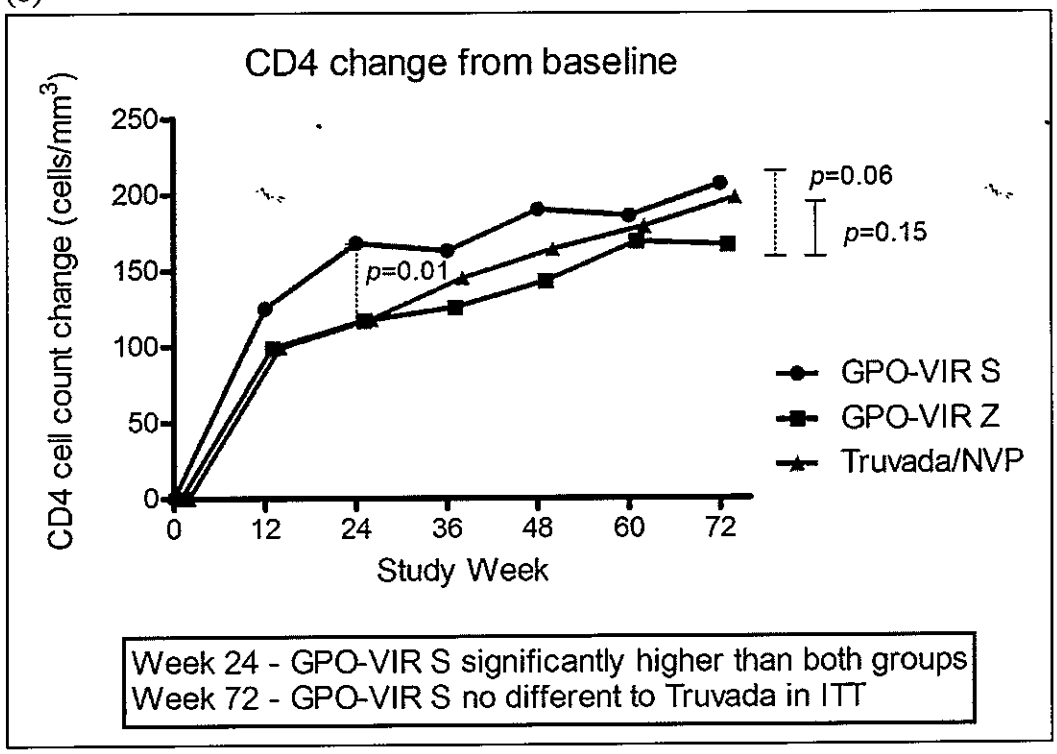
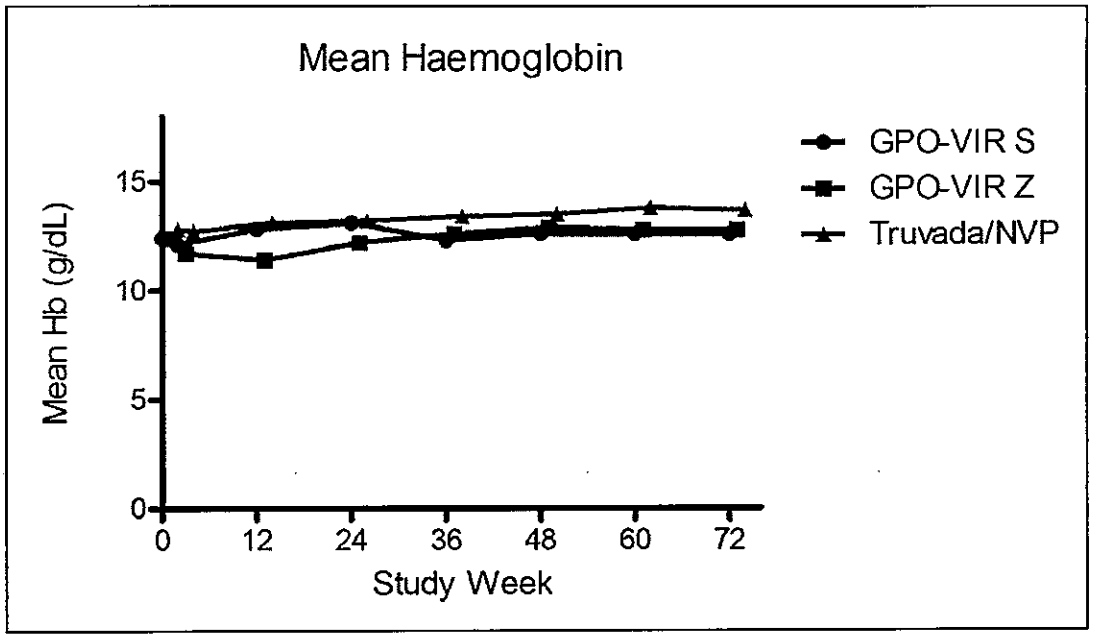


Figure 2: Mean CD4 count and mean CD4 count change from baseline, by study arm. (a) Mean CD4 count by study arm and (b) mean CD4 count change by study arm. Absolute CD4 count increased more in arm 1 than arms2 and arm 3 from baseline to week 24 (168 (126) vs. 117 (93) and 118 (75.8) cells/mm^3, p=0.01 and 0.02, respectively) but was similar among arms by week 72.

(a)



(b)

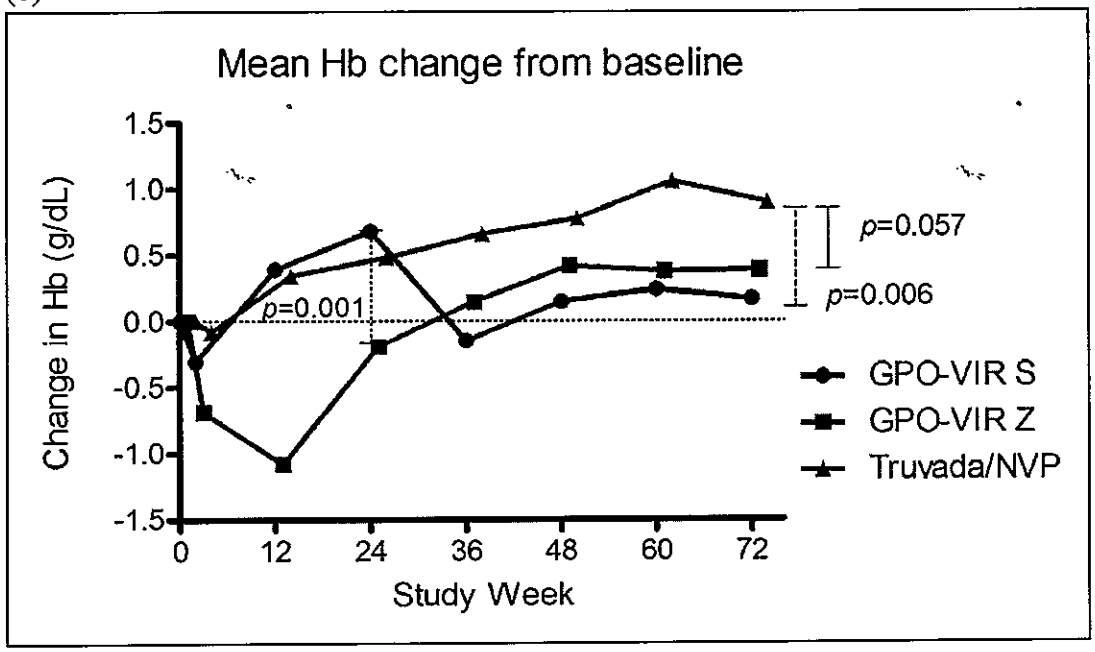
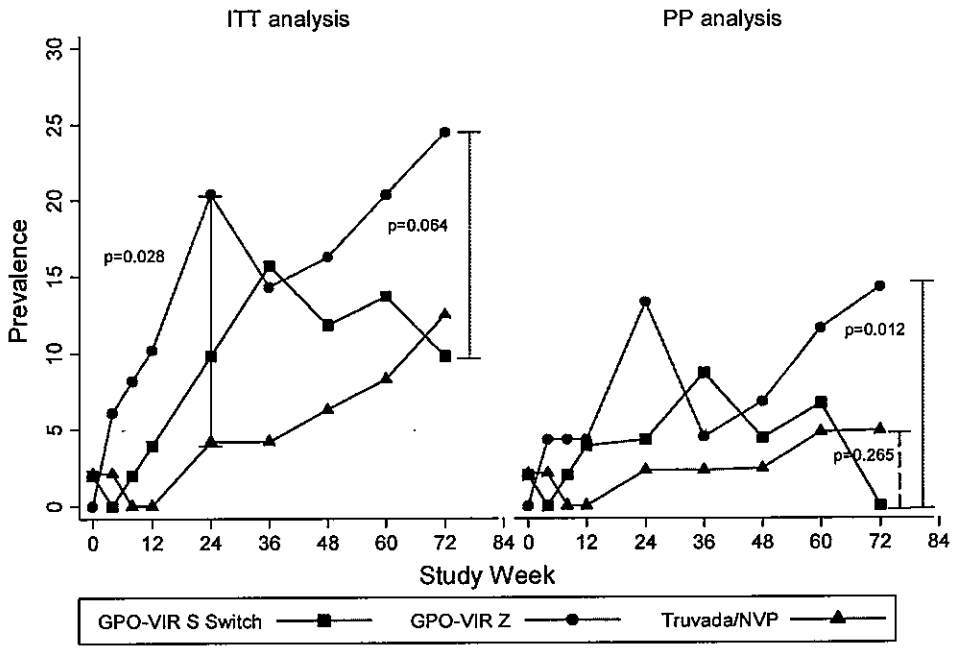


Figure 4: Mean hemoglobin and mean hemoglobin change from baseline, by study arm., (a) Mean Hb by study arm and (b) mean Hb change from baseline by study arm. At week 24, mean Hb in arm 2 decreased significantly compared to arm 1 (-0.19 (1.25) vs. 0.68 (1.23) g/dL, p=0.001) and arm 3 (0.48 (1.29) g/dL, p=0.010). At week 72, mean Hb in arm 3 significantly increased from baseline compared to arm 1 (0.90 (1.27) vs. 0.17 (1.50) g/dL, p=0.006).

(a)



(b)

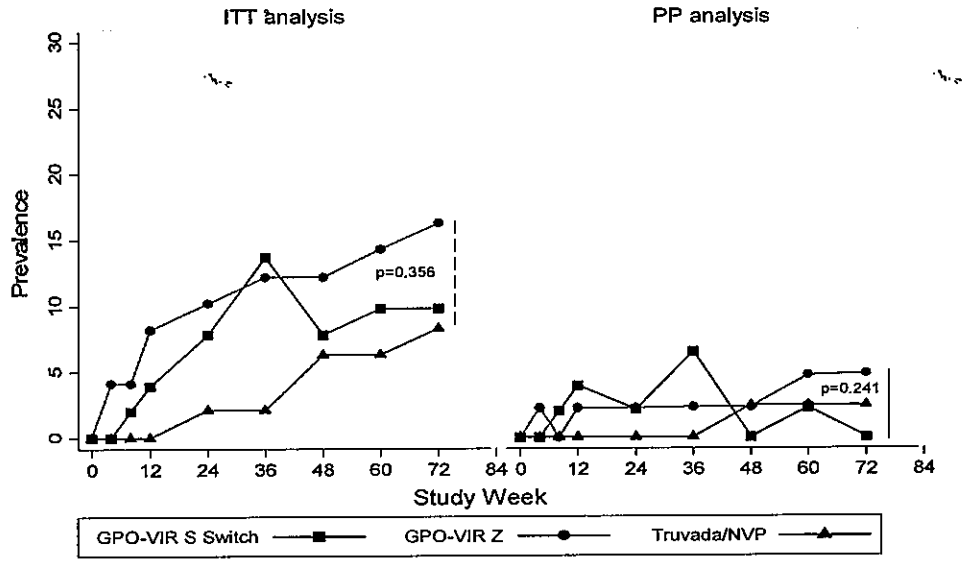


Figure 6: Proportion of peripheral neuropathic signs and peripheral neuropathy, by study arm. Proportion of patients with (a) neuropathic signs, defined as diminished sensation by any modality (pin, touch, temperature, vibratory, or joint position) detected bilaterally in the lower extremity or absent or diminished ankle reflexes relative to knees, at week 24 was higher in arm 2 compared to arm 3 (20.4% vs. 4.2%, p=0.028) but was not significantly different between arms at week 72 by ITT analysis, and (b) peripheral neuropathy, using the AIDS Clinical Trials Group (ACTG) definition of reduced vibration sensation in both great toes or absent or diminished ankle reflexes bilaterally relative to knees, was not significantly different between arms at week 24 and week 72.

Treatment outcome and safety of zidovudine/lamivudine/nevirapine fixed-dose combination in HIV-infected Thai patients

TITLE: Treatment outcome and safety of zidovudine/lamivudine/nevirapine fixed-dose combination in HIV-infected Thai patients

ชื่อภาษาไทย: ผลการรักษาและความปลอดภัยของยาเม็ดรวม ซิโดวูดีน/ลามิวูดีน/เนวิราปีน ในผู้ติดเชื้อเอชไอวีชาวไทย

ABSTRACT

Background:

GPO-VIR Z 250, a fixed-dose combination antiretroviral regimen containing AZT 250 mg + 3TC 150 mg + NVP 200 mg, will be increasingly used in Thailand as one of the preferred regimens for treatment-naive patients and recommended switched regimen as part of the d4T phase out plan.

Methods:

This is a retrospective study at the Thai Red Cross AIDS Research Centre (TRC-ARC) and HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration. Demographic, clinical and laboratory data were obtained from the databases at baseline and at different time points after the initiation of or the switch to GPO-VIR Z 250.

Results:

There were 143 patients (41.7%) who started (start group) and 200 patients (58.3%) who switched to GPO-VIR Z 250 (switch group). Median age was 35 years (IQR 31-42 years) and 65.3% were women. After 1 year of GPO-VIR Z 250 treatment, 56 of 82 patients in the start group and 96 of 153 patients in the switch group who reached this time point had plasma HIV-1 RNA results. Plasma HIV-1 RNA was <50 copies/mL in 78.6% of the start group and 91.7% of the switch group. No risk factor was identified for treatment failure. Anemia was found more frequently in the start group (26.7% vs. 7.6%, $p<0.001$) than the switch group. Rash (2.8% vs. 1.0%, $p=0.211$) and hepatotoxicity of any grade (29.2% vs. 21.0%, $p=0.174$) were found at similar rates in the start and the switch groups. Only patients in the start group, however, experienced grade 3-4 anemia (3.3%) and grade 3 hepatotoxicity (3.4%).

Conclusions:

GPO-VIR Z 250 was an effective antiretroviral regimen for HIV-infected Thai patients. Common side effects from AZT and NVP were found in the ranges previously reported and mostly were mild to moderate side effects. Our findings support the recommendations to use

ต้านไวรัสเอชไอวีในประเทศไทย พ.ศ. 2553 ซึ่งแนะนำให้ยา GPO-VIR Z 250 เป็นหนึ่งในสูตรยาที่แนะนำให้ใช้เป็นสูตรแรก รวมถึงเป็นหนึ่งในสูตรยาที่ให้ใช้เมื่อต้องการเปลี่ยนสูตรยาจากสูตรเดิมอื่นๆ

INTRODUCTION

GPO-VIR Z 250 is a fixed-dose combination (FDC) antiretroviral regimen produced by the Thai Government Pharmaceutical Organization (GPO). The tablet contains AZT 250 mg + 3TC 150 mg + NVP 200 mg and can be taken 1 tablet every 12 hours. The 2010 Thailand National Antiretroviral Treatment Guidelines, which was launched at the end of 2010, includes GPO-VIR Z 250 as one of the preferred antiretroviral regimens for eligible, treatment-naive HIV-infected Thai patients. This recommendation was made in Thailand at the same time the World Health Organization (WHO) recommended to phase out stavudine (d4T) use [1] to avoid long-term undesirable side effects, including lipoatrophy and dyslipidemia, from d4T. Therefore, it can be foreseen that the use of GPO-VIR Z 250 will gradually replace GPO-VIR S [2], the commonly used FDC which contains d4T+3TC+NVP, both as the initial antiretroviral regimen and as the substituted regimen for those previously on d4T-based regimens in Thailand.

There is no published data on the treatment outcome of GPO-VIR Z 250 in HIV-infected Thai patients. Previous studies among treatment-naïve patients in other countries reported 69% - 74% virologic suppression rate at 1 year after the use of AZT+3TC+NVP [3-5]. A few studies evaluated treatment outcome in treatment-experienced patients after the switch from d4T-based regimens to AZT shown no significant changes in CD4 count and HIV-1 RNA level [6].

Common side effects from the antiretroviral component of GPO-VIR Z 250 include anemia from AZT and rash and hepatotoxicity from NVP. In this study, we evaluated the immunologic and virologic efficacy of GPO-VIR Z 250 among HIV-infected Thai patients who started GPO-VIR Z 250 as their initial regimen and those who switched from other antiretroviral regimens to GPO-VIR Z 250. The common side effects of the antiretroviral components of GPO-VIR Z 250 were also assessed in this study.

points were compared using t test or non-parametric equivalents as appropriate. Logistic regression analysis was used to assess factors associated with virologic efficacy. Prevalence of anemia, rash and hepatotoxicity was estimated by proportion of patients who have the event by the total number of patient and the 95%CI according to severity grading of each adverse event. Logistic regression analysis was performed for each adverse event to identify risk factors. All variables with significant level less than 0.1 were selected into multivariate model. In all analyses, effect sizes and 95%CI around this effect size were given in addition to p values. All hypothesis tests were two-sided comparison. Statistical significance was taken at level of 5%.

RESULTS

Study participant baseline characteristics (Table 1)

A total of 343 HIV-infected Thai patients met eligibility criteria and were included into the analyses. There were 143 patients (41.7%) who started GPO-VIR Z 250 as their initial antiretroviral regimen (start group) and 200 patients (58.3%) who switched from other antiretroviral regimens to GPO-VIR Z 250 (switch group). The study population was composed of 65.3% women and 34.7% men. Median age was 35 years (IQR 31-42 years).

The start group was younger (p=0.017) and was more likely to have the BMI out of the normal range (p=0.002). They also had lower median baseline CD4 count (171 vs. 400 cells/mm^3, p<0.001) and higher baseline $\log_{10}$ HIV-1 RNA level (5.2 vs. 1.7 copies/ml, p<0.001) than the switch group. Baseline anemia of grade 1 and above (hemoglobin, Hb, <10g/dL) was found in 12.6% of the start group and 1.6% of the switch group (p<0.001). Baseline ALT elevation of grade 1 and above (≥1.25 times of upper limit of normal) was found in 4.0% of the start group and 13.5% of the switch group (p=0.035). The switch group had higher baseline cholesterol (p<0.001), higher HDL-cholesterol (p<0.001), higher LDL-cholesterol (p=0.003), and higher triglyceride (p=0.011) than the start group. The majority of the switch group used NVP-based regimens (91.5%) prior to the switch and the median time of previous regimens use was 2.6 years. Hepatitis B coinfection and hepatitis C coinfection was identified in 6.6% and 8.3%, respectively. Median time of follow-up after GPO-VIR Z 250 use was shorter in the start group (78 vs. 102 weeks, p=0.001) than the switch group.

Among the start group, those with CD4 count ≤100 cells/mm^3 (Table 1.1) were more likely to be male, had low BMI, had CDC clinical stage C than those with CD4 count ≥100 cells/mm^3.

worsening of anemia was more frequent (p<0.001) with earlier onset (p=0.008) in the start group than in the switch group.

All-grade rash was identified in 2.8% of the start group and 1% of the switch group (p=0.211). There was no rash in the switch group who previously used NVP-based regimens while rash was found in 12.5% of the switch group who previously used non-NVP-based regimens (p=0.001, compared 3 groups). Grade 4 rash was found in one (0.7%) patient in the start group only. Onset of rash was similar between the start group and the switch group who previously used non-NVP-based regimens (2.5 vs. 3.5 weeks, p=0.481).

All-grade hepatotoxicity was identified in 29.2% of the start group 21.0% of the switch group (p=0.174). The rates were 19.4% in the switch group who previously used NVP-based regimens and 36.4% in the switch group who previously used non-NVP-based regimens (p=0.183, compared 3 groups). Grade 3 hepatotoxicity was found in 3.2% of patients in the start group only. The start group tended to have earlier onset of hepatotoxicity than the switch group (3.7 vs. 23.3 and 14.4 weeks, p=0.083) but this did not reach statistically significant level. Among those who already had elevated ALT at baseline, worsening of ALT elevation was more frequent (p=0.005) in the start group than in the switch group.

Among 15 participants in the start group who did not have NVP lead-in period, 4 (26.7%) developed anemia (3 with grade 1-2 and 1 with grade 3-4), 1 developed grade 1 rash (6.7%), and 5 (33.3%) developed hepatotoxicity (all with grade 1-2).

Hypercholesterolemia of all grades was found in 37.5% of the start group, in 67.3% of the switch group who previously used NVP-based regimens, and in 63.6%% of the switch group who previously used non-NVP-based regimens (p<0.001). LDL-cholesterol above 130 mg/dL was found in 25.0% of the start group, in 43.4% of the switch group who previously used NVP-based regimens, and in 54.6% of the switch group who previously used non-NVP-based regimens (p=0.012). Low HDL (<50mg/dL in women and <40mg/dL in men) was found in 88.6% of the start, in 83.9% of the switch group who previously used NVP-based regimens, and in 100.0% of the switch group who previously used non-NVP-based regimens (p=0.245). Hypertriglyceridemia of all grades was found in 1.3% of the start group, in 6.0% of the switch group who previously used NVP-based regimens, and in none of the switch group who previously used non-NVP-based regimens (p=0.174). High plasma glucose level of all grades was found in 6.6% of the start group,15.0% of the switch group who previously used NVP-based regimens, and in none of the switch group who previously used non-NVP-based

development of hepatotoxicity from GPO-VIR Z 250. At baseline, male participants had higher ALT ($p<0.001$) and higher triglyceride ($p=0.011$) than female participants (Table 10).

DISCUSSION

In this study, we found GPO-VIR Z 250 to be an effective antiretroviral regimen in naïve HIV-infected Thai patients. Undetectable plasma HIV-1 RNA level was achieved among 78.6%, 84.4%, and 95.8% of treatment-naïve patients at year 1, year 2, and year 3 of GPO-VIR Z 250 treatment, respectively. The virologic success rates among treatment-naïve patients in our study were comparable to previous studies conducted using AZT+3TC+NVP. The OzCombo 2 study carried out in Australia shown that 73% of naïve, HIV-infected patients randomized to start AZT+3TC+NVP had HIV-1 RNA below 50 copies/ml at 52 weeks of treatment [3]. Another randomized study in China also shown that 69% of naïve, HIV-infected patients who started on AZT+3TC+NVP had HIV-1 RNA below 50 copies/ml at 52 weeks of treatment [4]. The rate of virologic success in patients started on AZT+3TC+NVP was comparable to those on d4T+3TC+NVP regimen in both studies [3, 4]. In another study assessing the efficacy of AZT+3TC+NVP in women exposed to single-dose NVP or AZT for the prevention of mother to child transmission of HIV and their male partners in Zimbabwe, 85.1% and 73.8% of the patients had HIV-1 RNA below 400 copies/ml at 24 and 48 weeks of treatment, respectively [5]. A study in Cameroon showed that 91% of patients on AZT+3TC+NVP had HIV-1 RNA below 400 copies/ml at 24 weeks of treatment, the percentage was not statistically different from 86% of patients on d4T+3TC+NVP in the same study and the increases in CD4 count were similar in both groups [7]. CD4 count increase of 114 cells/mm^3 after 6 months of GPO-VIR Z in our study was quite similar to the increase of 97 cells/mm^3 with GPO-VIR S (d4T+3TC+NVP) use among Thai patients in another study, although their baseline CD4 count was lower than our patients [8]. As expected, due to a more rapid increase in CD4 count normally seen during the early treatment period, patients in the start group in our study had a higher increase in CD4 count than those in the switch group.

The virologic success rate of 91.7%, 98.3%, and 100.0% at 1 year, 2 years, and 3 years after the switch from other antiretroviral regimens to GPO-VIR Z 250 in our study was similar to other few studies which evaluated immunologic and virologic efficacy after the switch from d4T-based regimens to AZT. The only study looking at change in HIV-1 RNA level after the switch from d4T to AZT was performed among 78 HIV-infected Thai children and showed no

switch [9]. Low BMI (≤18 kg/m^2) and low CD4 count (<200 cells/mm^3) at the time of switch, found to be associated with severe anemia in the Cambodian study, were less common in our switch group [9]. A study among 78 HIV-infected Thai children showed a statistically significant decrease in Hb level, total white blood cell count and absolute neutrophil count. However, the decreases never reached grade 3-4 severity, and none of the patients had clinical symptoms or signs of anemia, leukopenia, or neutropenia [6].

Rash and hepatotoxicity are common side effects from NVP use. NVP-related rash has been reported in 4.3–36% of adults [13-26], but Stevens–Johnson syndrome is relatively infrequent, occurring in fewer than 1% of adults on treatment [14, 17, 21, 26]. Similar risk factors to those for NVP-related hepatotoxicity have been identified, including female sex, high baseline CD4 cell count, low baseline HIV-1RNA and high NVP blood level [15, 19-22]. The occurrence of rash in our study could be underreported due to the nature of the retrospective study as we found a much lower rate of rash (1.8%) compared to those previously reported in other studies. Grade 4 rash was found in one (0.7%) patient in the start group only. We did not identify any risk factors for the development of rash in this study.

Abnormal baseline transaminase levels and coinfection with hepatitis B and C viruses have been reported to be independent risk factors for antiretroviral-associated hepatotoxicity, including NVP-related hepatotoxicity [13, 14, 27, 28]. Symptomatic hepatotoxicity from NVP has been reported in 1.0–4.9% of adults [15-17, 27-31], while the incidence of all hepatotoxicities ranges widely from 3.2 to 12.0% [16, 17, 27-29, 32]. A number of factors have also been associated with NVP-related hepatotoxicity [13, 14, 27, 28, 32], including female sex, high baseline CD4 cell count, high NVP blood level, alcohol abuse and certain human leucocyte antigen (HLA) types [13, 14, 16, 27-29, 32, 33]. Grade 1-3 hepatotoxicity was identified in high proportions of our study participants, 29.2% and 21.0% of patients in the start group and switch group, respectively. Grade 4 hepatotoxicity was not identified in this study and grade 3 hepatotoxicity was found in 3.2% of patients in the start group only. The switch group tended to have higher rate of hepatotoxicity, all with grade 1-2, with later onset than the start group. This high frequency of hepatotoxicity may be the result of ALT selectively performed in those with abnormal baseline ALT or those who developed symptoms suggestive of hepatotoxicity as ALT was not regularly monitored in our study. The switch group were also previously exposed to other antiretroviral drugs for certain period of time which might pose them at risk for ALT elevation regardless of the switch to GPO-VIR Z 250. Being male and having high baseline ALT were significant risk factors for the development of hepatotoxicity

CONCLUSION

Our study population had a unique mixture of treatment-naïve and treatment-experienced patients similar to the population who will increasingly use GPO-VIR Z 250 in the country. We demonstrated that GPO-VIR Z 250 was an effective antiretroviral regimen, both as the first regimen or switched regimen. Common side effects such as anemia, rash, and hepatotoxicity were found in the ranges previously reported and mostly were mild to moderate side effects. Our findings support the recommendations made in the 2010 Thailand National Antiretroviral Treatment Guidelines to include GPO-VIR Z 250 as one of the preferred antiretroviral regimens for eligible, treatment-naive HIV-infected Thai patients and to phase out the use of d4T by switching to other nucleoside or nucleotide reverse transcriptase inhibitors in order to avoid long-term undesirable side effects, including lipoatrophy and dyslipidemia, from d4T.

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Previous PMTCT exposure, n (%) (female only)	41/91 (45.05)	55/133(42.42)	96/224 (50.89)	
AZT	13/41 (31.71)	34/55 (61.82)	47/96 (48.96)	
AZT/single-dose NVP	11/41 (26.83)	16/55 (29.09)	27/96 (28.13)	
HAART	17/41 (41.46)	5/55 (9.09)	22/96(22.92)	
Discontinued prior to GPO-VIR Z initiation	41/41(100.00)	55/55 (100.0)	96/96 (100.0)	
Previous ART before the switch, n (%)				
NVP-based HAART	n/a	183 (91.50)	183 (91.50)	
EFV-based HAART	n/a	8 (4.00)	8 (4.00)	
PI-based HAART	n/a	7 (3.50)	7 (3.50)	
Dual NRTIs	n/a	2 (1.00)	2 (1.00)	
Duration of previous ART (years), median (IQR)	n/a	2.6 (1.1-5.9)	2.6 (1.1-5.9)	
Reasons for the switch, n (%)				
Simplification	n/a	57 (28.50)		
Resistance	n/a	2 (1.00)		
Side effects	n/a	101 (50.50)		
Others	n/a	40 (20.00)		
Baseline CD4 count (cells/mm^3), median (IQR)	171 (63-214) (n=128)	400 (275-574) (n=188)	271 (167-451) (n=316)	**<0.001**
<100, n (%)	41 (32.03)	6 (3.19)	47 (14.87)	**<0.001**
100-199	49 (38.28)	19 (10.11)	68 (21.52)	
≥200	38 (29.69)	163 (86.70)	201 (63.61)	
Baseline log_{10} HIV-1 RNA (copies/ml), median (IQR)	5.2 (4.7-5.6) (n=51)	1.7 (1.7-1.7) (n=102)	1.7 (1.7,4.8) (n=154)	**<0.001**
Baseline hemoglobin (g/dL), median (IQR)	11.6 (10.6-12.7) (n=127)	13.2 (12.3-14.0) (n=182)	12.6 (11.5,13.8) (n=309)	**<0.001**

Duration on GPO-VIR Z (weeks) , median (IQR)	78 (13-148)	102 (53,177)	92 (38-162)	**0.001**
Adherence , n (%)				0.552
<95%	6 (4.20)	6 (3.00)	12 (3.50)	
≥95%	137 (95.80)	194 (97.00)	331 (96.50)	

[a] *p*-value between normal vs. abnormal gradings

IQR= interquartile range; BMI=body mass index; PMTCT=prevention of mother-to-child transmission of HIV; ART=antiretroviral therapy; HAART=highly active antiretroviral therapy; n/a=not applicable; NRTI=nucleoside reverse transcriptase inhibitor; ALT=alanine aminotransferase; ULN=upper limit of normal; HDL=high density lipoprotein; LDL=low density lipoprotein

Table 1.1: Baseline Characteristics of Study Participants in the Start Group by Baseline CD4 Count

Characteristics	**<100 cells/mm^3 (n=41)**	**≥100 cells/mm^3 (n =87)**	**Total (n=128)**	**p-value**
Gender, n (%)				**<0.001**
Male	27 (65.85)	20 (22.99)	47 (36.72)	
Female	14 (34.15)	67 (77.01)	81 (63.28)	
Age (years) at baseline, median (IQR)	46 (33-46)	32 (29-37)	34 (30-45)	**<0.001**
Baseline BMI (kg/m^2), median (IQR)	20.9 (18.3-22.5) (n=37)	22.3 (19.8-25.2) (n=70)	21.4 (19.3-24.0) (n=107)	**0.003**
<18.5, n (%)	10 (27.03)	11 (15.71)	21 (19.63)	**0.009**
18.5-24.9	26 (70.27)	41 (58.57)	67 (62.62)	
≥25.0	1 (2.70)	18 (25.71)	19 (17.76)	
Baseline CDC clinical staging, n (%)				**<0.001**
A	10 (24.39)	68 (78.16)	78 (60.94)	
B	4 (9.76)	9 (10.34)	13 (10.16)	
C	27 (65.85)	10 (11.49)	37 (28.91)	

	(n=35)	(n=58)	(n=93)	
Normal, n (%)	33 (94.29)	56 (96.55)	89 (95.70)	0.602[a]
Grade 1 (1.25-2.5xULN)	2 (5.71)	1 (1.72)	3 (3.23)	
Grade 2 (2.6-5.0xULN)	0 (0.00)	1 (1.72)	1 (1.08)	
Grade 3 (5.1-10.0xULN)	0 (0.00)	0 (0.00)	0 (0.00)	
Grade 4 (>10.0xULN)	0 (0.00)	0 (0.00)	0 (0.00)	
Baseline cholesterol (mg/dL), median (IQR)	172(135,211) (n=27)	169(143,189) (n=36)	170 (141,192) (n=63)	0.589
Baseline HDL-cholesterol (mg/dL), median (IQR)	49(35,59) (n=27)	39.5(34,51) (n=30)	43(35,58) (n=57)	0.164
Baseline LDL-cholesterol (mg/dL), median (IQR)	101(82,136) (n=27)	102(84,119) (n=29)	102(82,121) (n=56)	0.583
Baseline triglyceride (mg/dL), median (IQR)	138(91,154) (n=27)	103(69,150) (n=31)	119(81,152) (n=58)	0.119
Baseline fasting plasma glucose (mg/dL), median (IQR)	85.5(81,95) (n=26)	86(79,97) (n=29)	86(80,95) (n=55)	0.625
Hepatitis B coinfection, n (%)	0/8 (0.0%)	2/36 (5.56 %)	2/44 (4.55 %)	0.495
Hepatitis C coinfection, n (%)	0/1 (0.0%)	3/6 (50.00%)	3/7 (42.86 %)	0.350
Duration on GPO-VIR Z (wk) , median (IQR)	48 (2,119)	88 (28,149)	75 (11,143)	**0.004**

[a] *p*-value between normal vs. abnormal grading

IQR= interquartile range; BMI=body mass index; PMTCT=prevention of mother-to-child transmission of HIV; HAART=highly active antiretroviral therapy; ALT=alanine aminotransferase; ULN=upper limit of normal; HDL=high density lipoprotein; LDL=low density lipoprotein

Baseline CD4 count (cells/mm^3), median (IQR)	125(56,171) (n=21)	173(61,220) (n=86)	161(61,201) (n=107)	0.027
Baseline log_{10} HIV-1 RNA (copies/ml), median (IQR)	5.4(5.1,5.7) (N=15)	5.1 (4.8,5.5) (N=25)	5.2(4.8,5.6) (N=40)	**0.089**
Baseline hemoglobin (g/dL), median (IQR)	11(9,12) (n=19)	12(11,13) (n=86)	12(11,13) (n=105)	0.017
Normal, n (%)	12(63.16)	78(90.70)	90(85.71)	0.002[a]
Grade 1 (8.5-10.0 g/dL)	5(26.32)	7(8.14)	12(11.43)	
Grade 2 (7.5-8.4 g/dL)	2(10.53)	0(0.00)	2(1.90)	
Grade 3 (6.5-7.4 g/dL)	0 (0.00)	0(0.00)	0 (0.0)	
Grade 4 (<6.5 g/dL)	0(0.00)	1(1.16)	1(0.95)	
Baseline ALT (mg/dL), median (IQR)	23(16,26) (n=19)	20(16,28) (n=68)	21(16,27) (n=87)	0.334
Normal, n (%)	17(89.47)	65(95.59)	82(94.32)	0.311[a]
Grade 1 (1.25-2.5xULN)	2(10.53)	2(2.94)	4(4.60)	
Grade 2 (2.6-5.0xULN)	0 (0.0)	1(1.47)	1(1.15)	
Grade 3 (5.1-10.0xULN)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 4 (>10.0xULN)	0 (0.0)	0 (0.0)	0 (0.0)	
Baseline cholesterol (mg/dL), median (IQR)	178(142,190) (N=18)	170(143, 202) (N=37)	172(142,192) (N=55)	0.946
Baseline HDL-cholesterol (mg/dL), median (IQR)	50(34,59) (N=16)	43(37,57) (N=32)	44(35,58) (N=48)	0.776

Table 2: Changes in CD4 Count at Different Time Points among Study Participants with At Least 6-Month Duration of GPO-VIR Z 250 Treatment

CD4 Count Change (cells/mm^3)	Start Group	Switch Group	Total	p-value
From baseline to month 6 (median, IQR)	(n=82)	(n=151)	(n=233)	**<0.001***
Baseline	176 (86,202)	429 (307,626)	312 (187,502)	
Month 6	284 (163,376)	486 (354,632)	390 (276,568)	
Change	114 (57,159)	34 (-44,111)	67 (0,127)	
From baseline to month 12 (median, IQR)	(n=69)	(n=135)	(n=204)	
Baseline	177 (112,212)	424 (286,626)	302 (188,504)	**<0.001***
Month 12	307(217,384)	462 (360,635)	399 (288,536)	
Change	136 (72,215)	44 (-31,123)	70 (-0.5,154)	

*p-value comparing CD4 count changes from baseline to each time point

400-1000	0 (0)	0 (0)	0 (0)
≥1000	0 (0)	0 (0)	0 (0)
Total	24 (100)	58 (100)	82 (100)
Number of participants who reached this time point	29	66	95

Onset (weeks), median (IQR)	3.7 (2.0, 33)	23.3 (12.0-34.0)	14.4 (3.6, 36.4)	15.3 (3.0-34)	0.083
Worsening from baseline	20 (22.47)	7 (6.48)	2 (18.18)	29 (13.94)	**0.005**
Worsening onset (weeks), median (IQR)	2.1 (2.0-21.4)	17.3 (11.1-25.0)	25.7 (3.3-48.1)	7.9 (2.0-25.0)	0.178
Lipodystrophy	(n=143)	(n=184)	(n=16)	(n=343)	n/a
	0 (0.00)	2 (1.09)	0 (0.00)	2 (0.58)	
Week of onset, median (IQR)	0	42.1 (36.3-47.9)	0	42.1 (36.3-47.9)	n/a
Cholesterol (mg/dL)	(n=80)	(n=150)	(n=11)	(n=241)	**<0.001**
Grade 1 (200-239)	19 (23.75)	63 (42.00)	3 (27.27)	85 (35.27)	
Grade 2 (240-300)	11 (13.75)	33 (22.00)	2 (18.18)	46 (19.09)	
Grade 3 (>300)	0(0)	5 (3.33)	2 (18.18)	7 (2.90)	
Total	30 (37.50)	101 (67.33)	7 (63.64)	138 (57.26)	
Onset (weeks), median (IQR)	48.9 (25.9- 82.0)	33.4 (17.9-67.3)	23.3 (12.0-24.9)	35.0 (20.6-68.7)	0.072
Worsening from baseline	8 (10.00)	24 (16.00)	2 (18.18)	34 (14.11)	0.426
Worsening onset (weeks), median (IQR)	47.4 (17.5-54.3)	26.5 (21.7-49.3)	24.1 (23.3-24.9)	26.5 (22.9-49.0)	0.706
Fasting plasma glucose (mg/dL)	(n=76)	(n=147)	(n=11)	(n=234)	0.085
Grade 1 (110-125)	0 (0)	13 (8.84)	0 (0.00)	13 (5.56)	
Grade 2 (126-250)	4 (5.26)	8 (5.44)	0 (0.00)	12 (5.13)	
Grade 3 (251-500)	1 (1.32)	1 (0.68)	0 (0.00)	2 (0.85)	
Grade 4 (>500)	0 (0)	0 (0)	0 (0.00)	0 (0)	
Total	5 (6.58)	22 (14.97)	0 (0.00)	27 (11.54)	
Onset (weeks), median (IQR)	48.4 (47.6-48.9)	39.0 (20.0-82.7)	0	47.0 (20.0-73.3)	0.950
Worsening from baseline	1 (1.32)	11 (7.48)	0 (0.00)	12 (5.13)	0.103
Worsening onset (weeks), median (IQR)	49.9	38 (12-78.3)	0	42.5 (14-73.5)	n/a
Triglyceride (mg/dL)	(n=80)	(n=149)	(n=11)	(n=240)	0.174
Grade 2 (500-750)	1 (1.25)	5 (3.36)	0 (0.00)	6 (2.50)	
Grade 3 (751-1200)	0 (0)	2 (1.34)	0 (0.00)	2 (0.83)	
Grade 4 (>1200)	0 (0)	2 (1.34)	0 (0.00)	2 (0.83)	

Table 5: Changes in Laboratory Values from Baseline to Last Visits among Study Participants

Study Group		Study Visit	n	Units	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
Start	Hb	Baseline	127	g/dL	11.71	1.80	4.90	10.60	11.60	12.70	17.40
		Last visit	120	g/dL	11.73	2.13	3.70	10.60	11.90	13.25	16.60
		Change	105	g/dL	-0.08	2.33	-7.90	-0.90	0.00	1.10	11.70
		Time to last test	120	week	86.75	64.59	1.71	44.86	75.36	125.50	238.86
Switch from NVP-based regimens	Hb	Baseline	168	g/dL	13.25	1.54	9.40	12.30	13.20	14.00	17.50
		Last visit	172	g/dL	12.67	1.61	8.40	11.60	12.60	13.60	17.30
		Change	158	g/dL	-0.54	1.22	-4.40	-1.30	-0.55	0.20	2.90
		Time to last test	172	week	109.21	69.14	2.00	49.93	96.21	168.50	268.00
Switch from non-NVP-based regimens	Hb	Baseline	14	g/dL	13.46	1.77	11.30	12.20	12.80	14.80	17.60
		Last visit	12	g/dL	12.76	1.28	10.70	11.90	12.70	13.55	15.00
		Change	12	g/dL	-0.56	1.27	-3.00	-1.50	-0.50	0.25	1.60
		Time to last test	12	week	103.35	70.09	3.29	54.00	91.00	161.50	206.57
Start	ALT	Baseline	100	mg/dL	24.34	14.72	8.00	16.00	21.00	28.00	118.00
		Last visit	83	mg/dL	35.61	52.18	8.00	15.00	20.00	35.00	378.00
		Change	69	mg/dL	9.52	36.79	-75.00	-4.00	1.00	11.00	238.00

Switch from non-NVP-based regimens	Cholesterol	Baseline	11	mg/dL	232.09	104.29	133.00	171.00	202.00	253.00	510.00
		Last visit	11	mg/dL	207.45	45.15	143.00	175.00	202.00	257.00	289.00
		Change	9	mg/dL	-30.78	91.84	-253.00	-43.00	0.00	16.00	43.00
		Time to last test	11	week	112.38	65.78	3.29	59.86	95.29	175.14	206.57
Start	FPG	Baseline	56	mg/dL	99.27	47.51	66.00	80.50	86.00	95.00	342.00
		Last visit	76	mg/dL	90.45	22.57	64.00	79.00	87.00	95.00	237.00
		Change	27	mg/dL	-3.96	27.13	-106.00	-5.00	0.00	5.00	47.00
		Time to last test	76	week	98.97	64.40	3.29	48.14	81.07	150.00	228.86
Switch from NVP-based regimens	FPG	Baseline	96	mg/dL	92.67	18.98	69.00	82.50	89.00	96.50	204.00
		Last visit	147	mg/dL	93.99	32.13	73.00	82.00	87.00	96.00	387.00
		Change	83	mg/dL	-2.22	16.20	-60.00	-9.00	-1.00	4.00	51.00
		Time to last test	147	week	106.01	66.27	2.00	52.00	93.57	158.00	245.14
Switch from non-NVP-based regimens	FPG	Baseline	10	mg/dL	93.70	11.47	71.00	90.00	94.00	101.00	112.00
		Last visit	11	mg/dL	82.55	7.34	71.00	77.00	81.00	88.00	94.00
		Change	8	mg/dL	-7.88	15.22	-41.00	-11.00	-6.50	1.50	10.00
		Time to last test	11	week	112.38	65.78	3.29	59.86	95.29	175.14	206.57
Start	Triglyceride	Baseline	59	mg/dL	125.29	65.26	37.00	81.00	116.00	152.00	377.00

		Change	73	mg/dL	-0.63	26.84	-51.20	-19.40	3.60	15.80	68.40
		Time to last test	143	week	105.03	65.65	2.00	52.00	93.57	154.00	245.14
Switch from non-NVP-based regimens	LDL-C	Baseline	9	mg/dL	142.14	83.25	68.40	111.00	122.80	154.40	347.50
		Last visit	11	mg/dL	125.45	42.85	58.80	97.20	111.00	167.00	194.20
		Change	8	mg/dL	-20.81	60.14	-158.30	-31.20	-6.20	18.90	28.80
		Time to last test	11	week	112.38	65.78	3.29	59.86	95.29	175.14	206.57
Start	HDL-C	Baseline	58	mg/dL	48.59	23.96	19.00	34.00	43.00	58.00	169.00
		Last visit	79	mg/dL	59.44	16.92	31.00	46.00	59.00	69.00	112.00
		Change	29	mg/dL	11.76	26.08	-92.00	6.00	11.00	27.00	66.00
		Time to last test	79	week	99.27	63.07	3.29	48.86	79.43	151.86	228.86
Switch from NVP-based regimens	HDL-C	Baseline	89	mg/dL	57.61	19.88	17.00	44.00	52.00	69.00	113.00
		Last visit	149	mg/dL	56.74	17.40	15.00	44.00	53.00	68.00	104.00
		Change	77	mg/dL	-0.75	15.07	-44.00	-10.00	-2.00	7.00	57.00
		Time to last test	149	week	105.40	66.21	2.00	52.29	93.57	154.00	245.14
Switch from non-NVP-based regimens	HDL-C	Baseline	9	mg/dL	50.56	10.54	39.00	42.00	46.00	60.00	68.00
		Last visit	11	mg/dL	60.82	10.37	42.00	53.00	59.00	69.00	80.00
		Change	8	mg/dL	6.75	12.33	-9.00	-1.50	3.50	15.50	28.00

Table 6: Univariate and Multivariate Logistic Regression Analyses of Risk Factors for Treatment Failure (plasma HIV-1 RNA >50 copies/ml or Treatment Discontinuation) after GPO-VIR Z 250 Treatment in the Start Group

Variables for treatment failure	Univariate model			Multivariate model		
	OR	95% CI	p-value*	OR	95% CI	p-value
Gender: Male	1.48	(0.69,3.18)	0.316			
Age (years)			**0.013**			0.086
<35	Ref			Ref		
≥35	2.62	(1.22, 5.65)		2.26	(0.89, 5.73)	
CDC stage C at baseline	1.78	(0.80,3.94)	0.159			
Baseline CD4 count (cells/mm^3)			0.111			
≤100	2.77	(0.93, 8.81)				
100-199	2.59	(0.90, 7.44)				
≥200	Ref					
Baseline plasma HIV-1 RNA			0.059			0.577
>50 copies/ml	2.10	(0.98,4.50)		1.31	(0.51, 3.33)	
Missing/unknown	Ref			Ref		
BMI (kg/m^2)			0.166			
<18.5	1.90	(0.56, 6.46)				
18.5-24.9	0.72	(0.25, 2.04)				
≥25.0	Ref	Ref				
Adherence			0.678			
<95%	1.46	(0.26,8.30)				
≥95%	Ref					

Table 7: Univariate and Multivariate Logistic Regression Analyses of Risk Factors for Treatment Failure (plasma HIV-1 RNA >50 copies/ml or Treatment Discontinuation) after GPO-VIR Z 250 Treatment in The Switch Group

Variables for treatment failure	Univariate model			Multivariate model		
	OR	95% CI	p-value*	OR	95% CI	p-value
Gender: Female	2.12	(0.58,7.77)	0.230			
Age (years)			0.325			
<35	1.70	(0.59, 4.89)				
≥35	Ref					
CDC stage C at baseline	0.94	(0.25,3.48)	0.921			
Baseline CD4 count (cells/mm^3)**			0.148			
<200	2.63	(0.77, 9.02)				
≥200	Ref					
Baseline plasma HIV-1 RNA			0.934			
<50 copies/ml	Ref					
>50 copies/ml	1.15	(0.13,10.42)				
Missing/unknown	1.23	(0.41,3.69)				
BMI (kg/m^2)***			0.459			
<25	Ref					
≥25.0	1.91	(0.38, 9.57)				
Adherence			0.448			
<95%	2.57	(0.28,23.55)				
≥95%	Ref					

Table 8: Univariate and Multivariate Logistic Regression Analyses of Risk Factors for Anemia from GPO-VIR Z 250

Variables for anemia	Univariate model*			Multivariate model		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender: Female	1.65	(0.80,3.40)	0.164			
Age (years)			0.349			
<35	Ref					
≥35	1.35	(0.72,2.54)				
BMI (kg/m^2)			**<0.001**			**0.021**
<18.5	22.2	(2.69, 183.34)		12.9	(1.23,136.1)	
18.5-24.9	6.29	(0.83,47.63)		6.38	(0.70,57.7)	
≥25.0	Ref			Ref		
CDC stage C at baseline	2.01	(1.01,4.01)	0.053	1.25	(0.46,3.41)	0.659
Baseline CD4 count (cells/mm^3)			**<0.001**			**0.023**
<100	8.03	(3.39,19.03)		4.11	(1.22,13.91)	
100-199	3.34	(1.51,7.41)		1.99	(0.65,6.14)	
≥200	Ref			Ref		
Treatment group: Start group	4.90	(2.46,9.79)	**<0.001**	2.18	(0.80,5.93)	0.126
Baseline anemia			**<0.001**			**<0.001**
Yes	21.08	(6.31,70.42)		12.89	(3.23,51.43)	
Missing/unknown	1.60	(0.57,4.50)		2.09	(0.46,9)	
No	Ref			Ref		

*Covariates with p-value less than 0.1 were adjusted for in the multivariate models.
OR=odds ratio; CI=confidence interval; BMI=body mass index