Efficacy and Safety of Generic Fixed-Dose Combination of Stavudine, Lamivudine and Nevirapine (GPO-vir) in Advanced HIV Infection

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Objectives: *To assess the efficacy and safety of generic fixed-dose combination of stavudine, lamivudine and nevirapine; GPO-vir in advanced HIV infection.*
Material and Method: *Open-label combined prospective and retrospective study involving 102 HIV infected patients with baseline CD4cell count < 100 cells/mm^3. All patients received GPO-vir for 48 weeks. The CD4 cell count and plasma viral load (pVL) was measured at 48 weeks.*
Results: *The median baseline CD4 cell count and pVL were 13 cells/mm^3 and 363,500 copies/ml, respectively. At 48 weeks, the median CD4 cell count increased to191 cells/mm^3 and 63.7% in intention-to treat and 82.3% in on-treatment analysis had pVL < 50 copies/ml. There was no significant difference in pVL between patients with baseline pVL > 100,000 or ≤ 100,000 copies/ml (p = 0.312). The incidence of hepatotoxicity, rash and peripheral neuropathy was 4.9%, 14.7% and 6.9%, respectively.*
Conclusion: *GPO-vir was well tolerated and effective in increasing CD4 cell count and suppressing plasma viremia in advanced HIV infection during the 48 weeks follow-up period.*

Keywords: *GPO-vir , Generic fixed-dose combination, Advanced HIV disease, HAART, Thailand*

J Med Assoc Thai 2006; 89 (9): 1472-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

The introduction of highly active antiretroviral therapy (HAART) has led to significant decline in AIDS associated morbidity and mortality. In resource-limited settings, the World Health Organization (WHO) recommends HAART in patients with clinically advanced HIV disease or CD4 cell count < 200/mm^3[1]. The combination of two nucleoside analogue reverse transcriptase (NRTIs) and one non-nucleoside analogue reverse transcriptase (NNRTI) is the recommended first line HAART in resource-limited countries. Worldwide, a considerable number of patients start their first line antiretroviral therapy at an advanced stage of HIV-1 infection. In the Antiretroviral Therapy Cohort Collaboration study from Europe and North America, 42% of the study participants had baseline CD4 cell count < 200cell/ml[2]. In Thailand, Leusaree et al, reported 50.6% of the 1,671 study participants had clinical AIDS at the start of HAART[3]. Despite the increased number of patients starting treatment at the advanced stage, there remain limited data to assess the efficacy and safety of treatment in this group of patients.

Presently, generic fixed-dose combination (FDC) of two NRTIs and one NNRTI, mainly nevirapine (NVP) are among the most widely prescribed first line regimens in developing countries. In Thailand, the Government Pharmaceutical Organization (GPO) began production of several generic antiretroviral drugs in 1995. The FDC of stavudine (d4T), lamivudine (3TC) and NVP; GPO-vir has been available in the market since March 2002. GPO-vir is the standard first line

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regimen for HIV infection in Thailand and costs only US$1 per day[4]. Clinical trials from Cameroon, India and Thailand have demonstrated the safety, tolerability and efficacy of generic antiretroviral regimens[3,5-9]. However, no such trials have reported on virologic response in association with baseline plasma viral load (pVL) or baseline CD4 cell count on the efficacy of treatment. Therefore, the authors aimed to assess the efficacy and safety of GPO-vir among treatment naive patients with advanced HIV infection and examined the effect of baseline pVL and CD4 cell count on treatment efficacy.

Material and Method

The present study was a combined retrospective and prospective study, conducted at Bamrasnaradura Infectious Disease Institute, Thailand. Inclusion criteria were: HIV-1 infection, baseline CD4 cell count < 100 cells/ml, age ≥ 15 years and no previous treatment with antiretroviral drugs (excluding prevention of mother to child transmission). The data collection period was from December 18, 2003 to February 12, 2004. One hundred and six eligible patients visiting the ambulatory care unit were enrolled. All patients gave written informed consent prior to enrolment.

Statistical analysis

Baseline medical history and physical examination were conducted prior to initiation of therapy. The pVL, CD4 cell count, complete blood count, renal and liver function tests, total cholesterol and triglyceride levels were assessed at baseline. During the first two weeks of treatment all patients were given the FDC of GPO-vir (containing d4T 30mg or 40 mg if weight > 60 kg, 3TC 150 mg and NVP 200 mg) in the morning and separate tablets of d4T 30 mg/40 mg and 3TC 150 mg in the evening. There after, all the subjects received GPO-vir twice daily to complete 48 weeks of treatment. In the event of toxic effect depending on the degree of toxicity and patient's intolerance, GPO-vir was discontinued and the offending drug was substituted by the second line drugs: zidovudine for d4T, efavirenz (EFV) for NVP and indinavir/ritonavir for EFV & NVP. All patients received primary or secondary prophylaxis for opportunistic infections.

Study subjects were evaluated at week two and four, then every four weeks until week 24 and every eight weeks until week 48. The pVL and CD4 cell counts were repeated at week 24 and 48. Measurements of pVL and CD4 cell count were carried out at Bamrasnaradura Infectious Disease Institute Laboratory. At baseline, HIV RNA was measured by RT-PCR Amplicor monitor standard assay where the lower limit of detection was 400 copies/ml. Subsequently, at week 24 and 48 HIV RNA was measured by RT-PCR Amplicor monitor ultra sensitive assay where the lower limit of detection was 50 copies/ml. $CD4^+$T cell count was determined using a cytometer FACscan.

The primary end point of the present study was the proportion of patients with pVL < 400 copies/ml or < 50 copies/ml at week 24 and 48, respectively. Disease progression was considered in the occurrence of new and/or recurrence of category C disease conditions after 12 weeks of therapy or death.

The data were entered and analysed using EPI info version 6.04 program. Efficacy analysis was done for intention-to-treat (ITT) and on-treatment (OT) analysis at 24 and 48 weeks of therapy. The ITT analysis included 102 study subjects while OT group included those patients who were on treatment at 24 and 48 weeks of therapy. The pVL as well as the incidence of clinical and laboratory related adverse events were calculated at 24 and 48 weeks and presented as percentages. Hepatobiliary laboratory toxicities were considered in the event of increased alanine aminotransferase (ALT) and high total bilirubin associated with an increase in the ALT. Grading of hepatotoxicity was done as follows: grade 1: ALT 1.25-2.5 X upper limit of normal (ULN), grade 2: ALT 2.6-5 X ULN, grade 3: ALT 5.1-10 X ULN and grade 4: ALT > 10 X ULN. Proportions between groups were compared by the chi-square or Fisher's exact test and p values of less than 0.05 were considered as statistically significant. Paired samples were analysed by the Wilcoxon signed-ranks test. The median survival time and cumulative probability of remaining alive or free of new CDC category C conditions at 48 weeks of therapy were estimated using the Kaplan Meier method.

Results

Baseline data

Out of the 106 patients identified and started treatment with GPO-vir , four patients were excluded from analysis: one had baseline CD4 cell count > 100, two had a previous history of treatment and one had an incomplete medical record. The median age was 33 years (range 22-56) and 46.1% were females. The median baseline CD4 cell count and pVL were 13 cells/mm^3 (range 1-99) and 363,500 copies/mm^3 (range 21,600 - > 750,000), respectively. Baseline demographic, clinical and laboratory characteristics of the subjects are shown in Table 1.

Table 1. Baseline demographic, clinical and laboratory characteristics of the 102 study subjects

	N	Number of patients (%)	Median (range)
Demographic profile:			
Age (years):	102		33 (22-56)
Sex:	102		
Female		47 (46.1)	
Male		55 (53.9)	
Anthropometry:			
Weight (kg)	101		50.8 (28.8-80.1)
HIV infection:			
CD4 T cell count (cells/mm^3)	102		13 (1-99)
CD4 T cell percentage (%)	102		1 (0-12)
Plasma viral load (copies/ml)	102		363,500 (21,600 $\geq$ 750,000)
pVL $\leq$ 100,000		22 (21.8)	
pVL > 100,000		80 (78.4)	
ART history:	102		
Naïve		97 (95.1)	
ART for PMTCT* (AZT or AZT+NVP)		5 (4.9)	
Laboratory:			
Hemoglobin (gm/dl)	101		11.6 (7.4-15.6)
Neutrophils (%)	101		59 (22-94)
Platelets (/mm3)	101		245,000 (86,000-568,000)
ALT (u/l)	102		31.5 (11-231)
Total bilirubin (mg/dl)	100		0.43 (0.18-3.0)
Cholesterol (mg/dl)	100		164 (90-262)
Triglycerides (mg/dl)	100		153.5 (49-561)
Creatinine (mg/dl)	101		0.74 (0.57-1.2)
BUN (mg/dl)	102		10 (3-32)

* Prevention of mother to child transmission

Table 2. Virologic efficacy at 24 and 48 week of treatment

	Overall	baseline pVL $\leq$ 100,000 copies	baseline pVL >100,000 copies	p-value
Proportion of patients with pVL < 400 copies/ml at 24 weeks				
ITT	78.4% (80/102)	72.7% (16/22)	80.0% (64/80)	0.559*
OT	95.2% (80/84)	88.9% (16/18)	96.7% (64/66)	0.200*
Proportion of patients with pVL < 50 copies/ml at 48 weeks				
ITT	63.7% (65/102)	54.5% (12/22)	66.3% (53/80)	0.312**
OT	82.3% (65/79)	73.3% (11/15)	84.4% (54/64)	0.451*

* p-value by Fishers Exact test, ** p-value by Chi-square test

Efficacy

The virologic success at week 48, defined as pVL < 50copies/ml, was 63.7% (65/102) by the ITT analysis and 82.3% (65/79) by OT analysis (Table 2). The median decline in plasma viral load from the baseline was 3.7 $\log_{10}$ copies/ml (range 1.11-4.19) at week 24 and

3.8 $\log_{10}$ copies/ml (range 0.2-4.2) at week 48. Four patients had pVL > 1,000 copies/ml at week 48. There was no statistically significant difference in virologic success between patients with high (> 100,000 copies/ml) or low (≤ 100,000 copies/ml) baseline pVL (p = 0.312, the Chi-square test). Patients with baseline CD4 cell count > 50 cells/mm^3 had higher virologic success compared with patients whose baseline CD4 cell count was < 50 cells/mm^3 (80% versus 60.9%), however this difference was not statistically significant (p = 0.156, the Chi-square test). The median CD4 cell count increased significantly from 13 cells/mm^3 at baseline to 191 cells/mm^3 at week 48 (p < 0.001, the Wilcoxon signed-ranks test). Forty-seven percent of patients (37/79) had CD4 cell count > 200 cells/mm^3 at week 48.

The overall disease progression was 17.9 per 100 person-years (95% CI 9.4-26.4). Ten (9.8%) patients died and mortality rate was 12.8 per 100 person-years (95% CI 5.4-20.2). Eighty percent of the deaths were attributed to HIV related infection: five non-tuberculosis mycobacterium infection (NTM), one recurrent cryptococcal meningitis, one multi-drug resistance tuberculosis and one chronic diarrhoea. The median time to death was 6 weeks. The cumulative probability of remaining alive or free of new CDC category C conditions after 48 weeks of treatment was 0.82 (Fig. 1).

Safety

Thirty eight clinical adverse events were reported during the follow up period. The three common clinical adverse events were skin rash 14.7% (15/102), itching without skin rash 6.9% (7/102) and peripheral neuropathy 6.9% (7/102). Five patients (4.9%) developed at least one grade-3 or grade-4 hepatotoxicity and only one of them developed clinical jaundice. Three patients with grade 4-toxicity had clinical conditions improved and ALT normalized not necessitating treatment change. Two patients had grade 3 toxicity; one died of NTM at week 22 and one was lost to follow up at week 8. At 48 weeks, the median total cholesterol increased from the baseline of 164 to 190 mg/dl (p < 0.001), whereas the median triglyceride declined significantly from 153.5 at baseline to 108 mg/dl (p = 0.003, the Wilcoxon signed-ranks test).

Overall, six patients changed therapy because of severe clinical adverse effects: namely skin rash (2 patients), skin rash plus peripheral neuropathy (1 patient), peripheral neuropathy (2 patients) and grade

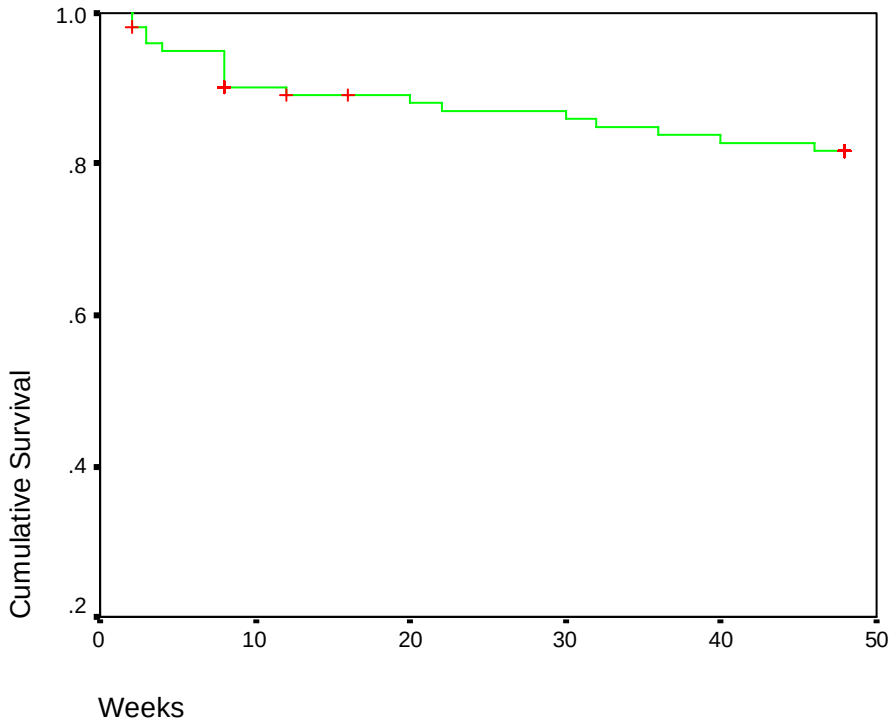

Fig. 1 Kaplan Meier survival curve showing the probability of remaining alive or free of new CDC category C conditions at 48 week of therapy

2 hepatobiliary toxicity plus jaundice (1 patient). One of the patients with peripheral neuropathy changed treatment at 48 weeks, therefore, this case was included in all analysis. Eight patients stopped treatment: one patient (1%) requested treatment discontinuation after severe side effects and seven patients (6.9%) were lost to follow up.

Discussion

The main objective of the present study was to assess the efficacy of GPO-vir in advanced HIV infection. At 24 and 48 weeks of therapy, 78.4% and 63.7% of the presented patients in ITT analysis had undetectable viral load, respectively. Almost 50% of patients had CD4 cell count > 200 cells/mm^3 at 48 weeks. The present results are comparable with the findings in clinical trials and cohort studies that assessed the efficacy of NVP-based HAART regimens[3,5,6,9,10]. Thanomsak et al carried out a prospective study to assess efficacy of GPO-vir among 101 patients. The mean baseline CD4 cell count and pVL were 58.7 cells/mm^3 (range 0-191) and 5.4 $\log_{10}$ copies/ml (range < 2.6 - > 5.9), respectively. At 52 weeks 58.4% in ITT and 77.6% in OT analysis had undetectable viral load (pVL < 50 copies/ml)[5,9]. In Cameroon, Laurent et al evaluated the efficacy of generic FDC of d4T, 3TC and NVP from India (n = 60) and observed significant viral suppression at 24 weeks (80% in ITT and 92% in OT analysis had pVL < 400 copies/ml)[6]. Similarly, Leusaree et al (n = 1,671) demonstrated significant increase in the median CD4 cell count from the baseline of 42 cells/mm^3 (range 0-404) to 168.5 cells/mm^3 and 197 cells/mm^3 at 6 and 12 months of GPO-vir treatment, respectively[3].

The authors also compared the efficacy results with the 2NN study. The 2NN study was a large (n = 1,216), open label, multicentre trial which assessed the efficacy of NVP (once/twice daily n = 607), EFV (600 mg qd; n = 400), or NVP plus EFV (800 mg qd, n = 209), together with d4T + 3TC. At 48 weeks, 65.4% (154/387) of patients in the nevirapine (twice daily) arm had pVL < 50 copies/ml[10] Compared with the NVP-based regimen of 2NN study, the virologic efficacy of GPO-vir in the present study is highly satisfactory even though all the presented patients had advanced HIV infection.

In the present study the virologic response did not associate with baseline pVL (> 100,000 or ≤ 100,000 copies/ml) or baseline CD4 cell count (≤ 50 or > 50 cells/mm^3). The present results are in line with the findings of two studies that assessed the impact of pVL on responses to NVP-based HAART. Thanomsak et al demonstrated no significant difference in virologic response at 48 weeks between patients with baseline pVL ≤ 100,000 or > 100,000 copies/ml[5]. However, the present study did not report virologic efficacy according to CD4 cell count strata. Similarly, the meta-analysis which combined results of two clinical and six cohort studies showed that baseline pVL didn't affect virologic outcome at 12 months (83% of patients with baseline pVL > 100,000 and 77% of patients with baseline pVL ≤ 100,000 had undetectable viral load at 12 months)[11]. In contrast, the post hoc analysis of the randomized 2NN study reported increased the risk of virologic failure at 48 weeks among patients with pVL > 100,000 copies/ml and patients who had an extremely low CD4 cell count < 25 10^6 cells/l[12].

The safety profiles of GPO-vir were also assessed in the present study. The incidence of skin rash and peripheral neuropathy was 14.7% and 6.9%, respectively. This rate was similar to the previous studies[3,5,9]. The incidence of grade ≥ 3 hepatotoxicity (4.9%) was lower than those reported previously[10,13,14]. In the present study GPO-vir was well tolerated, only 7% of patients changed or stopped treatment due to adverse events. At the end of the present study, 82% of patients were alive or free of new CDC category C conditions and 77% patients were on treatment.

The small sample size and the single arm design are limitations of the present study. In general, the present study demonstrates that GPO-vir is well tolerated and effective in suppressing HIV RNA and increasing CD4 cell count in advanced HIV infection. Further follow up of these patients is on going to evaluate the long-term virologic and immunologic efficacy of GPO-vir .

Acknowledgement

The authors wish to thank Dr. Chureeratana Bowonwatanuwong for her advice and assistance during the writing and revision of this paper.

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ประสิทธิผลและความปลอดภัยของการรักษาผู้ป่วยโรคเอดส์เต็มขั้นด้วยยาต้านไวรัสในรูปเม็ดรวมซึ่งประกอบด้วยสตาวูดีน ลามิวูดีน และ เนวิราพีน (จีพีโอเวียร์)

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***วัตถุประสงค์**: เพื่อประเมินประสิทธิผลและความปลอดภัยของการรักษาผู้ป่วยโรคเอดส์เต็มขั้นด้วยยาต้านไวรัสในรูปเม็ดรวมซึ่งประกอบด้วยสตาวูดีน ลามิวูดีน และ เนวิราพีน (จีพีโอเวียร์)*

***วัสดุและวิธีการ**: การศึกษาแบบเปิดทั้งศึกษาไปข้างหน้าและย้อนหลัง ผู้ป่วยติดเชื้อเอชไอวีจำนวน 102 คนที่มี CD4 น้อยกว่า 100 เซลล์ต่อลบ.มม. โดยผู้ป่วยรับประทานยาจีพีโอเวียร์ 48 สัปดาห์และได้รับการตรวจเลือดหาจำนวน CD4 และจำนวนเชื้อไวรัสในพลาสมา (pVL) ในสัปดาห์ที่ 48*

***ผลการศึกษา**: ก่อนเริ่มให้ยาต้านไวรัสผู้ป่วยมีค่ามัธยฐานของจำนวน CD4 เท่ากับ 13 เซลล์ต่อลบ.มม.และ pVL 363,500 copies ต่อมล. หลังได้รับการรักษา 48 สัปดาห์ค่ามัธยฐานของจำนวน CD4 เพิ่มขึ้นเป็น 191 copies ต่อมล. และ pVL ของผู้ป่วยลดลงต่ำกว่า 50 copies ต่อมล. คิดเป็นร้อยละ 63.7 โดยการวิเคราะห์แบบ intent-to-treat และร้อยละ 82.3 โดยการวิเคราะห์แบบ on-treatment เมื่อเปรียบเทียบผู้ป่วยกลุ่มที่มี pVL ก่อนให้ยามากกว่า 100,000 copies ต่อมล. กับกลุ่มที่มี pVL น้อยกว่าหรือเท่ากับ 100,000 copies ต่อมล. พบว่า pVL หลังได้รับยาต้านไวรัสไม่แตกต่างกันอย่างมีนัยสำคัญ (p = 0.312) อุบัติการณ์ของการเกิดพิษต่อตับ การเกิดผื่นและการทำลายเส้นประสาทส่วนปลายเท่ากับร้อยละ 4.9, 14.7 และ 6.9 ตามลำดับ*

***สรุป**: จีพีโอเวียร์เป็นยาที่ปลอดภัยและมีประสิทธิผลดีในการเพิ่มปริมาณ CD4 และลดเชื้อไวรัสเอชไอวีใน พลาสมาของผู้ป่วยเอดส์เต็มขั้นในช่วงการติดตาม 48 สัปดาห์*