DEMOGRAPHIC, SOCIO-ECONOMIC, BEHAVIORAL AND CLINICAL FACTORS PREDICTING VIROLOGIC FAILURE WITH GENERIC FIXED-DOSE COMBINATION ANTIRETROVIRAL THERAPY BEFORE UNIVERSAL HEALTH INSURANCE COVERAGE IN NORTHERN THAILAND

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Abstract. We conducted a 2-year prospective cohort study to investigate multiple aspects of factors predicting the outcome of fixed-dose combination antiretroviral (ARV) therapy with lamivudine, stavudine, and nevirapine (GPOvir®) at a government referral hospital in northern Thailand. At 6 and 24 months after the initiation of GPOvir®, viral load (VL) was measured to determine virologic failure (>400 RNA copies/ml) and demographic, socio-economic, behavioral and clinical data were collected. From 10 April 2002 to 31 January 2004, 409 patients participated in this study: 64/364 (17.0%) at 6 months and 55/345 (15%) at 24 months virologically failed treatment. On univariate analysis, besides ARV experience [odds ratio (OR), 3.08, 95% confidence interval (CI), 1.71 -5.57] and the frequency of delayed doses (OR, 2.97; 95% CI, 1.47-6.00), we identified one socioeconomic factor significantly associated with virologic failure: "not having child" (OR, 1.85; 95% CI, 1.03 - 3.34). Although the association with "not having child" became marginal on multivariate analysis, results of in-depth interviews and group discussions indicated that having a child was a strong motivating factor for good treatment compliance. We suggest that patients without children may need more attention. Further investigation of socio-economic factors is warranted.

INTRODUCTION

The "Treat 3 Million by 2005" (3 by 5) initiative to expand HIV treatment access in developing countries has made substantial progress. In 2005, the goal was broadened to "Universal access" (WHO, 2007). By December 2006, it was estimated that 2,015,000 (1.8-2.2 million) people living with HIV/AIDS were receiving treatment in low- and middle-income countries, representing 28% (24-34%) of the estimated 7.1 million (6.0-8.4 million) people in need (WHO, 2007). In Thailand, with a population of approximately 62 million, 580,000 people were living with HIV in 2005 (UNAIDS/WHO, 2005,

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2006). In the past two decades, over 500,000 Thai citizens were estimated to have died of AIDS (UNAIDS/WHO, 2005). At that time, HIV-1 infected patients were either not treated or treated with suboptimum antiretroviral (ARV) drug therapy, such as mono therapy (1995-1997) or dual therapy (1997-1999) (Pathipvanich *et al*, 2003). However, the Thai Government has substantially reduced the cost of a multiple ARV drug regimen by locally producing a generic fixed-dose combination of ARV (GPOvir®: stavudine, lamivudine, nevirapine). It was recommended as a first-line regimen in 2001. Since the "National Access to Antiretroviral Program for people living with HIV/AIDS (NAPHA)" launched in 2003, free ARV therapy had rapidly expanded. In December 2006, the estimated ARV coverage in Thailand was 88% (54-100%) (WHO, 2007).

For successful outcomes and improvement of ARV treatment, the challenge is to deliver it effectively with a high ARV treatment success rate in a resource constrained setting (Gallant, 2000). HIV RNA viral load testing was considered the ideal method for assessing the efficacy of the ARV regimen (Murray *et al*, 1999; Haubrich *et al*, 2001). However, it is still not readily available as a routine test in developing countries because of its cost and limitation of infrastructure (Kent *et al*, 2003; Colebunders *et al*, 2006). Hence, identifying risk factors predicting treatment outcomes would be an effective alternative for achieving a high success rate and it would be useful for providing more effective support to patients at risk for treatment failure before or during treatment.

Several factors have been reported to be associated with the failure of ARV therapy. These are base-line CD4+ cell count, baseline viral load, gender, previous treatment with ARV, younger age, intravenous drug use (IDU), race and poor adherence to medication (Lucas *et al*, 1999; Chesney, 2000). Adherence to ARV drugs is the most important factor in determining successful viral suppression(Gallant, 2000; Paterson *et al*, 2000; Sethi *et al*, 2003). Only a small number of published cohorts have so far reported socioeconomic factors predicting virologic failure due to ARV treatment. A metaanalysis of published studies from resource-constrained countries showed that the availability of free medication associated with a significantly higher proportion of subjects with undetectable viral loads (Ivers *et al*, 2005; Braitstein *et al*, 2006). We conducted this 2-year prospective cohort study to investigate the multiple factors predicting the outcome of fixed-dose combination ARV therapy at a government referral hospital in northern Thailand.

METHODS

Study setting and participants

All HIV positive patients started on GPOvir therapy from 10 April 2002 to 31 January 2004 at the Day Care Center (DCC) in Lampang Hospital were approached by well-trained research staff and recruited for this study after giving informed written consent. The Lampang Hospital is a government referral hospital with approximately 800 beds situated in the center of Lampang Province in northern Thailand. The DCC was established in October 1995 as an outpatient clinic providing treatment, care and support for HIV infected patients; 1 clinician and 2 nurses had treated 2,055 patients as of February, 2007.

The ARV treatment initiation criteria and clinical management followed the Thai guidelines for ARV treatment (National guidelines for the clinical management of HIV infection in children and adults. 6th ed. Ministry of Public Health, Thailand, 2000). Prophylaxis of opportunistic infections followed the guidelines of Lampang Hospital.

Before and after starting GPOvir treatment, the doctor and nurses taught each patient the importance of treatment compliance and a peer support group held monthly meetings to exchange experiences for coping with problems including the matter of treatment compliance.

This study was conducted as a part of the Lampang HIV-Cohort Phase I and Lampang and Phayao HIV Cohort Phase II, which were approved by Thai Ministry of Public Health Ethics Committee in December 1999 and on 29 December 2005, respectively. The qualitative study with in-depth interview and discussion was approved by the ethics committee of Lampang Hospital in September 2007.

Collection of baseline data

For each participant in the study, sociodemographic data (age, gender, marital status, children, income and education level) and medical history (HIV-related symptoms, duration after diagnosis of HIV, history of ARV therapy, mode of transmission) were obtained at the initial visit by research staff through face-to-face interviews based upon structured questionnaires.

Collection of follow-up data

After the first prescription of GPOvir, patients were instructed to visit the clinic every other week for the first month and every month thereafter. At 6 and 24 months after the onset of treatment, a follow-up interview was conducted by the research staff using a newly-structured questionnaire. Research staff attempted to contact patients by telephone and letter to minimize loss of follow-up. The follow-up questionnaire identified the level of adherence, the presence of reminder to keep optimal adherence, the presence of supporters, perceived side effects, the financial burden of continuing ARV, the range of disclosure, reasons for missing doses, change of marital status and perceived behavioral, mental and physical conditions after GPOvir was started and the frequency of meeting medical staff or other PHA (People living with HIV/AIDS). The level of adherence was asked in 4 simple questions (Table 4): 1) have you forgotten to take GPOvir® during the last month? 2) Have you failed to take GPOvir® at the scheduled time during the last month? 3) Is the frequency of forgetting the medication increasing? 4) What do you think of your adherence in general during the last month?

The survival status of patients was ascertained using the hospital records, death certificates, mailed letters, and contacting families or relatives.

Laboratory testing

At enrollment, a complete blood count (CBC), CD4 T-lymphocyte count and viral load (VL) were measured. A VL was measured at 6 and 24 months after initiating GPOvir using the Cobas Amplicor HIV-1 Monitor Test. Virologic failure was defined as a VL higher than 400 RNA copies/ml. Viral load testing was done retrospectively using the frozen stored samples from patients who had received GPOvir therapy before antiretroviral therapy was covered by the universal insurance scheme.

Statistical analysis

We analyzed the data based on intention-to-treat analysis. To identify the factors predicting virologic failure, univariate and multivariate analyses were performed. Factors associated with virologic failure on univariate analysis using chi-square test and risk factors for virologic failure reported by previous studies were entered into multivariate models using logistic regression. A significance level of $p<0.05$ was chosen. *P*-values for statistical tests were 2-sided, and 95% CIs were estimated. All analyses were conducted using SPSS version 12 (SPSS Inc, Chicago, Illinois, USA).

Qualitative analysis

We conducted a semi-structured in-depth interview and group discussion on 17 and 18 October 2007 to deepen our understanding of the results of this quantitative study. We selected 3 males and 5 females for the interview and added 2 females who experienced delivery after initiation of ARV for group discussion. One Thai-fluent investigator and a well-trained local Thai assistant facilitated the interview and discussion in the informants' local language (northern Thai dialect). Notes and audio recordings were transcribed and translated from the local language into English.

RESULTS

Participant recruitment and characteristics

We approached 428 patients, of these, 409 (184 men and 225 women) agreed to participate in the study. Two hundred thirty-four (52.7%) patients were younger than age 35 years old. Most of patients (94.4%) reported they acquired HIV through heterosexual intercourse. Three hundred seventy-seven (92.2%) patients were married, and more than half (64.3%) had children. The majority (71.1%) had never been treated with ARV drugs previously. Of the patients who had been treated with ARV before, dual therapy with AZT and ddI or ddC was the most common regimen. Nearly 40% of the patients had no income and 50% had an education level less than secondary school. Thirteen patients or their families paid 1,200 baht (≃USD 36) per month for GPOvir therapy because they wanted to start the therapy before the NAPHA program commenced. On enrollment, 362 patients (88.5%) had AIDS-related symptoms. The median baseline CD4+ cell count was 44.0/μl with IQR (15.0-109.0) and the median baseline VL level was 246,834 copies/ml with IQR (86,978-547,520 copies/ml). Fig 1 summarizes the studied patients. Of the 409 patients who participated, 16 died before Month 6 and 17 others died before Month 24. The overall mortality rate was 4.32 per 100 person-year-observation (PYO) (95% Confidence interval: 2.85-5.79 per 100PYO). VL data at Month 24 was available for 347 subjects. Thirty-two patients had VL data at Month 6 only. There were no significant differences in baseline characteristics between those who completed the 24 month follow-up and those who did not.

Treatment outcome

Table 1 shows the treatment outcomes at 6 months and 24 months after initiation of GPOvir therapy. All VL measurements taken from 3 months to 9 months post initiation of GPOvir therapy were regarded as

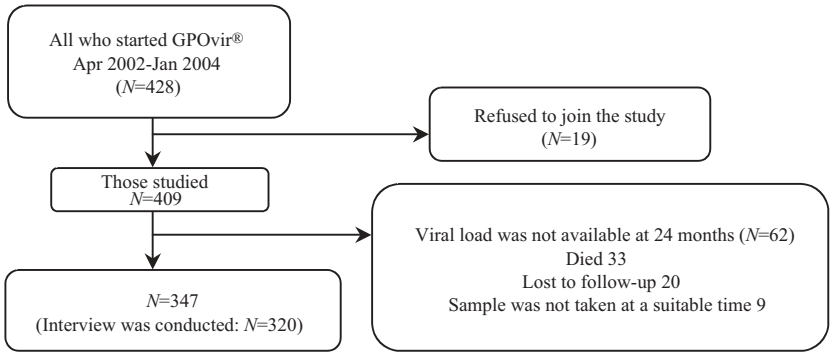

Fig 1–Recruitment of patients and follow-up for 24 months.

Table 1
Treatment outcomes at 6 and 24 months after the initiation of GPOvir®.

	Naïve (%)	Experienced (%)	PMTCT[a] (%)	Total (%)
Intention to treat analysis				
Virologic failure at 6 M	29/256 (11.3)	32/93 (34.4)	3/15 (20.0)	64/365 (17.0)
Virologic failure at 24 M[b]	27/244 (11.1)	25/87 (28.7)	3/14 (21.4)	55/345 (15.0)
As-treated analysis				
Virologic failure at 6 M	24/238 (10.1)	27/87 (31.0)	2/12 (16.7)	53/337 (15.7)
Virologic failure at 24 M	26/230 (11.3)	21/81 (25.9)	3/12 (25.0)	50/323 (15.5)

[a]PMTCT, prevention of mother-to-child transmission; [b]ARV history was not available for 2 patients; Virologic failure was defined as a VL higher than 400 RNA copies/ml.
M, months

Table 2
Association of demographic and clinical variables with virologic failure at 24 months.

Variables	Number of failures/ total	OR (95% CI)
ARV		
Naïve	27/244	Ref
Experienced	28/101	3.08 (1.71-5.57)
PMTCT		
Naïve	52/331	Ref
Experienced	3/14	1.46 (0.40-5.43)
Age		
≥35	19/146	Ref
<35	35/199	1.42 (0.77-2.61)
Gender		
Female	27/193	Ref
Male	27/152	1.32 (0.74-2.37)
CD4 at baseline		
<50	30/163	Ref
≥50	22/164	0.69 (0.38-1.25)
AIDS symptom status		
Asymptomatic	3/-37	Ref
Symptomatic	49/309	0.97 (0.39-2.46)

OR, Odds ratio; CI, Confidence interval

a 6 month VL (Mean duration of 220.0 days with SD of 84.2 days). The mean duration for the 24 month VL measurement was 757 days with a SD of 98.1 days, ranging from 420 days to 1210 days. In total, 64/365 patients (17.0%) at 6 months and 55/345 patients (15%) at 24 months failed treatment. There were 12 cases, who had "failure" at 6 months and "not failure" at 24months. Nine of these cases had treatment interruption (<30 days), more than once, before viral load testing at 6 months. The highest failure rate was observed in the ARV experienced group at 6 months. Interestingly patients who experienced only a short-course of zidovudine for the prevention of mother-to-child transmission (PMTCT) before GPOvir therapy showed a higher failure rate than ARV naïve patients.

Univariate analysis

The results of univariate analysis are presented in Table 2. ARV experience but not PMTCT was strongly associated with virologic failure. We did not find any association between virologic failure and CD4+ cell count or clinical status at the time of starting the GPOvir on univariate analysis.

The results on univariate analysis of the socioeconomic factors associated with virologic failure at 24 months are shown in Table 3. The factor "not having child" was significantly associated with virologic failure. No other socioeconomic factors were associated with treatment outcomes, except that ARV naïve patients who themselves or

Table 3
Association of socio-economic variables with virologic failure at 24 months.

Variables	Number of failuress/total	OR (95% CI)
Education		
Secondary/higher	26/163	Ref
None/Primary	28/180	0.97 (0.54-1.37)
Income		
None	20/132	Ref
<5,000 THB	18/122	0.97 (0.49-1.93)
≥5,000 THB	16/91	1.20 (0.58-2.45)
Marital status		
Single	5/26	Ref
Married	49/317	0.77 (0.28-2.13)
Having child		
Yes	28/222	Ref
No	26/123	1.85 (1.03-3.34)
Nobody is aware that you are HIV positive		
No	22/119	Ref
Yes	25/199	1.58 (0.84-2.94)
People at home are aware that you are HIV positive		
No	42/291	Ref
Yes	5/27	0.74 (0.26-2.06)
People at work are aware that you are HIV positive		
No	25/204	Ref
Yes	22/114	1.71 (0.96-3.21)
Neighbors are aware that you are HIV positive		
No	27/207	Ref
Yes	20/111	1.45 (0.78-2.75)
[a]Feel difficult in taking GPOvir® at nowhere		
No	4/26	Ref
Yes	46/290	1.03 (0.34-3.15)
[a]Feel difficult in taking GPOvir® at home		
No	48/312	Ref
Yes	2/7	5.50 (0.76-40.0)
[a]Feel difficult in taking GPOvir® at working place		
No	46/301	Ref
Yes	4/15	2.01 (0.62-6.60)
[a]Feel difficult in taking GPOvir® at other places		
No	48/294	Ref
Yes	2/21	0.54 (0.12-2.39)
[a]Pay for GPOvir® by oneself or family		
No	45/297	Ref
Yes	5/17	2.33 (0.78-6.94)[b]
There is a specific person who reminds you to take your medication		
Yes	21/155	Ref
No	26/163	1.21 (0.65-2.26)

OR, Odds ratio; CI, Confidence interval; [a]asked at 6 months after initiation of GPOvir®;
OR (95% CI) was 4.35 (1.01 - 18.8) in the as-treated analysis.

Table 4
Association of behavioral variables with virologic failure at 24 months

Variables	Number of failures/total	OR (95% CI)
Perceived side-effect due to GPOvir®		
None	40/296	Ref
Yes	7/22	2.99 (1.15-7.78)
Frequency of meeting the doctor		
Every month/every week/every day	13/57	Ref
Not frequent	34/261	0.50 (0.24-1.04)
Frequency of meeting the nurse at the hospital		
Every month/every week/every day	15/62	Ref
Not frequent	32/256	0.44 (0.22-0.89)
Frequency of meeting the nurse at the health center		
Every month/every week/every day	3/5	Ref
Not frequent	44/313	0.10 (0.01-0.67)
Frequency of meeting other PHA		
Every month/every week/every day	15/130	Ref
Not frequent	32/188	1.58 (0.81-3.03)
Frequency of receiving advice about ARV by doctor in the last year		
Once/few times/many times	12/64	Ref
None	38/251	1.29 (0.63-2.65)
Frequency of receiving advice about ARV by pharmacist in the last year		
Once/few times/many times	25/155	Ref
None	25/160	0.96 (0.51-1.76)
Frequency of receiving advice about ARV by nurse at the hospital in the last year		
Once/few times/many times	12/49	Ref
None	38/266	0.51 (0.24-1.07
Frequency of receiving advice about ARV by nurse at the health center in the last year		
Once/few times/many times	59/306	Ref
None	1/9	0.65 (0.74-5.34)
Frequency of receiving advice about ARV by other PHA in the last year		
Once/few times/many times	27/144	Ref
None	23/170	0.67 (0.36-1.25)
Have you forgotten to take GPOvir® in the last month?		
No	41/293	Ref
Yes	6/25	1.94 (0.73-5.15)
Have you failed to take GPOvir® as scheduled during the last month?		
No	32/266	Ref
Yes	15/52	2.97 (1.47-6.00)
What do you think of your adherence in general during the last month?		
Good	34/248	Ref
Fair/Poor	13/70	1.44 (0.71-2.90)[a]
Is the frequency of forgetting the medication increasing?		
Decreasing	29/157	Ref
Increasing/No change	18/161	1.79 (0.95-3.38)

OR, Odds ratio; CI, Confidence interval; [a]OR (95% CI) among ARV naïve patients was 3.10 (1.24 - 7.75) in the as-treated analysis.

Table 5
Multivariate analysis.

Variables	OR (95%CI)	*p*-value
ARV experienced	2.94 (1.51-5.61)	<0.01
<35years old	1.59 (0.80-3.14)	0.18
Baseline CD4<50	1.47 (0.78-2.80)	0.24
Male gender	1.12 (0.57-2.19)	0.74
Not having child	1.89 (0.95-3.77)	0.07
Pay for GPOvir by oneself or family	3.22 (0.97-10.6)	0.06

OR, Odds ratio; CI, Confidence interval.

whose family paid for GPOvir were significantly associated with virologic failure in the as-treated analysis.

Table 4 shows behavioral factors associated with virologic failure. The question asking the frequency of delay in taking the medication during the previous month was significantly associated with treatment outcome. Self evaluation of adherence to treatment as "fair" or "poor" was associated with virologic failure at 24 months only when the ARV naïve group was analyzed on as-treated analysis. The question regarding the frequency of missing a dose was not associated with virologic failure. Disclosure status was not associated with outcome. Changes in marital status, perceived behavioral, mental and physical condition after starting GPOvir were also not associated with virologic failure. Frequency of contact with nurses was significantly associated with virologic failure. Patients who reported perceived side effects showed poorer viral suppression at 24 months than those who did not have side effects. Besides self-evaluation of adherence, the results did not differ from the as-treated analysis.

More than half (51%) the patients had a person (family member or relative) or an alarm (TV, radio or clock) as reminders at 24 months. On statistical analysis, the presence of a reminder was not associated the viral suppression. However, in in-depth interviews and group discussions, some patients mentioned their children reminded them to take the drug on time.

Multivariate analysis

Gender, age, CD4 count at baseline, previous ARV experience, presence of children, and self-funded treatment were included on multivariate analysis (Table 5). Previous ARV experience retained a significant association with virologic failure. Those who did not have a child, tended to fail treatment. This trend became significant on as-treated analysis. Other factors were not associated with virologic failure.

Their responses to each question at 6 months were similar to those at 24 months (data is not shown). Analysis using 6 month treatment outcome results were not significantly different from 24-month treatment outcome results.

Drug-taking behavior and perceived motivation for adherence

Common ways for taking ARV on time included using a cell-phone alarm and having their family reminder them. All those having children answered that their children reminded them to take their ARV on time. When we asked them "Why do you continue with good compliance to the ARV regimen?", all the patients having children answered "*Phua Louk* (for my children)", while patients without children answered, "for my nephew", "for my niece", or "for my parents". Answers from patients with children included: "I want to survive until my daughter graduate from university", "I want to see my children grow up and get jobs", or "I want to survive until my children get marry". However, one woman who had a small child and experienced treatment failure said, "Sometimes it was difficult for me to take medicine on time because I was too busy car-

ing for my baby".

It is interesting to note that many patients commented positively they had improvement in their physical fitness after starting the ARV drugs, and experienced less discrimination from the community. They used to feel discrimination (*Rang Kiat*) especially at wedding ceremonies, funeral ceremonies and "*Ngaan Buat*" (entering priesthood ceremonies) where their neighbors did not want to sit at the same table with them or were reluctant to eat dishes they cooked. Some patients answered they tried to be compliant with the treatment because "I want to show my neighbors that I am well and I can do anything, even if I have HIV/AIDS", or "I want to reduce AIDS-related discrimination". Several patients reported "I became much healthier after taking ARV, so discrimination against me was reduced". They also said the situation was getting better, because people had better knowledge regarding HIV/AIDS, and they credited the education of the community to mass media.

DISCUSSION

We found that "not having child" was associated with virologic failure on univariate analysis and on multivariate analysis, although the significance of the association became only marginal on multivariate analysis of the intention-to-treat. Byakika-Tusiime *et al* (2005) reported a marital status of being single as being associated with non-adherence in Uganda but in their study, they did not analyze the presence of children, nor did they measure virologic failure. We think the presence of children may have confounded the marital status. Several studies have been published and reported socio-economic factors influencing ARV adherence (Gordillo *et al*, 1999; Weiser *et al*, 2003). However, there have been only few published studies, which investigated the socioeconomic factors predicting virologic outcomes with ARV therapy (Ivers *et al*, 2005). Our as-treated analysis suggested that self-funded treatment ("need to pay for GPOvir") may predict virologic failure in ARV-naïve patients. This finding conveys an important message that when considering the initiation of ARV, the cost should be covered in full. Fortunately, in Thailand the cost of ARV has become fully covered since 2003.

Besides socio-economic factors, our results showed that simply asking the question about the frequency of delayed medication dosing during the previous month was significantly associated with virologic failure with the highest odds ratio. Previous studies have also reported that self reported adherence tended to over-estimate but was significantly associated with treatment outcome (Haubrich *et al*, 1999; Bangsberg *et al*, 2000; Liu *et al*, 2001). Ideally, adherence should be evaluated using multiple techniques, including objective ones, such as pill-counts and MEMS (Medication Electronic Monitoring System). However, these are difficult to use and sustain in our hospital because of cost and limited time and human resources. There are no gold standards for measuring adherence to treatment even in developed countries. Among other factors, being male tended to result in ARV failure at 24 months in ARV naive subjects. This is compatible with the results of previous studies (Nicastri *et al*, 2005; Calmy *et al*, 2006). Patients who met the nurse at the hospital often had a higher failure rate. This was not interpreted as a risk factor but as the result of clinical failure, since patients in bad clinical condition with adverse events or opportunistic infections tended to visit medical personnel often.

The virologic failure rate of our patients at 24 months is comparable with previous studies in developed countries (Ledergerber *et al*, 1999) or in some developing countries

using the same fixed dose regimen (Laurent *et al*, 2004; Severe *et al*, 2005). Although virologic response to GPOvir was good among ARV-naïve patients, we found a considerable number of patients failed to suppress their viral load, especially when they who were exposed to suboptimal therapy as previously shown (Ledergerber *et al*, 1999). We also found the failure rate of PMTCT experienced mothers was higher than naïve ones. It remains unknown what influence the PMTCT regimen has on subsequent ARV treatment outcomes in mothers and to what degree. There are several studies reported that mothers who received mono or dual ARV prophylaxis for PMTCT, including nevirapine, were more likely to fail treatment due to ARV-drug resistance mutations (Kamkamidze *et al*, 2001; Lockman *et al*, 2007). However, the adverse effects of short course of zidovudine prophylaxis on subsequent ARV-drug therapy for mothers has not been reported.

The virologic failure rate at 24 months was similar to that at 6 months. The failure rate at 24 months may have been underestimated because this rate was calculated only among patients who continued the GPOvir therapy for 24 months. It would have been ideal to monitor patients for VL more frequently but it was not feasible because of financial constraints at that time, We had fewer patients at Month 6 than at Month 24. The reasons for absence from follow-up at the two points in time (*eg*, being busy, ignorance, illness and death, etc) may be different. These differences might have led to different levels of under- or over- estimation of failure rates. Thus, our findings regarding about virological failure rates must be used with precaution.

In this study, we succeeded in recruiting nearly all the patients attending the government hospital. Our hospital is a referral hospital, however, we believe our study population represents HIV-patients receiving care in northern Thailand. Our results indicate that patients without children need more attention before or during treatment as this predicts virologic failure with ARV therapy. Our in-depth interview confirmed that patients with children were very conscious of their health since they bore a responsibility in parenting their children. Of interest, most patients stated that lessening social discrimination was a part of their motivation for good adherence. For successful outcomes and improvement in ARV treatment in a resource-constrained setting, further investigations of socio-economic factors are warranted.

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