

The Incidence and Risk Factors of Virologic Failure in HIV-infected Patients Receiving the First Regimen of Antiretroviral Therapy

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ABSTRACT

Background: Since antiretroviral therapy (ART) has been widely available in Thailand, the survival and quality of life among HIV-infected patients are markedly improved. However, some patients experience virologic failure and HIV drug resistance has developed. Currently, the data of the incidence of virologic failure and its associated factors in Thailand is still limited.

Methods: A retrospective cohort study was carried out among HIV-infected patients who were initiated with ART during 2006-2007 at Ramathibodi Hospital and had followed up at least for a year. The incidence of virologic failure and the associated factors were assessed.

Results: There were 110 patients with mean (SD) age of 38.6 (10.6) years and 51.8% were males. Median (IQR) baseline CD4 was 63 (21-186) cells/mm³. Of all, 98.2% received NNRTI-based regimens in which 95.3% were nevirapine-based regimens. Stavudine/lamivudine and zidovudine/lamivudine were the most common nucleoside reverse transcriptase inhibitor (NRTI) backbones of the regimens. During a median (IQR) follow-up duration of 44.3 (35.8-50.2) months, 26 (23.6%) patients developed virologic failure. The incidence of virologic failure was 6.96/100 person-years. From Kaplan-Meier analysis, the probabilities of virologic failure at 6, 12, 24, 36, and 48 months of first regimen ART were 1.9%, 5.4%, 13.6%, 20.1%, and 22.0%, respectively. From Cox proportional hazard model, only poor adherence was significantly associated with virologic failure [hazard ratio 2.028; 95% CI, 1.050-3.922; p=0.035]. Demographics, baseline CD4 and type of regimen were not associated with virologic failure (p>0.05).

Conclusions: Incidence of virologic failure of the first regimen ART is 6.96/100 person-years and the rate is higher over time. Poor adherence is the only factor associated with virologic failure, regardless of baseline CD4 and ART regimens. Intervention to improve the adherence on ART in this population is essentially needed. Education for better adherence and its importance should be continuously performed. (*J Infect Dis Antimicrob Agents* 2011;28:161-68.)

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INTRODUCTION

HIV infection has become a global pandemic for more than two decades. According to "Global Report AIDS/HIV Epidemic 2009" from World Health Organization, 33.3 million people are living with HIV and Sub-Saharan Africa and South and South-East Asia are the two regions that have the highest HIV prevalence, with 22.5 and 4.1 million people infected, respectively.¹ Following the widespread use of combined antiretroviral therapy (ART), the incidence of AIDS-defining condition, opportunistic infection, progression to AIDS and death are markedly declined.²⁻¹⁴ ART is now considered as a standard treatment of HIV infection. Estimated number of people receiving ART in December 2009 is 5,254,000 persons, which are about 36% global coverage.¹⁵ After rapid scaling up of ART worldwide, treatment failure and HIV drug resistance have become common problems. The development of HIV drug resistance limits the efficacy of ART. Continued viral replication in the presence of drug pressure allows for the progressive accumulation of mutations that can lead to virologic failure and subsequent treatment failure.¹¹

Further concerns for emerging treatment failure are increased direct and indirect health costs associated with the need to use more costly second-line treatments for the patients, the spread of resistant strains of HIV and the need to develop new anti-HIV drugs. Thailand as a resource-limited country has started a National AIDS Program since 2002 which results in the 50-80% ART coverage according to the World Health Organization Report in 2009.¹⁵ Some patients have experienced treatment failure during rapid scaling up of ART. However, we still lack the data of incidence of treatment failure in HIV-infected patients who are treated with the first regimen of ART in Thailand. This information would be very helpful for the national plan of ART

particularly during preparation of the second regimen, as well as improving HIV care in Thailand. This study was aimed to determine the incidence and risk factors of virologic failure in HIV-infected patients receiving the first regimen of ART in Thailand.

PATIENTS AND METHODS

The design of the present study is a retrospective cohort study. HIV-infected patients who had been initiated ART between 2006 and 2007 in Ramathibodi Hospital and had followed up for at least a year were included. Medical records and related laboratory results were reviewed. The following data was collected: patient demographics and baseline data (age, sex, nationality, marital status, occupation), medical history (underlying disease, current medication, opportunistic infection, mode of HIV transmission), laboratory data including CD4 cell count and HIV viral load before and after ART initiation, ART regimen, adherence to ART, date of virologic failure and date of last follow-up. The definition of virologic failure is the event of any detectable HIV viral load (>50 copies/mL) after ART initiation for more than 6 months or any event of rebound HIV viral load (>50 copies/mL) in previously complete suppression. The endpoint of the study is virologic failure. The study was approved by the institutional review board.

We used SPSS version 16.0 (SPSS Inc., Chicago, Illinois, U.S.A) for statistical analysis. Mean (\pm standard deviation, SD), median (interquartile range, IQR) and frequencies (%) were used to describe patients' characteristics. The incidence of virologic failure was determined with standard method. Kaplan-Meier curve was used to analyze the probability of virologic failure and Cox proportional hazard model was used to determine the risk factor of virologic failure. A p-value at <0.05 was considered statistically significant.

RESULTS

We included 110 HIV-infected patients who had been initiated the first ART regimen between 2006 and 2007 in Ramathibodi Hospital. The mean (SD) age was 38.6 (10.6) years and 51.8% of patients were males. Median (IQR) baseline CD4 was 63 (21-186) cells/mm³. Of all, 84 (76.4%) patients were in virologic success group and the others were in virologic failure group. The baseline characteristics including age, sex, occupation, marital status, health insurance and CD4 cell count of the two groups were similar, as shown in Table 1. Only patients' adherence to ART was significantly different between the two groups ($p = 0.011$). Of all, 108 (98.2%) patients received non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens in which 103 (95.4%) patients were nevirapine-based regimens. Stavudine/lamivudine and zidovudine/lamivudine were the most common NRTI backbones of the regimens with 91.8% of prescription. The other NRTI backbones in the present study included didanosine/lamivudine (2.7%) and tenofovir/lamivudine (5.5%).

During a median (IQR) follow-up duration of 44.3 (35.8-50.2) months, 26 (23.6%) patients developed virologic failure. The incidence of virologic failure was 6.96/100 person-years. From Kaplan-Meier analysis (Figure 1), the probabilities of virologic failure at 6, 12, 24, 36, and 48 months of the first regimen of ART were 1.9%, 5.4%, 13.6%, 20.1%, and 22.0%, respectively. When patients were categorized into two groups according to the good or poor adherence, the probability of virologic failure was significantly higher in patients with poor adherence (Figure 2, log-rank test, $p = 0.005$). From Cox proportional hazard model, only poor adherence was significantly associated with virologic failure [hazard ratio 2.028; 95% CI, 1.050-3.922; $p = 0.035$].

Demographics, baseline CD4 cell count and type of regimen were not associated with virologic failure ($p > 0.05$).

Of 26 patients with virologic failure, 13 had been tested for HIV genotypic resistance assay. NRTI and NNRTI resistance were observed in 61.5% and 66.7%, respectively. Lamivudine was the most common NRTI resistance (61.5%), followed by abacavir (15.4%), stavudine (15.4%), zidovudine (15.4%), didanosine (7.7%) and tenofovir (7.7%). Efavirenz and nevirapine resistance were detected in 66.7% of patients whereas etravirine resistance was found in 42.9% of patients. Protease inhibitor (PI) resistance was found to be only "possible resistance" to tipranavir (15.4%) and resistance to fosamprenavir (15.4%) due to the polymorphism of HIV subtype A/E.

DISCUSSION

As one of the resource-limited countries with rapid ART scaling up, Thailand has inevitably encountered the treatment failure and HIV drug resistance problem, as seen in many countries. The incidence of virologic failure with the first regimen of ART in the present study is 6.96/100 person-years and the rate is higher over time. Poor adherence is the only factor associated with virologic failure, regardless of demographic data, baseline CD4 and ART regimens. Adherence is the most contributed factor associated with treatment failure, corresponding with many previous studies.¹⁷⁻²⁴ Other possible factors which have been reported to be associated with treatment failure in previous studies are baseline plasma HIV viral load level¹⁹ and NNRTI-based regimen.²⁵ From the present study, the significance of these two factors was not demonstrated since almost all patients received NNRTI-based regimens and HIV viral load was not routinely performed at baseline in clinical practice among

Table 1. Baseline demographics of 110 study patients.

Characteristics	Total (n=110)	Virologic success (n=84)	Virologic failure (n=26)	P value
Sex, number (%)				0.654
Male	57 (51.8)	45 (53.6)	12 (46.2)	
Female	53 (48.2)	39 (46.4)	14 (53.8)	
Age, years, mean (SD)	38.6 (10.6)	38.8 (10.1)	37.9 (12.1)	0.727
Occupation, number (%)				0.137
Freelance	33 (30)	29 (34.5)	4 (15.4)	
Officer	30 (27.3)	25 (29.8)	5 (19.2)	
Housework	13 (11.8)	9 (10.7)	4 (15.4)	
Merchant	13 (11.8)	7 (8.3)	6 (23.1)	
Employee	11 (10)	8 (9.5)	3 (11.5)	
Student	6 (5.5)	4 (4.8)	2 (7.7)	
Business	3 (2.7)	2 (2.4)	1 (3.8)	
Agriculture	1 (0.9)	0 (0)	1 (3.8)	
Marital status, number (%)				0.395
Single	48 (43.6)	38 (45.2)	10 (38.5)	
Married	51 (46.4)	38 (45.2)	13 (50)	
Widow	7 (6.4)	4 (4.8)	3 (11.5)	
Divorce	4 (3.6)	4 (4.8)	0 (0)	
Health insurance, number (%)				0.492
Universal coverage	49 (38.2)	34 (40.5)	8 (30.8)	
Social security	13 (11.9)	8 (9.6)	5 (19.2)	
Government employee	45 (40.9)	35 (41.7)	10 (38.5)	
Self-payment	10 (9.1)	7 (8.3)	3 (11.5)	
Baseline CD4 cell count, cells / μ l, median (IQR)	63 (21-186)	51 (22-183)	94 (15-192)	0.854
ART regimen, number (%)				1.000
NNRTI-based	108 (98.2)	82 (97.6)	26 (100)	
PI-based	2 (1.8)	2 (2.4)	0 (0)	

Table 1. (Continued) Baseline demographics of 110 study patients.

Characteristics	Total (n=110)	Virologic success (n=84)	Virologic failure (n=26)	P value
NRTI backbone, number (%)				0.655
d4T+3TC	58 (52.7)	43 (51.2)	15 (57.7)	
AZT+3TC	43 (39.1)	33 (39.3)	10 (38.5)	
ddI+3TC	3 (2.7)	2 (2.4)	1 (3.8)	
TDF+3TC	6 (5.5)	6 (7.1)	0 (0)	
Adherence, number (%)				0.011
Good	55 (50.0)	48 (57.1)	7 (26.9)	
Poor	41 (30.3)	26 (31)	15 (57.7)	
Unknown	14 (12.7)	10 (11.9)	4 (15.4)	

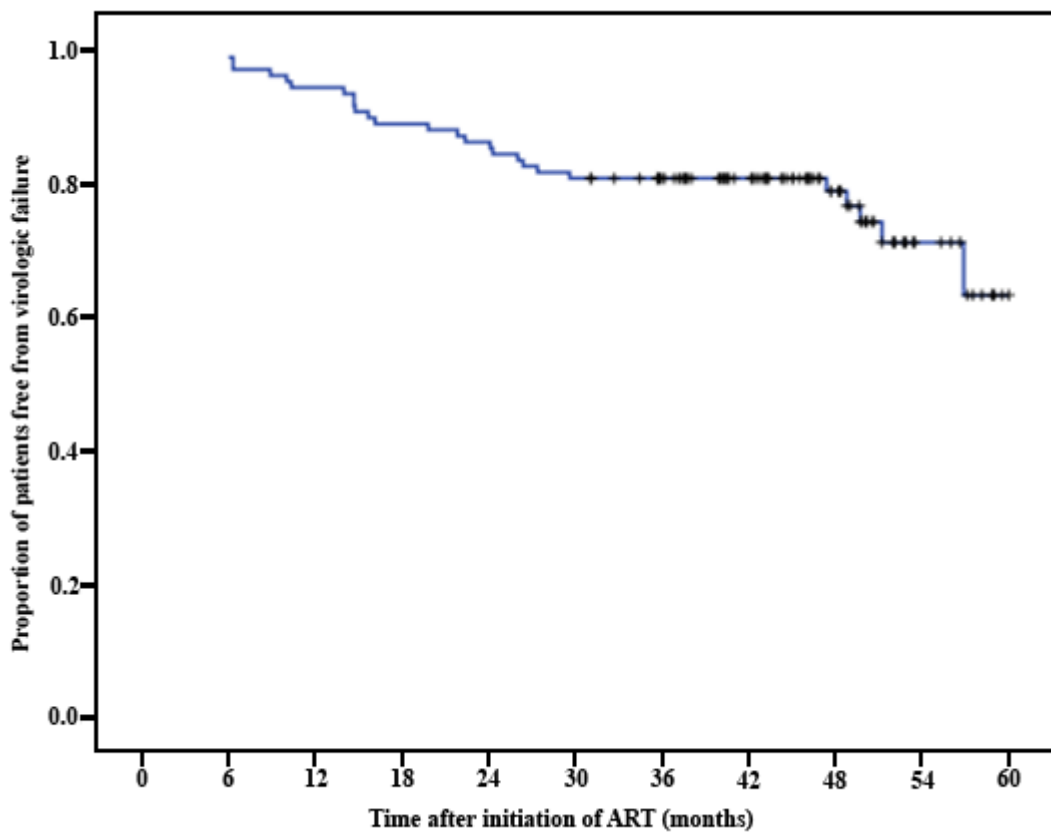


Figure 1. Kaplan-Meier analysis showing proportion of patients free from virologic failure.

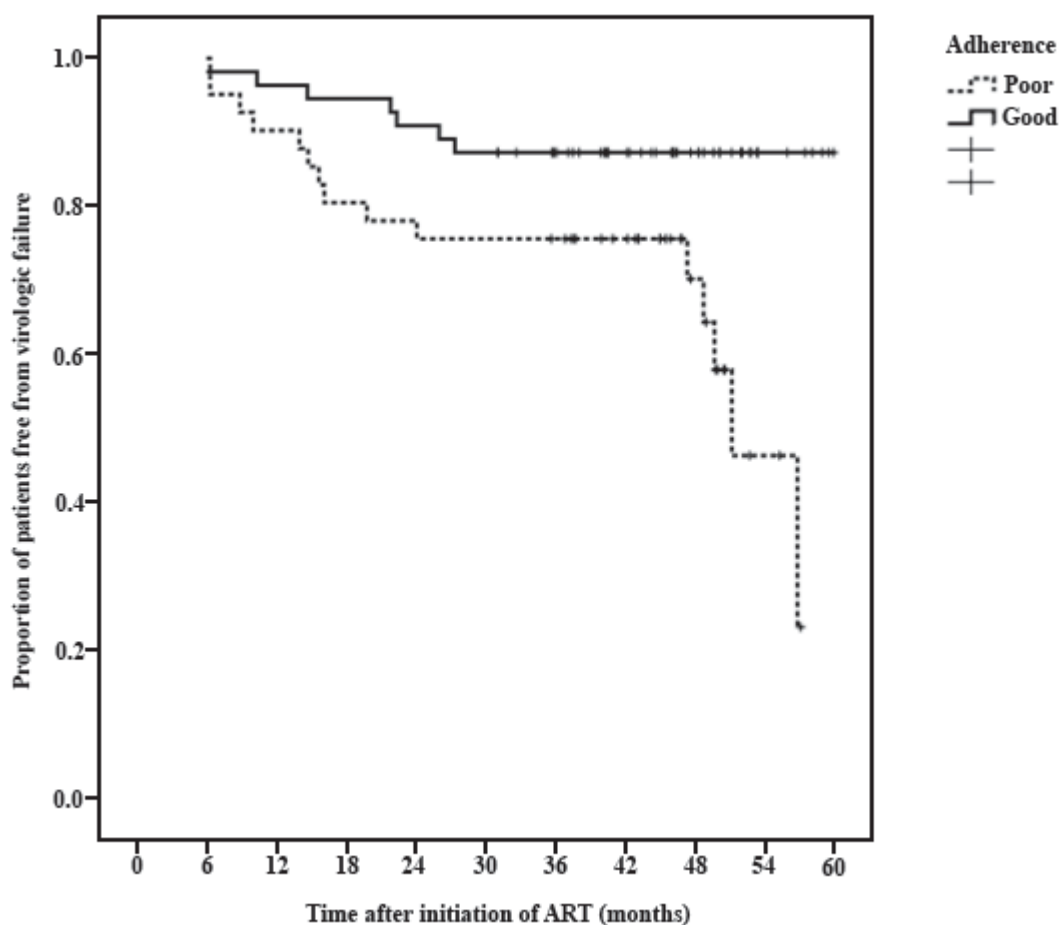


Figure 2. Kaplan-Meier analysis showing proportion of patients free from virologic failure categorized by adherence.

resource-limited settings. The reason of virologic failure in non adherence group could be explained with the selection pressure during suboptimal plasma drug level, which was not fully suppressive of viral replication.

HIV drug resistance among patients who had virologic failure in the present study has demonstrated the common patterns of treatment failure with NNRTI-based regimen. Resistance to NNRTIs and NRTIs particularly lamivudine are exclusively observed in patients failing NNRTI-based regimen.²⁶ However, the early detection of treatment failure with regular HIV viral load monitoring in the present study showed the lower rate of both NNRTI and lamivudine resistance.

There are some limitations in the present study. First, the nature of retrospective cohort design may have incomplete medical records, the difference of timing for monitoring of laboratory investigation and some results were missing. Second, the study consisted of a relatively small sample size. However, the sample size is enough to demonstrate the relevant risk factor of virologic failure. Another question that arises after this study is what factor is associated with poor adherence. The answer may lead to the appropriate intervention and policy construction to eliminate treatment failure among Thai patients. To answer this question, further prospective study should be conducted.

In conclusion, incidence of virologic failure of the first regimen ART is 6.96/100 person-years and the

rate is higher over time. Poor adherence is the only factor associated with virologic failure, regardless of baseline CD4 and ART regimens. To solve treatment failure problems, intervention to improve the adherence on ART in this population is essentially needed. Education for better adherence and its importance should be continuously performed. One study has proposed to reduce the number of pills and daily doses received²¹, which corresponds with Thai combined pills called “GPOVIR-S” and “GPOVIR-Z”, but the problem is still not completely resolved. We propose to construct the adherence assessment system and increase viral load surveillance frequency in national guideline from yearly viral load level to twice a year for early detection of treatment failure.

References

1. World Health Organization. AIDS/HIV: Data and statistics: 2009 global epidemic [Powerpoint slides]. 2010 [cited 2011 Mar 12]. Available from: http://www.who.int/hiv/data/2010_globalreport_core_en.ppt.
2. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008;372:293-9.
3. Ferrando SJ, Rabkin JG, Lin SH, McElhiney M. Increase in body cell mass and decrease in wasting are associated with increasing potency of antiretroviral therapy for HIV infection. *AIDS Patient Care STDS* 2005;19:216-23.
4. Jahn A, Floyd S, Crampin AC, et al. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet* 2008;371:1603-11.
5. Jongwutiwes U, Kiertiburanakul S, Sungkanuparph S. Impact of antiretroviral therapy on the relapse of cryptococcosis and survival of HIV-infected patients with cryptococcal infection. *Curr HIV Res* 2007;5:355-60.
6. Kiertiburanakul S, Sungkanuparph S, Rattanasiri S, Manosuthi W, Vibhagool A, Thakkinstian A. Virological and immunological responses of efavirenz-based HAART regimen initiated in HIV-infected patients at CD4 < 100 versus CD4 > or = 100 cells/mm³. *J Med Assoc Thai* 2006;89:1381-7.
7. Manosuthi W, Chimsuntorn S, Likanonsakul S, Sungkanuparph S. Safety and efficacy of a generic fixed-dose combination of stavudine, lamivudine and nevirapine antiretroviral therapy between HIV-infected patients with baseline CD4 < 50 versus CD4 > or = 50 cells/mm³. *AIDS Res Ther* 2007;4:6.
8. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006;43:42-6.
9. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853-60.
10. Patel K, Hernan MA, Williams PL, et al. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis* 2008;46:507-15.
11. Sungkanuparph S. Pathogenesis of HIV drug resistance [in Thai]. In: Sungkanuparph S, editor. *HIV Drug Resistance: Basic Principles & Clinical Implications*. Bangkok, Thailand: Folk Doctor Foundation Publishing, 2008: 1-9.
12. Sungkanuparph S, Kiertiburanakul S, Manosuthi W, Kiatatchasai W, Vibhagool A. Initiation of highly active antiretroviral therapy in advanced AIDS with CD4 < 50 cells/mm³ in a resource-limited setting: efficacy and tolerability. *Int J STD AIDS*

- 2005;16:243-6.
13. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Vibhagool A. Initiation of antiretroviral therapy in advanced AIDS with active tuberculosis: clinical experiences from Thailand. *J Infect* 2006;52:188-94.
 14. Waisman JL, Palmero DJ, Alberti FA, Guemes Gurtubay JL, Francos JL, Negroni R. Improved prognosis in HIV/AIDS related multi-drug resistant tuberculosis patients treated with highly active antiretroviral therapy. *Medicina (B Aires)* 2001;61:810-4.
 15. World Health Organization. HIV/AIDS: Antiretroviral therapy: data and statistics [Internet]. 2011 [cited 2011 Mar 12]. Available from: <http://www.who.int/hiv/topics/treatment/data/en/index.html>
 16. World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a Public Health Approach. 2006 Revision. Geneva: WHO; 2006.
 17. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000;14:357-66.
 18. Friedland GH, Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. *AIDS* 1999;13 Suppl 1:S61-72.
 19. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005;191:339-47.
 20. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med* 1999;131:81-7.
 21. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. *Clin Infect Dis* 2005;40:158-63.
 22. Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med* 2001;161:1962-8.
 23. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis* 2003;37:1112-8.
 24. Wang X, Yang L, Li H, et al. Factors associated with HIV virologic failure among patients on HAART for one year at three sentinel surveillance sites in China. *Curr HIV Res* 2011;9:103-11.
 25. Lima VD, Harrigan PR, Senecal M, et al. Epidemiology of antiretroviral multiclass resistance. *Am J Epidemiol* 2010;172:460-8.
 26. Sungkanuparph S, Manosuthi W, Kiertiburanakul S, Piyavong B, Chumpathat N, Chantratita W. Options for a second-line antiretroviral regimen for HIV type 1-infected patients whose initial regimen of a fixed-dose combination of stavudine, lamivudine, and nevirapine fails. *Clin Infect Dis* 2007;44:447-52.