THE EFFICACY AND ADVERSE EFFECTS OF GPO-VIR (STAVUDINE+LAMIVUDINE+NEVIRAPINE) IN TREATMENT-NAÏVE ADULT HIV PATIENTS

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Abstract. A descriptive, combined retrospective and prospective study was conducted at the Anonymous Clinic, Chon Buri Hospital, Chon Buri Province, Thailand from November 10, 2003 to January 4, 2004. A total of 83 adult HIV-treatment-naïve patients undergoing treatment with GPO-VIR (stavudine, lamivudine, and nevirapine) for at least one year were studied. The objectives of the study were to assess the efficacy of GPO-VIR by evaluating body weight changes, CD4 T-cell count changes, the occurrence of opportunistic infections, and long-term side effects, such as lipodystrophy, during treatment. Of 83 studied patients, approximately half (52.3%) of them had a body weight increase >10% of pre-treatment body weight after 12 months treatment. After taking GPO-VIR, CD4 T-cell counts increased rapidly, by a median of 78 $x10^6$ cells/l during the first three months. 39.5% of the patients attained median CD4 counts >200$x10^6$ cells/l, and 11.6% achieved >500 $x10^6$ cells/l after 2 years of treatment. The occurrence of opportunistic infections was significantly lower after treatment with GPO-VIR ($p = 0.001$). Subjective assessment of lipodystrophy by physicians and patients showed that 16.8% had symptoms of lipodystrophy within 2 years of GPO-VIR treatment. There was a significant association between older age group (40-49 years) and occurrence of lipodystrophy ($p = 0.043$). GPO-VIR is an inexpensive and effective antiretroviral drug regimen for initiating treatment of naïve patients, but careful assessment for lipodystrophy is necessary, especially after one year of treatment.

INTRODUCTION

Widespread use of highly active antiretroviral therapy (HAART) has led to dramatic reductions in morbidity and mortality among individuals infected with the human immunodeficiency virus (HIV-1) (Carpenter *et al*, 2000). HAART (2004) is the combination of at least three drugs from the various classes of antiretroviral drugs into a 'cocktail' that typically produces a dramatic reduction in viral load and prevents further immune damage. There are several regimens with acceptable antiviral potencies available, particularly for patients being treated for the first time. The use of protease inhibitor (PI) containing regimens has been the first choice for initiating antiretroviral therapy since 1997 and there is sufficient data on their effectiveness, but the occurrence of its long-term toxicity limits the acceptability of this regimen (Munderi *et al*, 2000). Recently, several randomized clinical trials in antiretroviral-therapy-naïve patients have shown that a regimen based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) is at least as effective as a regimen that includes a protease inhibitor (Van Leeuwen *et al*, 2003).

In Thailand, AIDS has become the leading cause of death, and one in 60 people out of the country's population of 62 million are infected with HIV/AIDS (UNAIDS/WHO, 2003), but only a few patients can access antiretroviral therapy because of its high cost. It has been estimated that there were nearly 700,000 HIV-infected people in Thailand, of which an estimated 50,000 people need anti-retroviral drugs in 2002. The

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government of Thailand produced a low-priced, combination-therapy antiretroviral drug called GPO-VIR in 2002 to give HIV patients access to antiretroviral treatment. The pill is a '3-in-1' combination, containing stavudine (Zerit) 30-40 mg, lamivudine (Epivir) 150 mg, and nevirapine (Viramune) 200 mg. These are usually prescribed separately to patients to be taken twice a day (Anonymous, 2002). The combination of GPO-VIR, nevirapine plus 2 NRTI, is one of the alternatives of NNRTI-based HAART for resource poor settings (WHO Guidelines, April 2002). However, there are limited data on the long-term clinical efficacy of NNRTI containing regimens.

In the present study, the efficacy of GPO-VIR in adult HIV patients was assessed after using this cocktail for one year by evaluating body weight changes, CD4 T- cell count changes, and occurrence of new opportunistic infections as well as its long-term side effects such as lipodystrophy.

PATIENTS AND METHODS

A descriptive mixed retrospective and prospective study (ambispective study) was conducted at Chon Buri Hospital, Thailand from November 10, 2003 to January 4, 2004. Study participants were HIV-positive patients who have been taking GPO-VIR twice a day for at least one year. Eligible patients were antiretroviral-therapy naïve, aged more than 13 years with an absence of other concomitant diseases, such as cancer, liver cirrhosis, etc. All HIV patients who met the inclusion criteria were selected and a total of 83 patients were studied.

Retrospectively, the patients' cards were reviewed and information on demographic data, antiretroviral treatment, body weight, clinical symptoms and signs, opportunistic infections and concomitant use of drugs during treatment, laboratory data and physician's diagnosis of lipodystrophy were recorded. Prospectively, the patients who met the inclusion criteria were also interviewed for possible risk behaviors, clinical symptoms, opportunistic infections before treatment and the patients' perceptions of lipodystrophy. Of the 83 studied patients, only 39 patients who came for follow-up visits during the data collection period could be interviewed.

Statistical analysis

All data collected were analyzed using the statistical software Epi Info, version 6.04. For analysis of body weight changes and CD4 T-cell count changes, all 83 studied patients were classified into 3 groups according to their pre-treatment CD4 T-cell counts as $<50 \times 10^6$ cells/l, 51-199 $\times 10^6$ cells/l, and 200-349$\times 10^6$ cells/l. The patients from the groups with CD4 T-cell counts of 51-199$\times 10^6$ cells/l and 200-349$\times 10^6$ cells/l were combined and compared with those in the group with a CD4 T-cell count $<50\times 10^6$ cells/l.

The 83 patients were classified into 3 groups according to the 1993 revised classification of HIV infection (Vermund and Drotman, 1995). These included categories A, B, and C. Their body weight changes and CD4 T-cell count changes were compared between these groups by using the Kruskal-Wallis one way analysis of variance test. Further comparison between the 2 groups was done using the Mann-Whitney *U* test.

Lipodystrophy was assessed subjectively by patients and physicians using the HIV Outpatient Study (HOPS) scale. The degree of lipodystrophy was rated as absent (score of 0), mild (noticeable on close inspection, score of 1), moderate (readily noticeable by patient/physician, score of 2) or severe (readily noticeable by casual observers, score of 3) (Carr and Law, 2003). The severity rating for each sign was based on patient and physician agreement.

Categorical variables were then tested by chi-square or Fisher's exact test as appropriate. Paired proportions were compared by the McNemar's test and agreement of paired proportions was judged by the *kappa* statistic which was interpreted as the chance-corrected proportional agreement. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 83 patients who had GPO-VIR treatment for at least one year at Anonymous Clinic Chon Buri Hospital were included in the study. The demographic and baseline charac-

Table 1
Demographic characteristics of 83 adult HIV positive patients.

Characteristics	No. of patients	%
Age (year)		
Median (Range)	34 (23-75) [a]	
Sex		
Male	40	48.2
Female	43	51.8
Possible risk factors for HIV infection	39	
Heterosexual	31	79.0
Heterosexual & homosexual	1	3.0
Heterosexual & IVDU	2	5.0
Heterosexual & blood transfusion	5	13.0
Pre-treatment CD4 T-cell counts (10^6cells/l)	77	
<50	31	40.2
50-199	35	45.5
200-349	11	14.3
Median (Range)	69 (5-300)[a]	
Revised classification for HIV infection[b]	77	
Category A	21	27.3
Category B	27	35.0
Category C	29	37.7

[a]Median (Range)
[b]According to the 1993 revised AIDS definition

teristics of the patients are summarized in Table 1. The median age of the patients was 34 years with a range of 23-75 years. The study group consisted of 48.2% males and 51.8% females. Only 39 patients were interviewed, and all of them had a history of heterosexuality. The median pre-treatment CD4 T-cell count was 69 x10^6 cells/l with a range of 5-300 x10^6 cells/l. According to 1993 revised classification of HIV infection, 27.3% of patients were in category A, 35% in category B, and 37.7% in category C.

Body weight changes were analyzed for 65 patients who had records for both pre-treatment body weight and body weight at 12 months of treatment. It was found that 52.3% (34/65) of patients had a weight gain of >10% of their pre-treatment body weight after taking GPO-VIR for one year and 16.9% (11/65) had no weight gain or had weight loss by 1 year of treatment (Fig 1). Patients with low pre-CD4 T-cell counts of <50x10^6 cells/l had a significantly greater increase in median percentage of body weight changes than those groups of patients with pre-treatment CD4 T-cell counts of ≥ 50x10^6 cells/l during 4-6 months (p=0.035), 7-9 months (p=0.008), 10-12 months (p=0.009), and 13-15 months (p=0.037) of treatment, respectively (Fig 2a).

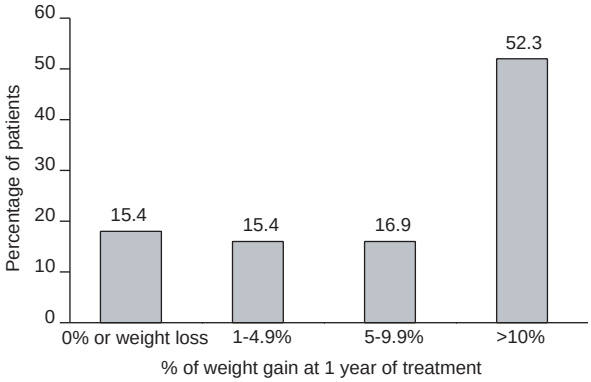
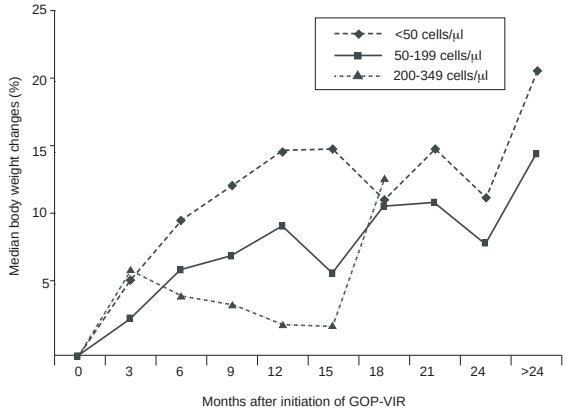


Fig 1–Percentage of body weight changes from baseline during GPO-VIR treatment in 65 studied patients.

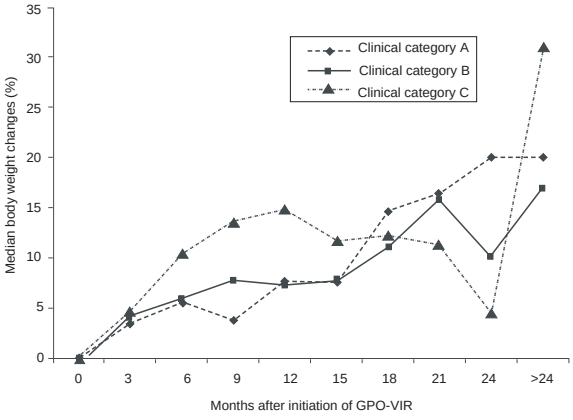
There was also a significant difference in the median percentage of body weight changes among the clinical categories A, B, and C, during 4-6 months (p=0.005), 7-9 months (p= 0.004), and 10-12 months (p=0.031) of treatment among these three groups (Fig 2 b). Such differences were observed when comparing category C with categories A and B during 4-6 months (p=0.006 and p=0.019), 7-9 months (p=0.003 and p= 0.027), 10-12 months (p=0.043 and p= 0.023), respectively (Fig 2 b).

The CD4 T-cell counts increased by a median of 78x10^6 cells/l during the first three months of treatment with GPO-VIR. Following the initial rapid increase in CD4 T-cell counts in the first 3 months of therapy, the median CD4 T-cell counts increase gradually until 21 months (Fig 3). After 2 years of treatment with GPO-VIR, 39.5% (17/43) of patients attained median CD4 T-cell counts of >200x10^6 cells/l and 11.6% (5/43) achieved median CD4 T-cell counts of >500x10^6 cells/l. There was no significant difference in the three-monthly increment of median CD4 T-cell counts from the time of initiation of GPO-VIR over a period of 2 years of treatment between the patients with pre-treatment CD4 T-cell counts



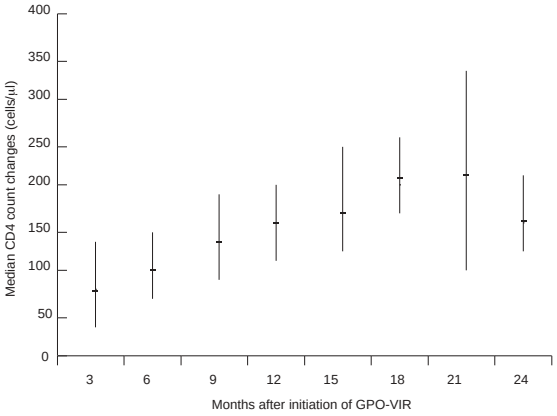
Pre-treatment CD4 count (10^6 cell/l)	No. of patients at each time point								
<50	0	31	30	27	27	21	15	8	4	2
50-199	0	35	32	32	28	23	15	9	5	4
200-349	0	9	10	9	6	7	5	0	0	0

Fig (2 a)–Median percentage of body weight changes from baseline during GPO-VIR treatment in 83 studied patients with respect to pre-treatment CD4 T-cell counts.



Pre-treatment Clinical category	No. of patients at each time point								
A	0	20	20	21	17	15	10	4	2	2
B	0	26	23	22	20	19	13	8	4	2
C	0	29	29	25	24	17	12	5	3	2

Fig (2 b)–Median percentage of body weight changes from baseline during GPO-VIR treatment in 83 studied patients with respect to revised classification for HIV infection.



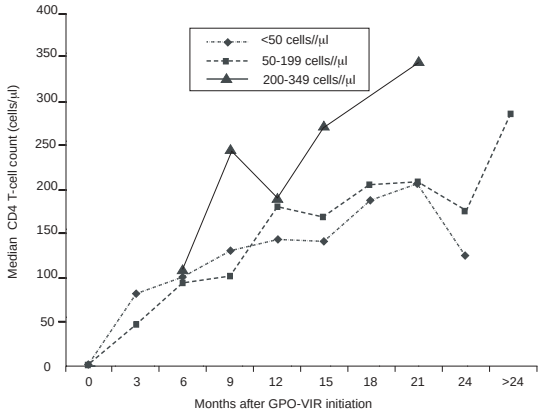
No. of patients							
9	38	29	42	22	17	9	5

Fig 3–Median (and interquartile) changes in CD4 T-cell counts after starting GPO-VIR treatment.

<50x10^6 cells/l and those with >50-199x10^6 cells/l ($p>0.05$) (Fig 4 a). It was also found that the median CD4 T-cell count increase was not significantly different between the patients with different pre-treatment clinical categories ($p>0.05$) (Fig 4 b).

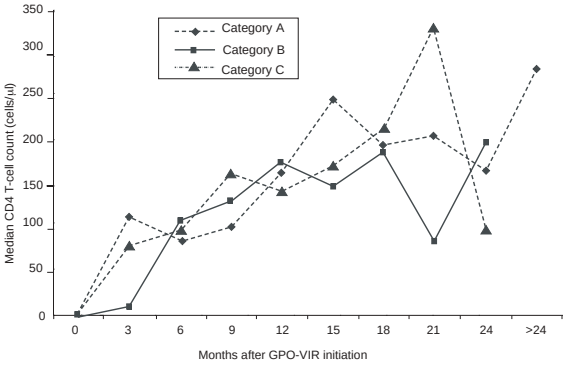
Most of the patients (71.1%, 59/83) had at least one opportunistic infection before starting GPO-VIR treatment. The most common opportunistic infections before treatment were oral candidiasis (42.0%, 35/83), tuberculosis (21.6%, 18/83), and herpes zoster (19.2%, 16/83). But an accurate time of occurrence for the opportunistic infections before treatment was difficult to verify because some of the data were collected by interview. Opportunistic infections were also found to occur within 18 months of treatment with GPO-VIR. However, the occurrences of the three common opportunistic infections were significantly lower after the initiation of GPO-VIR [oral candidiasis (42% *vs* 2.4%, $p<0.001$), herpes zoster (19.2% *vs* 3.6%, $p=0.001$), and tuberculosis (21.6% *vs* 3.6%, $p=0.001$)]. There were no new cases of vulvovaginal candidiasis, oral hairy leukoplakia, idiopathic thrombocytopenic purpura, esophageal candidiasis, cryptococcal meningitis, *Pneumocystic carinii* pneumonia, cytomegalovirus esophagitis or histoplasmosis after GPO-VIR treatment.

Lipodystrophy was observed subjectively in



Pre-treatment CD4 count (10^6 cell/l)	No. of patients at each time point									
<50	31	5	16	10	18	10	9	5	2	0
50-199	35	4	16	13	21	7	8	3	3	1
200-349	11	0	6	6	3	5	0	1	0	0

Fig (4 a)–Three-monthly median CD4 T-cell counts over time from the initiation of GPO-VIR, with respect to the pre-treatment CD4 T-cell count.



Pre-treatment Clinical category	No. of patients at each time point									
A	0	2	10	10	9	8	1	5	2	1
B	0	1	16	8	17	7	8	1	2	0
C	0	6	12	11	16	7	8	3	1	0

Fig (4 b)–Three-monthly median CD4 T-cell counts over time from the initiation of GPO-VIR, with respect to the clinical categories according to the revised classification of HIV infection.

14 patients taking GPO-VIR after a median time of 18 months with a range of 12-23 months of treatment. It was found that the occurrence of lipodystrophy assessed by the physicians and the patients was not significant different. Furthermore, there was significant agreement between the two assessment methods (κ=0.747, p<0.001). There was no significant association between lipodystrophy and the sex of the patients, pre-CD4 T-cell count, clinical category, pre-treatment body weight or duration of taking GPO-VIR (Table 2). There was a significant association between lipodystrophy and age group (p=0.043).

In a comparison between each pair of two age groups, there was no significant association in occurrence of lipodystrophy between the different age groups except the age groups 30-39 years and 40-49 years (p=0.004). Patients in the age group 40-49 years had a great chance of getting lipodystrophy than patients in the younger group. Thirteen of the 83 patients had stopped taking GPO-VIR and changed to another drug regimen due to the side effects of lipodystrophy after one year of treatment.

DISCUSSION

Monitoring the changes in body weight over the course of antiretroviral therapy is one of the basic parameters that is important and helpful to evaluate the effectiveness of the drug in resource poor settings where plasma viral loads and CD4 T-cell counts can not be used widely. The present study found the median percentage of body weight from baseline increased gradually over time throughout the treatment. The majority of patients (67.6%) who gained >10% of their pre-treatment body weight had a pre-treatment body weight ≤50 kg. A low pre-treatment body weight may be one factor that results in greater differences in weight changes between pre-treatment body weights and body weights at 12 months.

It also showed that the changes in median percentages of body weights in the patients with lower pre-treatment CD4 T-cell counts (≤50 cells/μl) were significantly higher than the changes in those with pre-treatment CD4 T-cell counts more than 50 cells/μl during 4-15 months of therapy. In addition, the changes in median percentages of body weights of the patients in clinical category C were significantly greater than the pa-

Table 2
Demographic and baseline characteristics of 83 studied patients with respect to signs of lipodystrophy.

Variables	Total (n)	With Lipodystrophy No. (%)	Without lipodystrophy No. (%)	p-value
Age (year)				0.043
20-29	20	4 (20.0)	16 (80.0)	
30-39	40	2 (5.0)	38 (95.0)	
40-49	14	5 (35.7)	9 (64.3)	
50-59	7	2 (28.6)	5 (71.4)	
>60	2	1 (50.0)	1 (50.0)	
Sex				0.187
Male	40	4 (10.0)	36 (90.0)	
Female	43	10 (23.3)	33 (76.7)	
Pre-CD4 count				0.578
<50	31	4 (12.9)	27 (87.1)	
50-199	35	8 (22.9)	27 (77.1)	
200-349	11	2 (18.2)	9 (81.8)	
Clinical category before treatment[a]				0.349
A	21	6 (28.6)	15 (71.4)	
B	27	4 (14.8)	23 (85.2)	
C	29	4 (13.8)	25 (86.2)	
Duration of GPO-VIR				1.000
12 months	12	2 (16.7)	10 (83.3)	
≥13 months	71	12 (16.9)	59 (83.1)	
Pre-treatment body weight				0.823
< 60 kg	61	11 (18.0)	50 (82.0)	
≥ 60 kg	19	3 (15.8)	16 (84.2)	

[a] According to the 1993 revised AIDS definition

tients in the other two categories during their first year of treatment. Since there are very few studies that focus on body weight changes, these findings could not be compared with other findings. There are some studies which demonstrated that low pre-therapy CD4 counts are associated with greater CD4 cell gains and rapid immunological responses (Hunt *et al*, 2003). The dramatic improvement in body weight in the clinical category C patients may reflect this effect.

Our study found that after taking GPO-VIR, the CD4 T-cell counts increased by a median of $78x10^6$ cells/l during the first three months of treatment. This result is not so different from the findings by Hunt *et al* (2003), who reported a median increase in the CD4 T-cell count from pre-therapy to month 3 was $65x10^6$ cells/l, and by Kaufmann *et al* (2000) who found a median CD4 count rise of $20x10^6$ cells/l per month in first three months.

Concerning the CD4 T-cell count changes, our study found that there was no apparent relationship between the rise in median CD4 T-cell counts during GPO-VIR treatment and the starting level. This finding is similar to the results of the study on response of HAART among antiretroviral-naïve patients by Lepri *et al* (2001). In contrast, it is differed from those of Hunt *et al* (2003) who recently reported that lower pre-therapy CD4 T-cell counts were associated with greater CD4 cell gains. The different findings may be due to different eligible criteria for the studied patients, since the study by Hunt *et al* (2003) included patients who had antiretroviral treatment prior to initiating HAART.

Although CD4 T-cell counts increase over

time during treatment, there was no significant association between pre-treatment clinical category and CD4 count. This is different from the findings of Kaufmann *et al* (2000) who found that clinical category A was one of the factors that influenced a better early CD4 cell response. The difference in findings may be due to different treatment regimens and eligible criteria for the studied patients in the two studies.

The occurrence of opportunistic infections during treatment was common in patients with lower CD4 T-cell counts (<50 cells/μl and 50-199 cells/μl) but there was no significant difference in the occurrence of opportunistic infections in patients with different pre-treatment CD4 T-cell counts. The study also found that the occurrence of opportunistic infections was significantly lower during treatment. This may be due to the dramatic increase in CD4 T-cell counts in response to the antiretroviral drug or concomitant use of drugs for prophylaxis of opportunistic infections. Most of the patients (71.1%) had opportunistic infections before receiving antiretroviral treatment and had already been treated for these opportunistic infections. This may be one of the factors that affects the low occurrence of opportunistic infections during treatment.

Most of the treatment regimens ware well tolerated, however with widespread use, previous unrecognized side effects are becoming more evident as the availability of the drugs improves and the duration of treatment increases. It is now clear that nucleoside analogues play a role in the development of lipodystrophy, and it is significantly associated with d4T or d4T/ddI (Saint-Marc *et al*, 1999). In our study, we found that 16.8% of studied patients had lipodystrophy and the rate of incidence was comparable to those of Martinez *et al* (2001) demonstrating that 17% of patients developed some type of lipodystrophy after a median follow-up of 18 months.

Our study also indicated that there was no significant association between sex, pre-CD4 counts, clinical category before treatment, duration of treatment and development of lipodystrophy. There was a significant association between the patient's age and the occurrence of lipodystrophy, with a high chance of developing lipodystrophy in older patients between 40-49 years of age. These findings are similar to in some points, and different from, in other points, the study by Lichtenstein *et al* (2003) indicating that lipodystrophy has an association with host factors, such as age, sex, severity of HIV disease, and duration of treatment. However, the physiological process of aging is also associated with body-fat changes that may bias the influence of age on the lipodystrophy seen in HIV infected patients (Martinez *et al*, 2001).

As the study is partly retrospective in nature, it has some weaknesses, such as non-consecutive data, limitation of laboratory data and difficulty in meeting all the studied patients for interview in the study period.

In conclusion, GPO-VIR is inexpensive and appears to be an effective antiretroviral drug combination for the treatment of naïve patients who have a low financial status. It costs 20 baht per pill (US$ 0.49), and a one-month supply costs about 1,200 baht or US$ 29.34 (1 US$= 40.9 baht). It can increase the patients' CD4 T-cell counts regardless of the pre-treatment CD4 values and clinical category. Since GPO-VIR is a twice-a-day pill, it has a low pill burden. Furthermore, it does not require any restrictions on food intake. This can contribute to better adherence to therapy by the patients, which is the most important component of long-term treatment. Careful assessment for lipodystrophy should be made, especially in older patients after one year of treatment.

Since many studies report that stavudine has been repeatedly associated with lipodistroophy and hyperlactatemia, physicians, as well as patients, together need to weigh the advantages and disadvantages of the regimen they are going to use for initial therapy. Randomized clinical trials will be required to confirm our findings and large studies should be performed to determine the long-term effects of treatment, and the factors that play a role in predisposition to develop toxicity.

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