EFFECTIVENESS OF FIXED-DOSE COMBINATION STAVUDINE, LAMIVUDINE AND NEVIRAPINE (GPO-VIR) FOR TREATMENT OF NAÏVE HIV PATIENTS IN THAILAND: A 3-YEAR FOLLOW-UP

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Abstract. Generic fixed dose combination stavudine (d4T), lamivudine (3TC) and nevirapine (NVP), named GPO-VIR is recommended in the HIV treatment guidelines for Thailand. The long term effectiveness and adverse effects of this drug combination for the treatment of HIV were evaluated in an ambispective study at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand from March 2002 to January 2006. A total of 152 adult treatment naïve HIV patients who had received at least 12 months of GPO-VIR were enrolled. The median (IQR) CD4 cell count increased from 23 (8-94) cells/μl at baseline to 126 (38-180), 136 (98-189), 199 (141-255) and 334 (243-414) cells/μl at 3, 6, 12 and 24 months (p<0.001), respectively. The median (IQR) percentage of body weights increased from baseline by 3.0% (0.3-6.3), 6.2% (2.2-9.3), 7.3% (3.9-10.9) and 8.1% (3.4-11.9) at 3, 6, 12 and 24 months, respectively and then remained at a plateau until the end of the 3-year study. The occurrence of new opportunistic infections decreased significantly (p<0.001) with GPO-VIR treatment. Drug resistance occurred in 5 cases (3.3%) with a median (IQR) time of 18.0 (16.5-32.5) months to occurrence. Adverse effects included hypercholesterolemia (43.2%), lipodystrophy (35.5%), hypertriglyceridemia (25%), hypertension (13.1%), peripheral neuropathy (11.9%), hyperlactatemia (2.6%) and lactic acidosis (1.3%). Thirty-six patients (27%) switched from GPO-VIR to other anti-retroviral drugs regimens due to lipodystrophy. This study showed GPO-VIR had clinical and immunological benefits, but one-third of patients had adverse effects.

Keywords: HIV, GPO-VIR, effectiveness, adverse effect, CD4 count

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INTRODUCTION

The epidemic of human immunodeficiency virus type 1 (HIV-1) infection poses a serious public health threat, but highly active antiretroviral therapy (HAART)

has reduced the morbidity and mortality associated with HIV-1 infection and the risk of progression to acquired immunodeficiency syndrome (AIDS) (Hogg *et al*, 1998; Pallela *et al*, 1998). Access to antiretroviral drugs for HIV-infected patients in developing countries is a global public health priority (Sow *et al*, 2007; Hammond *et al*, 2008). Updated guidelines from the World Health Organization (WHO) in 2010 (WHO, 2010) and the United States Department of Health and Human Services (DHHS) in 2011 (DHHS, 2011) recommended two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) for first-line therapy in treatment naïve HIV patients. This combination has shown to be effective, tolerable, simple, cost-effective and have good adherence to treatment (WHO, 2010; DHHS, 2011).

The estimated number of adult cases of HIV infection worldwide is 33.3 million, with two-thirds of cases from Sub-Saharan Africa (UNAIDS, 2009). In 2008, 2.6 million people became newly infected with HIV and 1.8 million people died from opportunistic infections (OIs) and AIDS related illnesses (UNAIDS, 2009). Four point nine million people are infected with HIV in Asia, and of these Southeast Asia is the second highest rank in the world and Thailand rank 17th highest in the number of HIV cases worldwide with a total of 530,000 cases (UNAIDS, 2009).

Generic fixed dose combination stavudine (d4T) 30 mg, lamivudine (3TC) 150 mg and nevirapine (NVP) 200 mg, a product of the Thai Government Pharmaceutical Organization (GPO), named GPO-VIR, is recommended as first-line HIV treatment in Thailand because it provides good effectiveness, is a simple formulation, has simple dosing, is well tolerated and inexpensive (USD 40 per month) (Phoolcharoen *et al*, 2004). There are only few short term reports evaluating the effectiveness and adverse effects of this combination (d4T, 3TC and NVP) (Anekthananon *et al*, 2004; Pujari *et al*, 2004; Calmy *et al*, 2006; Kiertiburanakul *et al*, 2007; Laurent *et al*, 2007). This ambispective study was conducted to evaluate the long term effectiveness and adverse effects of GPO-VIR in adult treatment naïve HIV patients after receiving the drug for at least 12 months.

MATERIALS AND METHODS

Study patients

An ambispective (mixed retrospective and prospective) study was conducted at the Ambulatory Care Unit of Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand from March 2002 to January 2006. We recruited adult HIV infected treatment naïve patients aged >13 years old who had taken GPO-VIR (d4T 30 mg + 3TC 150 mg + NVP 200 mg) twice a day for at least 12 months. Exclusion criteria were pregnant women and patients with history of underlying diseases, such as hypertension, dyslipidemia, diabetes, kidney disease, liver disease, malignancies or autoimmune diseases. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University and the Ethics Committee of Bamrasnaradura Infectious Diseases Institute.

Evaluation of patients and follow-up

Basic demographic data, clinical presentation and laboratory findings were obtained on recruitment and at 3 month intervals. Outcomes of treatment were recorded, including CD4 cell counts, body weight changes and occurrence of new OIs after initiation of GPO-VIR. The

adverse effects of GPO-VIR, including long term toxicities such as lipodystrophy and lactic acidosis, were also evaluated. Lipodystrophy is metabolic syndrome with abnormal loss (lipoatrophy) or accumulation (lipotrophy) of fat. Signs of lipoatrophy included thinning of cheeks, extremities, hips or buttocks, sinking of temporal region and/or sunken eyes, whereas signs of lipotrophy included fat accumulation in the neck, abdomen, upper back, hips or buttocks, gynecomastia and/or enlargement of the parotid region (Saint-Marc *et al*, 1999; Heath *et al*, 2001; Lichtenstein *et al*, 2001; Saves *et al*, 2002). Signs of lipodystrophy were assessed by physicians. An elevated lactate level (2.1-3.9 mmol/l) was defined as hyperlactatemia and lactic acidosis was defined as metabolic acidosis accompanied by a blood lactate level ≥4 mmol/l (Mizock and Falk, 1992; John *et al*, 2001). Clinical progression was defined as development of a new AIDS defining condition at or after one year of therapy (DHHS, 2009).

Sample size calculation

To assess effectiveness of HIV therapy, virological response should be evaluated, but plasma viral loads were not routinely performed at this study site during the study period. Therefore, the immunological response was used to determine the response to treatment. The sample size was based on a study from Thailand of the effectiveness of GPO-VIR in an ambispective study at Chon Buri Hospital, where 39.5% of treatment naïve HIV patients who had been taking GPO-VIR attained median CD4 counts >200 cells/µl by two years of treatment (Tin *et al*, 2005). We assumed the treatment success rate at one year would be approximately 39.5%; therefore, at least 92 patients should be included in the study based on this figure with a 10% error at a 95% confidence interval.

Statistical analysis

Data were analyzed using SPSS for Windows version 18.0 (SPSS, Chicago, IL). Qualitative data were summarized as frequencies and percentages and analyzed with the chi-square test or the Fisher's test where appropriate. Quantitative data were tested for normality using the Kolmogorov-Smirnov test, then summarized as a median (IQR) for non-normally distributed data. The Mann-Whitney *U* test was used for two group comparisons and the Kruskal-Wallis one way ANOVA test was used to compare 3 more groups. All tests for significance were 2- sided; $p \leq 0.05$ was considered statistically significant. The median time to develop lipodystrophy after treatment with GPO-VIR was assessed with Kaplan-Meier estimates.

RESULTS

A total of 176 patients attending the Ambulatory Care Unit of the Bamrasnaradura Infectious Diseases Institute were eligible for the study. Nine patients refused to be interviewed, 3 files were lost and 14 patients were unable to follow up. The remaining 152 patients were eligible for the study (Fig 1).

Baseline characteristics and laboratory findings of the subjects are presented in Table 1. The median [inter-quartile range (IQR)] age of the patients was 37 (32-41) years. The majority of patients were males (65.8%, 100/152) and 51.9% (79/152) were married. Three-fourths of patients (114/152) presented with clinical category C level of infection according to the revised classification of HIV infection (CDC, 1993) and 62.8% of patients (71/152) had a CD4 count <50 cells/µl at the time of enrollment. The median (IQR) body weight of the patients was 49 (44-58)

Table 1
Demographic and baseline data of 152 studied subjects.

Characteristics	No. (%)	Median (IQR[a])
Age (yrs)		37 (32-41)
Gender, Male	100 (65.8)	
Marital status, Married	79 (52.0)	
Baseline body weight (kg)	149	49.0 (44.0-58.0)
Baseline clinical category, category C	114 (75.0)	
Baseline CD4 cell count,	113	23 (8-94)
<50 cells/µl	71 (62.8)	
Hemoglobin (g/dl)	82	10.8 (9.0-12.1)
Hematocrit (%)	83	32 (28-37)
Cholesterol (mg/dl)	45	173 (144-191)
Triglyceride (mg/dl)	44	112 (94-128)

[a] Interquartile range

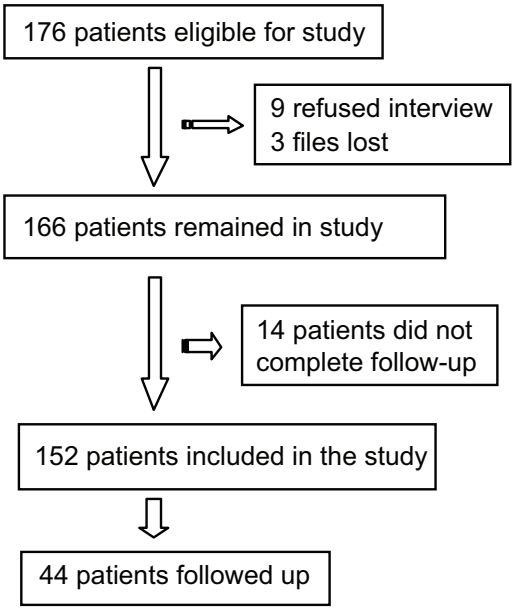

Fig 1–Flow chart of studied subjects.

kilograms. Of 152 study subjects, only 113 had pre-treatment CD4 cell counts available with a median (IQR) of 23 (8-94) cells/µl. The median (IQR) hemoglobin (10.8 g/dl, 9.0-12.1) and hematocrit (32%, 28-37) at baseline were slightly lower than normal limits, but the median cholesterol (173 mg/dl, 144-191) and triglyceride (112 mg/dl, 94-128) levels at baseline were within normal limits.

After initiation of GPO-VIR treatment, the median (IQR) CD4 cell counts dramatically increased from 23 (8-94) cells/µl at baseline to 126 (38-180), 136 (98-189), 199 (141-255), 269 (212-383) and 334 (243-414) cells/µl at 3, 6, 12, 18 and 24 months (p<0.001) (Fig 2). There were no significant differences in median CD4 cell count changes by the different groups of CD4 cell counts and clinical categories at baseline. Kaplan Meier analysis showed that the median (95% CI) times to achieve CD4 cell counts ≥100 cells/µl and ≥200 cells/µl after initiation of GPO-VIR was 12.0 (11.1-12.9) months and 24.0 (18.4-29.6) months, respectively. After 24 months of GPO-VIR treatment, 54.7% of patients (35) achieved a CD4 cell count ≥200 cells/µl. Of the 152 study subjects, drug resistance occurred in 5 cases (3.3%) and the median (IQR) time to developing drug resistance after initiation of GPO-VIR was 18.0 (16.5-32.5) months.

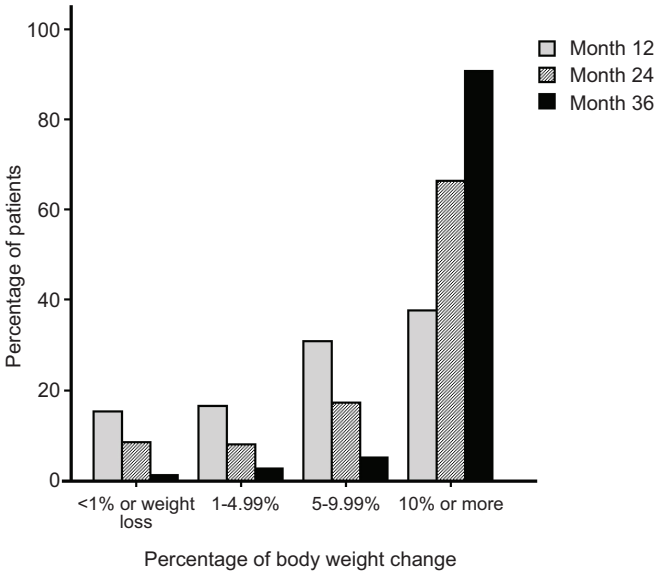

Fig 2–Body weight change at 12, 24 and 36 months of GPO-VIR treatment among 152 studied subjects.

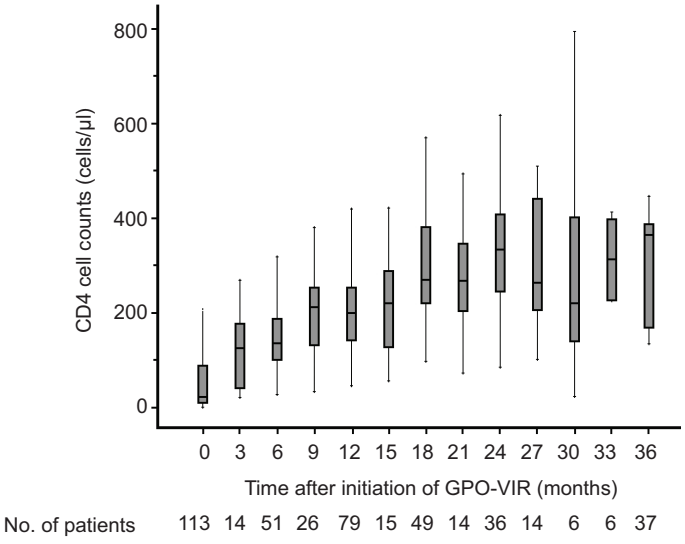

Fig 3–The median CD4 cell counts after initiation of GPO-VIR treatment among 152 studied subjects.

After 3 months GPO-VIR treatment, median (IQR) percentage increase in body weight was 3.0% (0.3-6.3), rose to 6.2% (2.2-9.3) by 6 months, 7.3% (3.9-10.9) by 12 months, 8.1% (3.4-11.9) by 24 months and 8.0% (3.8-12.8) by 36 months. The proportions of patients who achieved a weight gain >10% from baseline at 12, 24 and 36 months was 37.5, 66.4 and 90.8%, respectively (Fig 3). The greatest weight gain was observed in patients with HIV Clinical Category C infection ($p<0.05$). There were no significant differences in body weight change by baseline CD4 cell count.

Seventy-five point seven percent of patients (115/152) developed OIs prior to treatment; common OIs were tuberculosis (43.4%, 66/152) and oral candidiasis (41.4%, 63/152). Besides GPO-VIR treatment, patients also received Co-trimoxazole (94.7%, 144/152), fluconazole (39.5%, 97/152) and anti-tuberculosis drugs (39.5%, 60/152). After GPO-VIR treatment, the occurrence of new OIs, such as tuberculosis, oral candidiasis, *Pneumocystis jiroveci* pneumonia and cryptococcal meningitis, were significantly reduced ($p<0.001$), but *Mycobacterium avium* complex (MAC) ($p=0.065$), cytomegalovirus (CMV) retinitis ($p=0.629$) and herpes zoster ($p=1.000$) did not showed a significant reduction. Only one patient had an AIDS defining illness after 12 months of GPO-VIR treatment.

Adverse effects occurred in 38% (48/152) of patients after initiation of GPO-VIR treatment. These

adverse effects included hypercholesterolemia in 43.2% (63/146), lipodystrophy in 35.5% (54/152), hypertriglyceridemia in 25% (35/142), hypertension in 13.1% (19/145), peripheral neuropathy in 11.9% (17/144), hyperlactatemia in 2.6% (4/152) and lactic acidosis in 1.3% (2/152). The median (IQR) times to develop hypertension, lipodystrophy, peripheral neuropathy, hypercholesterolemia, hypertriglyceridemia, hyperlactatemia and/or lactic acidosis after initiation of GPO-VIR were 9 (3-15) months, 21 (13-27) months, 6 (3-13.5) months, 15 (9-21) months, 18 (9-27) months and 19.5 (12-21) months, respectively. Thirty-six patients (27%) switched from GPO-VIR to another anti-retroviral drug regimen due to lipodystrophy (75%, 27/36), peripheral neuropathy (11.1%, 4/36), hypertriglyceridemia (8.3%, 3/36), hyperlactatemia (5.5%, 2/36) or lactic acidosis (2.8%, 1/36).

DISCUSSION

Our study aimed to assess the effectiveness and adverse effects of GPO-VIR treatment. After initiation of GPO-VIR, a rapid increase in the CD4 cell count was seen in as early as 3 months and the counts continued to rise even after one year of treatment. The median CD4 count increased ≥100 cells/µl from baseline by the first year and ≥200 cells/µl from baseline by the second year. Our findings are similar to previous reports (Anekthananon *et al*, 2004; Kiertiburanakul *et al*, 2007; DHHS, 2009). Fifty-four point seven percent of patients had an increase in CD4 cell count ≥200 cells/µl from baseline by the end of the second year of GPO-VIR treatment. This percentage is higher than a previous study by Tin *et al* (2005) who found 39.5% of patients had a CD4 count >200 cells/µl after 2 years treatment. It is possible the exclusion of patients lost to follow-up might be one of the factors responsible for the higher effectiveness found in the present study. Only 3.3% of our patients in this study had drug resistance. This is lower than a study by Manosuthi *et al* (2008) who found 9.3% of HIV patients had drug resistance.

In our study, body weight changes from baseline were used to evaluate the effectiveness of GPO-VIR treatment. Patients treated with GPO-VIR had an average weight gain of 3% from baseline by 3 months, 6.2% at 6 months, 7.3 % at 12 months and a plateau by 36 months. More than 60% of patients achieved a 10% weight gain from baseline by 2 years of treatment. Patients with the greatest weight gain were clinical category C at baseline. These results are similar to a study by Tin *et al* (2005) who found 52.3% of patients had 10% weight gain by 2 years.

The adverse effects of antiretroviral therapy can have a significant impact on adherence to the treatment regimen. In our study, the adverse effects of GPO-VIR observed included hyperlipidemia (43.2% hypercholesterolemia and 25.0% hypertriglyceridemia), lipodystrophy (35.5%), hypertension (13.1%) and peripheral neuropathy (11.9%). The incidence of hyperlipidemia with GPO-VIR treatment in our study was higher than a previous study (Anekthananon *et al*, 2004), but the onset of hyperlipidemia after 52 weeks of treatment which is similar to that previous study. Saint-Marc *et al* (1999) found triglycerides were significantly higher in patients treated with d4T.

In our study, lipodystrophy occurred in 35.5% of patients, similar to a previous Swiss HIV cohort study (Bernasconi *et al*, 2002) which found 43% of patients had signs of abnormal fat distribution. The

occurrence of lipodystrophy is higher in patients receiving d4T for a longer time (Young *et al*, 2005).Twenty-seven percent of patients changed to a different HIV treatment regimen due to adverse effects, predominantly lipodystrophy (75%). A previous study of the safety and effectiveness of GPO-VIR at 4-6 months showed 12% of adult HIV patients discontinued the drug due to adverse effects, mainly rash and hepatitis (Anekthananon *et al*, 2004; Kiertiburanakul *et al*, 2007).

Hypertension was found in 13.1% of studied patients, similar to the general Thai population (11.3%) (Achananuparp *et al*, 1989); the occurrence of hypertension does not appear to be associated with GPO-VIR treatment. Peripheral neuropathy was found in 11.9% of patients, similar to a report by Spruance *et al* (1997) who found neuropathy in 13% of d4T treated patients. In our study, peripheral neuropathy developed by 6 months of GPO-VIR treatment. Kline *et al* (1995, 1998) found the neuropathy due to d4T usually resolves by 1-3 weeks after discontinuing the drug.

In conclusion the GPO-VIR treatment in Thailand resulted in good clinical and immunological outcomes, but one-third of patients had adverse effects during the 3 years of follow-up.

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