Efficacy of a Generic Fixed-Dose Combination of Stavudine, Lamivudine and Nevirapine (GPO-VIR) in Thai HIV-Infected Patients

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Background: *GPO-VIR , fixed-dose combination of stavudine 30/40 mg, lamivudine 150 mg, and nevirapine 200 mg are widely used in Thailand.*
Objective: *Determine the efficacy and tolerability of GPO-VIR in na ve HIV-infected patients.*
Material and Method: *Primary outcome was the time of initiation to achieve the goal of therapy, which was HIV RNA < 50 copies/mL or 50% increased of CD4 cell count. Ninety patients were eligible for the present study. Mean ± SD age was 35 ± 7 years and 51% were male. Median baseline CD4 and HIV RNA were 52 cells/mm^3 and 280,000 (5.4 log_{10}) copies/mL, respectively. Sixty-two (69%) patients had previous opportunistic infections.*
Results: *In a median follow-up period of 15 weeks, 49 (54%) patients achieved the goal of therapy. The probability of goal achievement showed that 12-, 24-, 36- and 48- weeks success rates were 8.5% [95% confidence interval (CI): 3.9-18.0%], 62.7% (95%CI: 50.8-74.6%), 80.0% (95%CI: 67.3-90.1%), and 93.3% (95%CI: 76.3-99.4%), respectively. The median success time to achieve the goal was 21 weeks. Eleven (12%) patients needed to discontinue GPO-VIR because of adverse drugs reaction.*
Conclusion: *GPO-VIR may be one of the antiretroviral regimens for HIV-infected patients in Thailand and other resource-limited countries. Its efficacy is good in patients with advanced HIV infection.*

Keywords: *GPO-VIR, Nevirapine, Antiretroviral therapy, HIV, Thailand*

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Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) is one of the major health problems in Thailand. Approximately 1 million people have been infected with HIV and 600,000 people are living with HIV/AIDS in Thailand[1]. Highly active antiretroviral therapy (HAART) has significantly improved the prognosis of HIV-infected patients and prolonged AIDS-free survival[2,3]. Access to antiretroviral drugs for Thai HIV-infected patients is limited due to the high cost of HAART.

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Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen is a preferred regimen for treatment of HIV-infected patients because of its good efficacy, tolerability and lower long-term toxicities[4-6]. In 2002, the Thai Government Pharmaceutical Organization developed GPO-VIR , a low cost (US$ 30 per month), fixed-dose combination of antiretroviral drugs. GPO-VIR composed of stavudine 30 (GPO-VIR S30) or 40 mg (GPO-VIR S40), lamivudine 150 mg, and nevirapine (NVP) 200 mg in a single tablet. GPO-VIR is widely used for scaling up HIV/AIDS treatment in Thailand. However, there are increased concerns that generic drugs may not be equivalent to original drugs and its efficacy has not been well established. The authors aimed to determine the efficacy and tolerability of GPO-VIR in Thai HIV-infected patients.

Material and Method

A retrospective cohort study of HIV-infected patients who attended the Infectious Diseases Clinic, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between April 2002 and November 2003 were included. Inclusion criteria were as follows. The patients (1) were ≥15 years old, (2) were na ve to antiretroviral therapy and (3) received GPO-VIR supported by the Ministry of Public Health. Each eligible patient was followed since receiving GPO-VIR until the end of the present study, in 31 January 2004.

Medical records were retrieved and reviewed. Information on demographic variables, i.e. sex, age, previous opportunistic infections (OIs), duration of HIV seropositivity, baseline CD4 cell count, and baseline HIV RNA were extracted. HIV RNA was determined by Amplicor HIV-1 Monitor test, version 1.5, Roche Diagnostics, Indianapolis, USA. The primary outcome of interest was (1) time to virological success, which was calculated by subtracting the date of the first undetectable HIV RNA (<50 copies/mL) from the date on which the patient was started on GPO-VIR or (2) time to a 50% increased of CD4 cell count, which was calculated by subtracting the date of 50% increased of CD4 cell count from the date the patient was started on GPO-VIR . Patients were censored at the date of last visit if the events did not occur at the end of the study or if they were lost to follow-up. Discontinuation of GPO-VIR , which was defined as completely cessation of GPO-VIR treatment, was also recorded and described. Treatment failure was defined as the first of two consecutive HIV RNA measurements ≥400 copies/mL after achievement of undetectable HIV RNA or at 6 months of antiretroviral treatment. The secondary outcomes were tolerability and adverse events.

Means [± standard deviations (SD)], median and frequencies (%) were used to describe patients' characteristics. The Kaplan-Meier test was used to estimate the probability of goal achievement and the median time to achieve the goal after receiving treatment. The log-rank test was used to compare the median time to achieve the goal among baseline characteristics factors: gender, age, previous OIs, duration of HIV seropositivity, baseline CD4 cell count and baseline HIV RNA. The Cox proportional hazard model was used to determine the chance of goal achievement by adjusting for confounding factors, i.e. age, previous OIs, duration of HIV seropositivity and baseline CD4 cell count. The hazard ratio (HR) and its 95% confidence interval (CI) were estimated. All analyses were performed using STATA version 8.0[7]. A *p*-value of less than 0.05 was considered statistically significant. The present study was approved by the Institutional Reviewed Board.

Results

Ninety patients who met the inclusion criteria were identified. Forty-six (51%) were male. Mean age ± SD was 35 ± 7 (range, 24-68) years. Sixty-two (69%) patients had previous major OIs, which were tuberculosis (43 patients), *Pneumocystis jeroveci* pneumonia (13), cryptococcosis (13), cytomegalovirus retinitis (9), toxoplasmosis (1), and disseminated *Mycobacterium avium* complex (1). Median duration of HIV seropositivity was 32 (range, 0-126) months. Baseline median CD4 cell count was 52 (range, 0-410) cells/mm^3 and HIV RNA was 280,000 (range, 5,820- >750,000) or 5.4 (3.8- >5.9) $\log_{10}$ copies/mL. Median follow-up period was 15 (range, 4-66) weeks. Baseline characteristics of the patients are shown in Table 1.

Forty-nine (54%) patients achieved the goal of therapy. The Kaplan-Meier test in Fig. 1 shows the

Table 1. Baseline characteristics of 90 patients

Characteristics	Number (%)
Male gender	46 (51)
Mean age ± SD, years (range)	35 ± 7 (24-68)
Previous major OIs	
Yes	62 (69)
No	28 (31)
Median duration of HIV seropositivity, month (range)	32 (0-126)
Median baseline CD4, cells/mm^3	52 (0-410)
Median baseline HIV RNA, copies/mL	280,000 (5,820- >750,000)
Median baseline HIV RNA, $\log_{10}$ copies/mL	5.4 (3.8- >5.9)

OIs = opportunistic infections, HIV = human immunodeficiency virus, SD = standard deviation

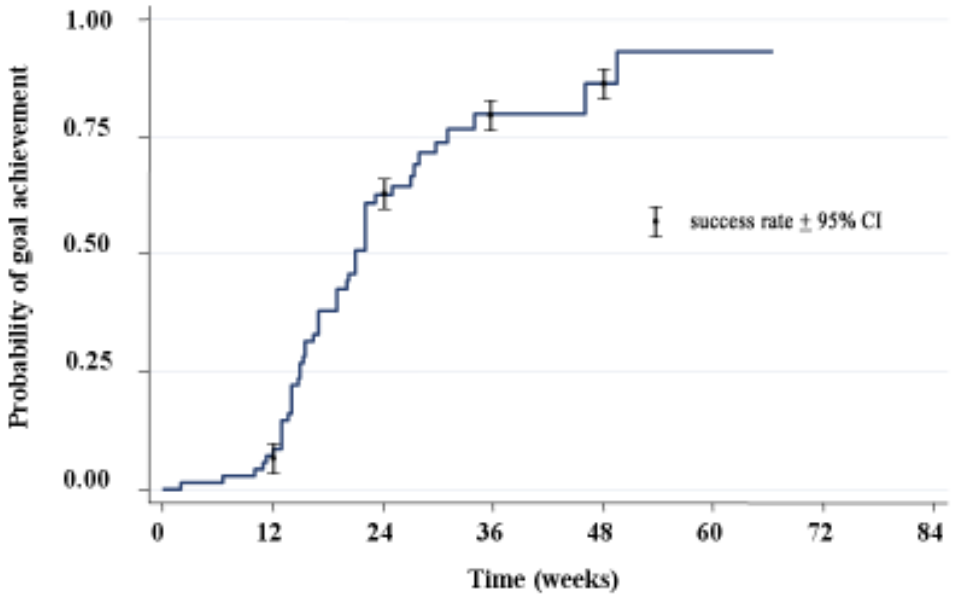

Fig. 1 Probability of goal achievement after initiation of GPO-VIR

probability of goal achievement, virological success or 50% increased of CD4 cell count, after receiving treatment. The 12-, 24-, 36- and 48-weeks success rates were 8.5% (95%CI: 3.9%, 18.0%), 62.7% (95%CI: 50.8%, 74.6%), 80.0% (95%CI: 67.3%, 90.1%) and 93.3% (95%CI: 76.3%, 99.4%), respectively. The median time to achieve the goal was 21 weeks, i.e. patients who received GPO-VIR would take 21 weeks to achieve the goal. The median times to achieve the goal among baseline characteristic factors were estimated and compared as shown in Table 2. The median times to achieve the goal for patients with baseline CD4 <100 and CD4 ≥100 cells/mm^3 were 21 and 15 weeks, respectively (p = 0.946). Other baseline factors including sex, gender, duration of HIV seropositivity and baseline HIV RNA were not significantly correlated with time to achieve the goal.

The Cox proportional hazard model was used to compare the chance of goal achievement after adjusting for age, previous OIs, duration of HIV seropositivity and baseline CD4 cell count (Table 3). Male patients had about 66% (HR 1.66, 95% CI: 0.9-3.1) more chance to achieve the goal than female. However, no baseline factors were significantly associated with time to achieve the goal.

Eighteen (20%) patients had adverse drug events including maculopapular rashes (12 patients), nausea/vomiting (2), drug-induced hepatitis (2), lactic acidemia (1) and Stevens-Johnson syndrome (1). Among 13 patients who developed skin rashes or Stevens-Johnson syndrome, six patients used slow dose escalation of NVP. Eleven (12%) patients needed to discontinue GPO-VIR because of adverse drugs reaction. To avoid drug-drug interaction between NVP and rifampicin, GPO-VIR was changed to efavirenz-based regimen in five patients who developed tuberculosis during antiretroviral treatment.

Treatment failure was found in three patients. Baseline CD4 cell count and HIV RNA of these patients was < 200 cells/mm^3 and > 100,000 (5 $\log_{10}$) copies/mL, respectively. Major genotypic resistance mutations were M184V, M41L, G190S, K103N, and Y181C conferring resistance to lamivudine and NNRTIs.

Discussion

GPO-VIR is one of the most widely prescribed as the first-line regimen in Thailand, yet the authors are aware of few available published clinical trials assessing its efficacy and safety[8-10]. The authors conducted a retrospective cohort study to assess the efficacy and tolerability of GPO-VIR in Thai HIV-infected patients. Most of the presented patients had an advanced stage of HIV disease; very low CD4 cell count, high HIV RNA and had previous OIs as other reports of Thai HIV-infected patients[11,12].

The authors found that about half of the patients achieved the goal of therapy and patients

Table 2. Median time to achieve goal rates by prognostic factors

Factors	Number of success n = 49	Total n = 90	Person-weeks	Success rate/ 100 person-weeks	Median time (weeks)	p-value
Sex						
Male	31	46	818	3.79	19	0.132
Female	18	44	739	2.43	22	
Age (years)						
< 50	47	87	1501	3.13	21	0.753
≥ 50	2	3	55	3.64	17	
Previous OIs						
Yes	37	61	478	2.51	20	0.273
No	12	29	1078	3.43	22	
Duration of HIV seropositivity (months)						
< 60	37	70	1255	2.95	22	0.218
≥ 60	12	20	301	3.98	20	
Baseline CD4 cell count (cells/mm^3)						
< 100	40	75	1223	3.27	21	0.946
≥ 100	8	12	261	3.06	15	
Baseline HIV RNA (copies/mL)						
< 100,000	8	12	237	3.38	23	0.154
≥ 100,000	29	43	695	4.17	16	

OIs = opportunistic infections

Table 3. Determination of chance of goal achievement controlling for confounding factors, using the Cox proportional hazard analysis (n = 49)

Factors	Hazard ratio	Standard error	p-value	95%CI
Sex				
Male	1.66	0.52	0.106	0.9-3.1
Female	1			
Previous OIs				
Yes	1.76	0.62	0.107	0.9-3.5
No	1			
Duration of HIV seropositivity (months)				
≥ 60	1.88	0.70	0.093	0.9-3.9
< 60	1			
Baseline CD4 cell count (cells/mm^3)				
≥ 100	1.19	0.49	0.664	0.5-2.6
< 100	1			

CI = confidence interval, OIs = opportunistic infections

took about 21 weeks after initiation to achieve HIV RNA < 50 copies/mL or 50% increased of CD4 cell count. The authors' findings are similar to the previous studies, i.e. NVP-based regimens suppressed HIV RNA to < 50 copies/mL in approximately 50% of patients, and these regimens are also effective in patients with advanced HIV infection[13,14]. HIV therapy response may be compromised by advanced disease at treatment initiation. It is noticed that the median times to achieve the goal was longer for patients with baseline CD4 < 100 than CD4 ≥100 cells/mm^3 (21 vs 15 weeks). There was no significant association between all baseline characteristics with time to achieve the goal. According to 2 prospective studies regarding efficacy of GPO-VIR , mean increase CD4 cell count from baseline to week 24 was 96.5 cells/mm^3 and 80.2% of

advanced patients had HIV RNA < 400 copies/mL[9]. Furthermore, median CD4 cell count increased to191 cells/mm^3 and 82.3% of patients with CD4 < 100 cells/mm^3 had HIV RNA < 50 copies/mL by intention-to-treat analysis at 48 weeks[10].

NVP-based regimens are recommended as alternative regimens because of its high incidence of adverse events. Adverse drug reactions were found in about one-fifth of the presented patients, mostly skin rashes. Previous studies reported that the most common adverse events for NVP were rashes and hepatotoxicity[15-17]. These were the main reasons for discontinuation of GPO-VIR . Severe skin rashes caused by a NVP-based regimen led to discontinuation of treatment in about 9-15% of patients[9,10,18] which was the same as the proportion that the authors found in the present study (12%). Use of a slowly escalating dose can diminish the incidence of rash associated with NVP-based regimens[19]. NVP induced clinical hepatitis was found in only 2% of the presented patients whereas the incidence of severe hepatotoxicity in Thai HIV-infected patients receiving NVP was 18.5/100 person-years[20]. The rate of adverse events from the present study may not be applicable for the patient population with higher CD4 cell count. Recently, it has been documented that CD4 cell count higher than 250 cells/mm^3 in females and 400 cells/mm^3 in males are associated with a higher risk of development of hepatotoxicity form NVP[21,22]. The authors might also under-recognize patients with asymptomatic increase of transaminase enzyme because liver function test was not routinely performed to monitor hepatotoxicity in the presented patients.

Treatment failure was found in three patients. All patients had an advanced HIV disease. The adherence to antiretroviral therapy is the key of successful treatment. Many factors can affect adherence to treatment, such as the patients' life style, patient provider relationship, cost of drugs, and tolerability[23]. GPO-VIR is a drug with low pills count that may improve patients' compliance.

The present results suggest that use of NVP-based regimens may be beneficial in developing countries where NVP is available as a single or combined pill generic drug and is more readily obtainable than other antiretroviral agents. The Thai government has launched a massive campaign to scale up antiretroviral therapy for people living with HIV/AIDS by providing HAART under Universal Coverage. GPO-VIR may be an alternative for HAART initiation for Thai HIV-infected patients because of low cost and low-pill count per day.

The limitations of the present study are small sample size, short follow-up period, and being a retrospective study, which is not the best study design to evaluate the efficacy and tolerability of antiretroviral therapy. As a result of the high cost per CD4 cell count test and HIV RNA, testing for these two laboratory investigations were not available for all patients at every visit. However, the results of the present study may be useful for physicians in Thailand and other resource-limited countries where this fixed drug combination has been widely used.

In summary, GPO-VIR may be used for treating HIV-infected patients who have less accessibility to other HAART regimens in developing countries. However, a large-scale randomized, controlled clinical trial is needed to confirm its efficacy.

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ประสิทธิภาพของยาแบบรวมเม็ดที่ประกอบด้วยสตาวูดีน ลามิวูดีนและเนวิราพีน (จีพีโอเวียร์) ในผู้ติดเชื้อเอชไอวีไทย

ศศิโสภิณ เกียรติบูรณกุล, สิรินาฏ คงนรเศรษฐ์, ศศิวิมล รัตนสิริ, สมนึก สังฆานุภาพ

มีการใช้ยาจีพีโอเวียร์ซึ่งเป็นยาแบบรวมเม็ดที่ประกอบด้วยสตาวูดีน ลามิวูดีนและเนวิราพีนอย่างแพร่หลายในประเทศไทย วัตถุประสงค์เพื่อศึกษาประสิทธิภาพและความทนต่อยาของจีพีโอเวียร์ในผู้ติดเชื้อเอชไอวีที่ไม่เคยได้รับยาต้านไวรัสมาก่อน เป้าหมายของการศึกษาคือ ประเมินระยะเวลาที่ผู้ป่วยถึงจุดหมายของการรักษาได้แก่ มีปริมาณไวรัสน้อยกว่า 50 คอปปี้/มล. หรือมีจำนวนซีดี 4 เพิ่มขึ้นมากกว่าร้อยละ 50 มีผู้เข้าร่วมการศึกษา 90 ราย อายุเฉลี่ย 35 ปี (ค่าเบี่ยงเบนมาตรฐาน 7) ร้อยละ 51 เป็นเพศชาย ค่ามัธฌิมของจำนวนซีดี 4 และปริมาณ ไวรัสตั้งต้นก่อนเริ่มยาเท่ากับ 52 เซลล์/ลบ.มม.และ 280,000 คอปปี้/มล. ตามลำดับ ผู้ป่วย 62 ราย (ร้อยละ 68) เคยเป็นโรคติดเชื้อฉวยโอกาสมาก่อน ค่ามัธฌิมของระยะเวลาที่ติดตาม 15 สัปดาห์ ผู้ป่วย 49 ราย (ร้อยละ 54) บรรลุจุดหมายของการศึกษา ความน่าจะเป็นของผู้ป่วยที่จะถึงจุดมุ่งหมายที่ 12, 24, 36 และ 48 สัปดาห์ เท่ากับร้อยละ 8.5 (ร้อยละ 95 ความเชื่อมั่น 3.9-18.0), ร้อยละ 62.7 (ร้อยละ 95 ความเชื่อมั่น 50.8-74.6), ร้อยละ 80.0 (ร้อยละ 95 ความเชื่อมั่น 67.3-90.1) และร้อยละ 93.3 (ร้อยละ 95 ความเชื่อมั่น 76.2-99.4) ค่ามัธฌิมของระยะเวลาที่ถึงจุดหมายคือ 21 สัปดาห์ ผู้ป่วย 11 ราย (ร้อยละ 12) ต้องหยุดยาเนื่องจากมีผลข้างเคียง สรุปยาจีพีโอเวียร์อาจจะเป็นหนึ่งในยาต้านไวรัสที่สามารถใช้ในการรักษาผู้ติดเชื้อเอชไอวีในประเทศไทยและประเทศอื่นที่ยากจน มีประสิทธิภาพดีแม้ในผู้ป่วยที่อยู่ในระยะท้าย