EVALUATE THE EFFICACY OF NEVIRAPINE BASED REGIMEN AND BOOSTED PI BASED REGIMEN FOLOWED BY NEVIRAPINE BASED REGIMEN IN TREATMENT NAÏVE ADVANCED HIV INFECTED PATIENTS AT CHONBURI HOSPITAL

THAW HTWE MIN

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Thematic Paper
Entitled

EVALUATE THE EFFICACY OF NEVIRAPINE BASED REGIMEN AND BOOSTED PI BASED REGIMEN FOLOWED BY NEVIRAPINE BASED REGIMEN IN TREATMENT NAÏVE ADVANCED AIDS PATIENTS AT CHONBURI HOSPITAL

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TO EVALUATE THE EFFICACY OF NEVIRAPINE BASED REGIMEN AND BOOSTED PI BASED REGIMEN FOLLOWED BY NEVIRAPINE BASED REGIMEN IN TREATMENT NAÏVE ADVANCED HIV PATIENTS

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ABSTRACT

OBJECTIVE: To evaluate the efficacy of a nevirapine-based regimen and a boosted PI-based regimen followed by a nevirapine-based regimen in the treatment of naïve advanced HIV patients.

METHOD: A retrospective, descriptive study of 156 patients initiating either NVP-based regimen (n=92) or boosted PI-based regimen followed by a NVP-based regimen (n=64) was conducted. Patients were excluded from further participation if they changed their original antiretroviral regimen for any reason.

RESULTS: The patients in the PI-based group had lower median baseline $CD4^+$ T-cell count (25 vs. 41 in NVP group) and a higher median baseline bodyweight (54 kg vs. 52 kg in the NVP group). After 2 years of therapy, the median increase from baseline $CD4^+$ T-cell count was 226 cells/ul in the NVP group and 287 cells/ul in the boosted PI group. 55.4% of patients had $CD4^+$ T-cell counts $>200x10^6$ cell/l in the NVP group and 85.4% in the boosted PI-based group at 2 years' treatment. The percentage median bodyweight gain from baseline was 10.2%, range 4.9-20%, in the NVP-based regimen and 12.3%, range 4.3-23.5%, in the boosted PI-based regimen after 2 years' treatment.

CONCLUSION: The 2NRTI+NVP-based regimen and the 2NRTI+boosted PI-based regimen, followed by the NVP-based regimen, were effective in incrementing bodyweight and $CD4^+$ T-cell counts in advanced HIV patients in the 2-year treatment time frame.

KEY WORDS: NVP BASED REGIMEN/ADVANCED AIDS/TREATMENT NAIVE/ BOOSTED PI BASED REGIMEN

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LIST OF ABBREVIATION

ABBREVIATION	TERM
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ABC	Abacavir
AZT	Zidovudine
ATV	Atazanavir
BUN	Blood urea nitrogen
CBC	Complete blood count
CDC	Centre for disease control and prevention
CMV	Cytomegalovirus
Cr	Creatinine
d4T	Stavudine
ddI	Didanosine
EFV	Efavirenz
f-APV	Fosamprenavir
FTC	Emtricitabine
HAART	Highly active anti retroviral therapy
HIV	Human immunodeficiency virus
Hb	Haemoglobin
IDV	Indinavir
IAS_USA	International AIDS society-united state of America
IRS	Immune reconstitution syndrome
LPV	Lopinavir
MAC	Mycobacterium avian complex
NVP	Nevirqapine
NFV	Nelfinavir

LIST OF ABBREVIATION
(CONTINUE)

ABBREVATION	TERM
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PCP	Pneumocystic carinii pneumonia
PI	Protease inhibitor
pVL	Plasma viral load
RTV	Rtonavir
SQV	Saquinavir
TDF	Tenofovir disoproxil furamate
TB	Tuberculosis
TLC	Total lymphocyte count
UNAIDS	United nation program on HIV/AIDS
WBC	White blood cell
WHO	World health organization
3TC	Lamivudine

CHAPTER I
INTRODUCTION

The human immunodeficiency viruses are the cause of the acquired immunodeficiency syndrome (AIDS) pandemic that is currently sweeping through the world. HIV belongs to the family of human retrovirus; sub family of lentivirus .There is two types of viruses: HIV-1 andHIV-2. Most disease is caused by HIV-1 –it is more virulent and widespread than HIV-2 which mostly occurs in the West Africa. (Eddleston et al 2005)

AIDS was first recognized in USA in the summer of 1981, when the US center for the disease control and prevention (CDC) reported the unexplained occurrence of Pneumocystis carinii pneumonia in five previously healthy homosexual men in Los Angeles, of Kaposi's sarcoma in 26 previously healthy homosexual men in New York and Los Angeles. In 1983, human immunodeficiency virus was isolated from a patient with lymphadenopathy, and by 1984 it was clearly demonstrate to be the causative agent of AIDS. (.Fauci and Lane 2005)

The estimate number of cases of HIV infection among adult worldwide is 39.4 millions, two thirds of whom are in sub Saharan Africa; 50% of cases are women (UNAIDS 2004).In addition, an estimate 2.5 millions children younger than age 15 are living with HIV/AIDS. According to UNIAIDS, in 2003 alone there were an estimate 5 million new cases of infection worldwide (>14,000 new infection each day) and 3 million deaths were from AIDS, making it the fourth leading cause of mortality worldwide. (UNAIDS 2003)

Up to now, there is currently no vaccine and no cure for HIV infection. Many therapies have been developed. Combination antiretroviral treatment can control viral replication and allow a considerable restoration of immune function that can last for many years (Eddleston et al 2005). Goals of antiretroviral therapy are to improve

clinical status and to get the greatest possible reduction in viral load. (Bartlett and Gallant 2004) There are many guidelines for the treatment of HIV infections. Suppression of HIV replication is an important factor for prolongation of life as well as improving the quality of life in HIV infected patients. Unfortunately, many of the important questions related to treatment of HIV infection lack definite answers. Among them are the questions of when therapy initiated should, what is the best initial regimen and when a given regimen should be changed. (Fauci and Lane 2005)

To mitigate the problems of HIV treatments, a series of frequently updated guidelines have been published. At present, extensive clinical trial network involving both clinical investigators and patient advocates are in place attempting to develop improved approach to therapy in many parts of the world.

To improve the quality of life and lifespan among advance HIV patients, prompt diagnosis and early accurate treatment are important. The aim of the study is to evaluate the efficacy of protease inhibitor based regimen sequential followed by NVP regimen and NVP base HAART regimens in treatment naive HIV/ADIS patient whose $CD4^{+}$ count less than 100 copies/ml. The retrospective study was conducted at Chonburi hospital from November 14 to January 9, 2006.

CHAPTER II
OBJECTIVE

To evaluate the efficacy of nevirapine based regimen and boosted PI based regimen followed by nevirapine based regimen by measuring $CD4^{+}$T-cell count change and boy weight change in treatment naive advance AIDS patients at Chonburi hospital.

CHAPTER III
REVIEW OF LITRATURE

Epidemiology of HIV

Joint United Nations Program on HIV/AIDS (UNAIDS) and WHO estimate nearly 39.4 million people were living with HIV/AIDS world wide; more than half of them in the in Sub Sahara Africa and nearly one fifth are in South and South-East Asia by the end of 2004.The number of people newly infected HIV is 4.9 million and number of death due to AIDS is 3.1 millions in 2004 (UNADIS 2004) In Thailand, cumulative HIV infections were 1,092,327; cumulative deaths were 551,505 and the number of people living with HIV/AIDS was 540,822. (Source: The Thai working Group on HIV/AIDS Project, Bureau of Epidemiology, Dept of Disease Control, as of Feb 28, 2005).Nearly 50,000 new AIDS cases will occur in Thailand every year (WHO/UNIAIDS,2004)

Effect of HIV infection

After the HIV infection, initial event that may occur is acute retroviral syndrome .It is similar to infectious mononucleosis with variety of signs and symptoms-malaise, fever, sore throat, myalagia, anorexia, arthralgia, headache, diarrhea, generalized lymph adenopathy, macular eruption involved trunks and arms, thrombocytopenia (Eddleston et al 2005). This syndrome accompanies by a decline in CD4+ count, high HIV plasma viremia and plasma concentration of the HIV RNA .This clinical symptoms resolved spontaneously in 1-3 weeks accompanied by a rapid decline in plasma viremia and the CD4 count may return to baseline.

The subsequent course generally shows a prolong period of clinical latency that accompanies by a high rate of HIV replication with an average 10^{10} new virons/day. The CD4 count gradually declines and is often accelerated during late

stage of this disease .The course of HIV infection without the therapy is average about 10 years from the time of initial infection to AIDS defining diagnosis.

After the certain period of time followed by HIV infection, immunity become defected , CD4 count will fall below a critical level (below 200 cells/mm3 average 10 years from initial infection to AIDS defining illness),at that point, patients become susceptible to opportunistic infections such as tuberculosis ,MAC , Pneumocystic carinii pneumonia, candidiasis, cyrptcoccosis and toxoplasmosis. (Eddleston et al 2005)

Highly Active Antiretroviral Therapy

HAART is defined as a regimen containing at least three drugs of which exactly two were from the NRTI class. The additional drug(s) needed to be either from the PI class or NNRTI, whereby simultaneous use of PI and NVP was not allowed. Additional use of a third NRTI, hydroxyurea or saquinaviras a single PI is also not permitted. Changes in the NRTI backbone were allowed, as long as exactly two NRTI were used. (Van Leth et al, 2004)Combination anti retroviral therapy or HARRT is the cornerstone of management of patients with HIV infection. Following the initiation of the widespread use of HAART, marked decline has been noted in the incidence of most AIDS defining condition (Fauci and Lane2005) .HAART has shown to be better than two drug therapy .In a Cochrane Review done in 2000, three or four drugs for maintenance in HIV patients were compared with two drug maintenance The review found that two drugs regimen was associated with a high risk of virologic failure (loss of HIV suppression to undetectable level).

Initiation of ARV

Indication for ARV initiation is divided into two categories, depending on whether $CD4^+$ T-cell count is available or not. The total lymphocyte count (TLC) can be used as a substitute for the $CD4^+$ T-cell count, although it is considered less useful in asymptomatic patients. The threshold for initiation of therapy using $CD4^+$ T-cell

count is <200x10^6 cell/ul. When the TLC is used, treatment is recommended at a TLC of <1200 cell/mm^3 in asymptotic patient. (WHO guideline 2004)

Antiretroviral therapy is generally recommended for the symptomatic HIV patient, irrespective of $CD4^+$ T-cell count, and patient who has $CD4^+$ T-cell count < 200x10^6 cell/ul will receive ART. If $CD4^+$ T-cell count is more than 200x10^6 cell/ul, treatment will be individualized based on $CD4^+$ rate of decline /year, HIV viral load, and risk of toxicity and drug-drug interaction. If the patient's rate of $CD4^+$ T-cell count decline >100x10^6 cell/ul /year or viral load >50,000-100,000, those will be treated with ART.(IAS-USA guideline 2002)

Symptomatic patient and whose $CD4^+$ T-cell count of < 350 /mm3 are generally recommended for ART. $CD4^+$ T-cell count of 350 -500/mm3, and viral load <50,000 will defer the treatment. The treatment is controversial if the patient who has viral load is between 50,000and 100,000. ARV will be given if the viral load is > 100,000. As for the patients with $CD4^+$ T-cell count of >500/mm3, treatment should be started if viral load is more than 100,000/ml and treatment should be defer if viral load is less than 100,000/ml (Bartlett and Gallant 2004)

NUCLEOSIDE ANALOG REVERSE TRANCRIPTASE INHIBITORS

NRTI is the first developed drug which act as inhibitor of and substrate for the HIV reverse transcriptase enymes.Following drugs are NRTIs;
1.Zidovudine 2.Zalicitine 3.Lamivudine 4.Didanosine 5Stavudine 6.Abicavir 7.Tenofovir

NON NUCLEOSIDE REVERSE TRANNSCRIPTASE INHIBITORS

NNRTI is the second class of drugs which attack reverse transcriptase but by a different mechanism. Three NNRTIs are as follow;
1.Nevirapine 2.Efavirenz 3.Delavirdine

PROTEASE INHIBITORS

PI is the third class of drugs which act by inhibiting the HIV protease enzymes. The drugs listed below are PIs.

1.Saquinavir 2.Indinavir 3.Ritnovir 4Neflinavir 5.Amprenavir 6.Atazanavir 7.Lopinavir+Ritonavir (the pharmaceutical journal vol 264, 7079, P 96-97, 2000)

Boosted protease inhibitor regimens (currently recommended)

Saquinavir1000mg+Ritonavir100mg BD

Lopnavir400mg+Ritonavir100mg BD

Indinavir800mg+Ritonavir100mg BD

Amprenaavir600mg+Ritonavir100mg-200mg BD (Eddleston et al 2005)

Fixed dosed combinations (currently available)

Combivir(zidovudine300mg+lamivudine150mg)1BD

Trizivir(zidovudine300mg+lamivudine150mg+abacavir300mg)1BD

Kaletra(lopinavir133.3mg+ritonavir33.3mg)3 BD((Eddleston et al 2005)

GPO-Z(zidovudine250mg+lamivudine150mg+nevirapine200mg)1BD

GPO-vir(stavudine40mg+lamivudine150mg+nevirapine200mg)1BD

Antiretroviral regimens recommended for treatment of HIV infection in antiretroviral naive patients

A. non-nucleoside reverse transcriptase Based regimen	B .protease inhibitor based regimen
Preferred initial regimen	**Preferred initial regimen**
EFV+(AZT or TDF or d4T)+3TC*	LVP/RTV+(AZT ord4T)+3TC
ALTERNATIVE REGIMENS	**ALTERNATIVE REGIMENS**
EFV+ (ddI or ABC) +3TC*	ATV+(3TC or FTC)+(AZT or d4T or ABC)
NVP+ (AZT or TDF or d4T)+3TC	f-APV+(3TC or FTC)+(AZT or d4T or ABC)
NVP+ (ddI or ABC) +3TC	IDV/RTV+ (3TC or FTC) + (AZTord4Tor ABC)
	F-APV/RTV+ (3TC or TC) + (AZTord4TorABC)
	LPV/RTVr +FTC+ (AZT or d4T or ABC)
	LPV/RTV+3TC +ABC
	NFV+ (3TC or FTC) + (AZTord4T or ABC)
	SQV/RTV+ (3TC or FTC) + (AZTord4T or ABC)

**except for the pregnant women or women with pregnant potential*

COMPARISON OF CLINICAL EFFICACY OF NEVIRAPINE BASED REGIMEN AND PI BASED REGIMEN

1. Differential CD4 T-cell response in HIV-1-infected patients using protease inhibitor-based or NVP-based highly active antiretroviral therapy

The CD4 T-lymphocyte count (CD4 count) is a well-defined predictor for disease progression and death in HIV infected individuals using antiretroviral therapy (Mellors JW et al 1997, Hogg RS, Yip B, Chan KJ et al.2001). Several studies comparing patients using either PI or NVP-based HAART reported that increases in CD4counts were comparable in the two groups, both in patients starting these regimens for the first time(Podzamczer D etal 2002) and in patients replacing their PI-based regimen with an NNRTI based regimen(Dieleman JP et al 2002) . Other

studies found smaller increases in CD4 counts in patients using NVP-based HAART compared with patients using PI-based HAART. Previously, in the Atlantic study, they reported a difference in CD4 count increase when comparing antiretroviral therapy-naive patients using either indinavir(IDV) or NVP in combination with stavudine (d4T) and didanosine (ddI), where the latter had a lower increase between baseline and 96 weeks of follow-up (Van Leeuwen et al 2003)In a group of 138 patients successfully treated with PI based HAART, Barreiro et al. compared continued therapy and replacement of the PI with NVP. They reported a continued increase of the CD4 count in the patients who continued PI-based HAART, and a decrease of the CD4count in the patients who substituted NVP for the PI, although the differences were not statistically significant. In another study, Barreiro et al. reported a similar differential effect on CD4 count increases when comparing patients using first-line PI-based HAART with those using NNRTI-based HAART (Barreiro Pet al 2002)

2. Virological suppression

The suppression of plasma HIV RNA viraemia to below detectable limits is a strong prognostic indicator for future reduction in both disease progression and clinical events (O'Brien WA, et al 1996) and ability to achieve this by 24 weeks is recognized as an indicator of antiretroviral efficacy.(Powderly WG et al 1999). The choice of antiretroviral drugs for HIV-1-infected individuals initiating a first-line regimen may be crucial in achieving optimal long-term viral control. Despite the increasing availability of drugs for use in second or third line therapy, the initial regimen has the greatest chance of achieving effective and durable viral suppression.(Fischl MA et al 1999) Therefore, there were triple therapy with a dual-nucleoside backbone and either a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) (Carpenter CCJ, 2000) . Both regimens are virologically and immunologically superior to dual nucleosides alone .The clinical-based study demonstrated a high proportion of patients (> 78%) in all therapy groups (PI based and NVP based regimen) achieving HIV RNA suppression < 500 copies/ml at 6 months. (Matthews, Gail V. et al2002)

An analysis of databases from the USA has compared NNRTI- and PI-containing regimens (Ghani AC et al2001).There was no differences seen between any types of regimen in the initial rate of viral suppression but a lower rate of viral rebound was suggested in the patients taking PI combinations. Again these patients were not antiretroviral-naive and the majority of NNRTI use was with NVP rather than efavirenz. (Matthews, Gail V. et al2002) Protease inhibitor based triple regimens resulted in a more substantial reduction of HIV-1 RNA concentrations (-0.79 log copies/ml) than NNRTI based regimens (-0.20 log copies/ml), and a higher proportion of patients reached undetectable viral load with the protease inhibitor regimens than with the NNRTI based regimens. (Yazdan Yazdanpanah et al,2004)

3. Adherence to highly active antiretroviral therapy

In HIV infection, adequate adherence to highly active antiretroviral therapy (HAART) is imperative to achieve and maintain virological and immunological success and to avoid the selection of drug resistance(.Paterson DL et al 2000 , Rodriguez-Rosado R et al 1998).Therefore, the difference between adherences to non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI)-based regimens was investigated. Better adherence was found in NNRTI-treated patients, compared with single PI-treated patients and in those with CD4 cell counts less than 200 × 106/l.(Trotta et al,2003) . Single protease inhibitor (PI)-based HAART is a difficult regimen to take because of multiple daily doses, the large number of pills, complicated dosing schedules, dietary instructions, an ability to incorporate treatment into daily routine, and adverse effects. In contrast, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART offers some advantages: high potency, good oral bioavailability, long half-life and the lack of food restrictions (Trotta et al, 2003)

Virological failure in PI based regimen

Patients who generally had $CD4^+$ T cell counts that remained greater than pre-therapy baseline levels, at least through 96 weeks of follow-up, experienced virologic failure (persistent HIV RNA >500 copies RNA/mL)(Deek et al 2005)

Virological failure in NVP based regimen

After 6 months with an undetectable viral load under a PI-containing regimen, the patients were switched to NVP with conservation of the associated nucleoside reverse transcriptase inhibitors (NRTIs). Patients were followed-up at 1 month and then every 3 months after switching therapy. Nucleotide sequence analysis of the pol gene was performed at the first points of virologic failure. Thirty-four patients were included. The NRTI-naive group (22 patients) had begun antiretroviral therapy with a PI-containing regimen, whereas 12 patients (experienced group) had been previously treated by nucleoside mono-and/or dual therapy. After a median follow-up of 40 weeks, no patient of the naive group, versus 41% of the experienced group, developed a virologic failure after the change toward NVP (p =.003). The virologic failures were associated with the appearance of NNRTI-resistant mutations. All rebound mutants also presented NRTI-resistance mutations.(**Masquelier B**, et al 2001)

Drug resistance to NRTI, NNRTI, and PI

Yerly *et al.* presented data from the Swiss cohort for the years 1996 to 2000. According to their findings, genotypic drug resistance among HIV seroconverters rose from 8.6% in 1996 to 14.6% in 1997, but then declined to 8.8% in 1998, to 5.0% in 1999 and, again, to 4% in 2000. Drug-resistant virus was detected in 11.3% of MSM, 6% of heterosexual transmissions (mainly clade non-B) and 13% of IVDU. Nucleoside resistance (mainly AZT and/or 3TC resistance) was detected in 5.8% of isolates, NNRTI resistance in 1.1% and PI resistance in 3.4%. Clusters of infected patients were detected for 29% of the isolates sequenced.

Chaix *et al.* presented data for 121 acute seroconverters enrolled in the French ANRS primary infection cohort in 1999. Overall 12 of 121 patients (10%) had evidence of drug resistance. NRTI resistance (mainly AZT and/or 3TC resistance) was detected in 6% of isolates, NNRTI resistance in 4% and PI resistance in 3%. Multidrug resistant (MDR) virus was detected in 1.6% of newly infected patients. No significant changes in the rate of transmission of drug-resistant virus were seen between 1996 and 1999. Drug resistant virus was only detected in transmissions of clade B virus.

Little *et al.* presented data from 394 treatment-naive, newly infected patients detected in nine North American cities. Resistance in this cohort was defined as phenotypic resistance with an IC_{50} for a drug greater than 10-fold above a wild-type reference HIV strain. From 1995 to 1998, 3.5% of all isolates had evidence of drug resistance: 2.7% had NRTI resistance, 1.3% had NNRTI resistance, 0.4% had PI resistance and 0.4% had MDR virus. Rates of drug resistance in newly infected patients rose during 1999-2000 to 14% of all HIV isolates: 8.3% NRTI resistance, 7.1% NNRTI resistance, 8.2% PI resistance and 5.8% MDR virus. Rates were even higher for a small number of HIV isolates from HIV seroconverters in 2000, with 7% NRTI resistance, 15% NNRTI resistance and 7% PI resistance. The reasons for a rising incidence of primary HIV drug resistance in North America and a falling rate in Switzerland was not clear although an increasing percentage of HIV infections in Europe are caused by non-clade B HIV-1

The switch strategy from protease inhibitor to non-nucleoside-based regimens

In a prospective study, patients who received PI-based therapy switched to NVP-based therapy had clinical reasons. The most common reason was treatment simplification (43 percent) followed by lipid abnormalities or lipodystrophy (32.5 percent) and kidney abnormalities (24.5 percent). The efficacy of switching strategy from PI to non –nucleoside-based regimen showed that slightly more than 91 percent of patients maintained viral load suppression below the limits of detection (Follow-up data was available for 114 subjects for one year, 106 subjects for two years and 96 subjects for three years. in the first, second and third years were 79.7 percent, 74.1

percent and 67.3 percent using an "intention to treat" analysis (missing = failure) and 96.6 percent, 98.1 percent and 97 percent using an "on treatment" analysis, respectively.) The mean $CD4^+$ cell counts were increased by 8.7 percent, 12.6 percent and 17.7 percent in years one, two and three, respectively. The drops in cholesterol and triglycerides were impressive. Patients who had TG levels greater than 1,000 mg/dL decreased to about 300 mg/dL after switching toNVP. Kidney function also improved.(Gil et al 2003)

IMPORTANT TOXICITIES OF HAART

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality. (Palella FJ Jr,et al,1998) Unfortunately, up to 25% of patients discontinued their initial HAART regimens because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/mL), toxic effects or noncompliance within the first 8 months of therapy (Lucas GM, et al 1999)

Lactic acidosis

This has been associated with AZT, ddI and d4T therapy (Valentina Montessori et al CMAJ • January 20, 2004; 170 (2)

Hepatic steatosis

The NRTIs are associated with risk of mitochondrial toxicity and hepatic steatosis. (Valentina Montessori et al CMAJ • January 20, 2004; 170 (2)

Hyperlactatemia

This occurs in 10% to 20% of patients undergoing long-term treatment with NRTI- containing regimens (Valentina Montessoriet et al CMAJ • January 20, 2004; 170 (2))

Hepatotoxicity

Hepatotoxicity are associated with most of the antiretroviral agents, although

initially most concern focused on the PIs. The NNRTIs are also associated with above toxicities (CMAJ • January 20, 2004; 170 (2))

Hyperglycemia

Patients receiving PI therapy have evidence of insulin resistance without frank diabetes. (Lee ECC et al 1999) However, insulin resistance may also be associated with HIV infection itself in patients not receiving PI therapy, perhaps resulting from the direct effects of the HIV virus on pancreatic ß cell function and insulin secretion. (Dube MP. 2000)

Lipodystrophy

PI therapy has been most strongly linked to the lipodystrophy syndrome, although NRTIs, especially d4T, have also been associated with lipodystrophy(Saint-Marc T, et al2000) The dyslipidemia is more profound among those receiving PIs and in those with fat redistribution (lipoaccumulation or lipoatrophy).(Lucas GM, et al 1999)

Increased bleeding episodes among patients with hemophilia

Soon after introduction of PIs, several case reports suggested an association between these drugs and increased frequency and severity of bleeding in patients with hemophilia. In most patients, bleeding increased within the first few weeks of PI therapy, but the onset ranged from a few days to many months after initiation of therapy. Not only did bleeding occur more frequently, but it occurred at unusual sites such as the small joints of the hands and the soft tissues of the palms (Hollmig KA et al 2001)

Skin rash

Rash is a common adverse effect of the NNRTIs, particularly NVP. Severe rashes occur in about 6.5% of NVP-treated patients, mainly during the first 4 weeks of treatment, including Stevens-Johnson syndrome and toxic epidermal necrolysis in less than 1% of all patients treated with NVP. Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash, with or without pruritus, on

the trunk, face and extremities, within the first 6 weeks on therapy. Most rashes are self-limited. (Fagot JP,et al 2001)

Anemia/neutropenia-Zidovudine(especially with co-trimoxazole),**Neuropathy-**stavudine, zalicitabine,didanosine, **Pancreatitis** zalcitabine,didanosine

CHAPTER IV
MATERIALS AND METHODS

Study site

This study was carried out at the Chonburi hospital, Chonburi,Thailand.

Data collection period

The duration of data collection was from November 14, 2005 to January 9, 2006.

Study design

This study was a descriptive retrospective study. There were two separated studies (2 groups but they are independently analyzed) in this study. Study A–NVP based regimen. Study B -protease inhibitor base regimen followed by NVP based regimen.

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Study population

All advanced HIV patient who were of age 14years and older were eligible for the study. All the patients were diagnosed as having HIV infection by standard serological test and classification of HIV infection was made in accordance with the CDC criteria. The HIV status, if unknown, was determined on one blood sample, on which two serological tests were performed. In cases where HIV status was known by previous tests at any hospital, this history with documentation was taken by hospital doctors as proven HIV infection.

Inclusion Criteria

1. HIV positive patient with the CD4 count < $100x10^6$ cell/ul
2. Age >14 years old.
3. Naïve to antiretroviral drug prior to study enrolment

Exclusion criteria;

1. Loss to follow up

Sample size estimation

Study A

In Thailand, the efficacy of GPO-vir (it has the equivalent efficacy as non generic regimen containing 2NRTI plus NVP) has been evaluate by a combined retrospective and prospective study from Chonburi hospital where the treatment efficacy as assessed by CD4 count increase in ITT analysis was found to be 39.5% at the 96 weeks of study(Tin Ei EI et al ,2005).Therefore, we have taken the results of study performing at the Chonburi hospital as the reference in order to estimate CD4 count increase for sample size calculation. Hence, we assume that treatment success at 96 weeks of therapy to be 39.5%.

$n=Z_\alpha^2 x\ pq\ /d^2$

Where

n =calculated sample size

Z_α=1.96 (α =0.05)

d=error allowance, in this study we use 10 %

p=proportion of patient whose CD4 count were >200x10 6 cells/ml at 96 weeks.

q=1-p

For the NVP based regimen,

$n= (1.96)^2 x (0.395) x (0.605) / (0.1)^2$

n=92

Therefore, the number of subjects for evaluations of NVP base regimen study is at

least 92.

Study B

The efficacy of protease inhibitor regimen has been taken from the result of study by (Piketty et al ,2001) which the treatment efficacy was assessed by CD4 count increase was found to be 79% at 48 weeks. Hence, we assumed that treatment success at the 48 weeks of therapy to be 79%.

For boosted PI based regimen followed by NVP based regimen

$n= (1.96)^2 x (0.79) x (0.21)/ (0.1)^2$

n=64

Therefore, the number of subjects for evaluations of PI base regimen sequential by NVP based regimen study is at least 64.

Study method

For the each enrolled patients, history and physical examination were documented in the data collection form. Base line investigation were recorded including (CBC, absolute lymphocyte count, fasting blood sugar, viral load, lipid profiled, CD4 count, liver function test, and renal function test and chest X ray).There were two groups of patients who were treated independently .One group received NVP based regimen and another group received IDV/RTV (400/100)12hrly for 6months followed by NVP base regimen. Patients from two independent groups have to follow up at least 2 years then we evaluated the clinical, immunological,and virological efficacy of IDV/RTV sequential by NVP based regimen and NVP based regimen in treatment naïve advanced ADIS patients. In addition, patients were scheduled to follow up every month to see the clinical improvement.

Criteria to switch from boosted PI based regimen to NVP based regimen

1. Wellbeing and CD4 count increase $>100x10^6$ cell/ul
2. VL<50 copies/ul
3. At least 6 months

Endpoint

Treatment failure (without an appropriate CD4+count response, clinical, and virological failure),

DATA ANALYSIS

The data obtained from the case record forms were entered into computer file and analyzed using EPI info version 6.04 programs.

1. Qualitative data was summarized as frequency and percentage then analyzed by the chi square test or the Fisher exact test as appropriate.
2. Quantitative data with normal distribution was summarized as mean and standard deviation, and then analyzed by the parametric test. Comparing two unpaired groups, we selected unpaired t test or Z test .Comparing two paired groups; we used paired t test or Z test. Comparing three or more for unmatched groups, we chose one-way ANOVA and comparing three or more for matched groups, we selected repeated measures ANOVA.
3. Quantitative data with non-normal distribution were summarized as median and range then analyzed by the non-parametric tests. Comparing three or more unmatched groups, we used Kurskal-Wallis test and comparing three or more for matched groups, we selected Friedman test. If we analyzed and compared two unpaired groups, we used Mann-Whitney U test .We chose Wilcoxon signed rank sum test to compare two paired groups. A p-value of less than 0.05 will be considered statically significant.

CHAPTER V
RESULTS

Background

NVP based regimen

A total of 94 patients identified from the Anonymous clinics at the chonburi hospital were shown in figure 1. After reviewing the medical records, two patients were deleted from analysis (one had previous ART history and other one had pre-treatment CD4 count morethan100x10^6 cell/l) .The number of patients were 92 on treatment at 1 year. Only 89 patients remained at 2 year study period because two patients change to other regimen. There were 66 patients left on treatment at 3 year. Between 2 year and 3 year period of treatment, 8 patients changed to other regimen. Fifteen patients who have been receiving ART more than 2years but less than 3 years were exclude at 3 year studied period .The combination of nucleoside reverse transcriptase inhibitor (NRTI)in the NVP based regimen were as follow; most of patients in NVP group received stavudine (d4T)and lamivudine(3TC) and followed by zidovudine(AZT) and lamivudine(3TC)(59%),ddI and stavudine (d4T) (37%) ,an ddI and d4T(4%).

Boosted PI based regimen

A total of 65 patients identified from anonymous clinic at chonburi hospital were seen in figure 2. After checking the medical records, one patient was excluded because of previous ART history. Only 64 patients were analysed .These patients were firstly received boosted PI based regimen for median 9 months with range of 6-12 months and then change to NVP based regimen based on $CD4^+$T-cell count and viral load condition. The combination of nucleoside reverse transcriptase

inhibitor (NRTI) in patients with the boosted PI based regimen were stavudine (d4T) and lamivudine(3TC). Among 64 patients, two patients developed NVP allergy when they changed boosted PI based regimen to NVP based regimen and then change to other regimen before completing one year study duration. Therefore, only 62 patients were available to study at 1 year of treatment. There were still 62 patients remain on 2 year of treatment. Between 2year and 3year of study timeframe, one patient change to other regimen due to development of severe hepatitis.43 patients who have been receiving boosted PI based regimen more than 2years but less than 3 years were excluded at 3 year studied span. Therefore, Only 18 patients remained at 3year of treatment.

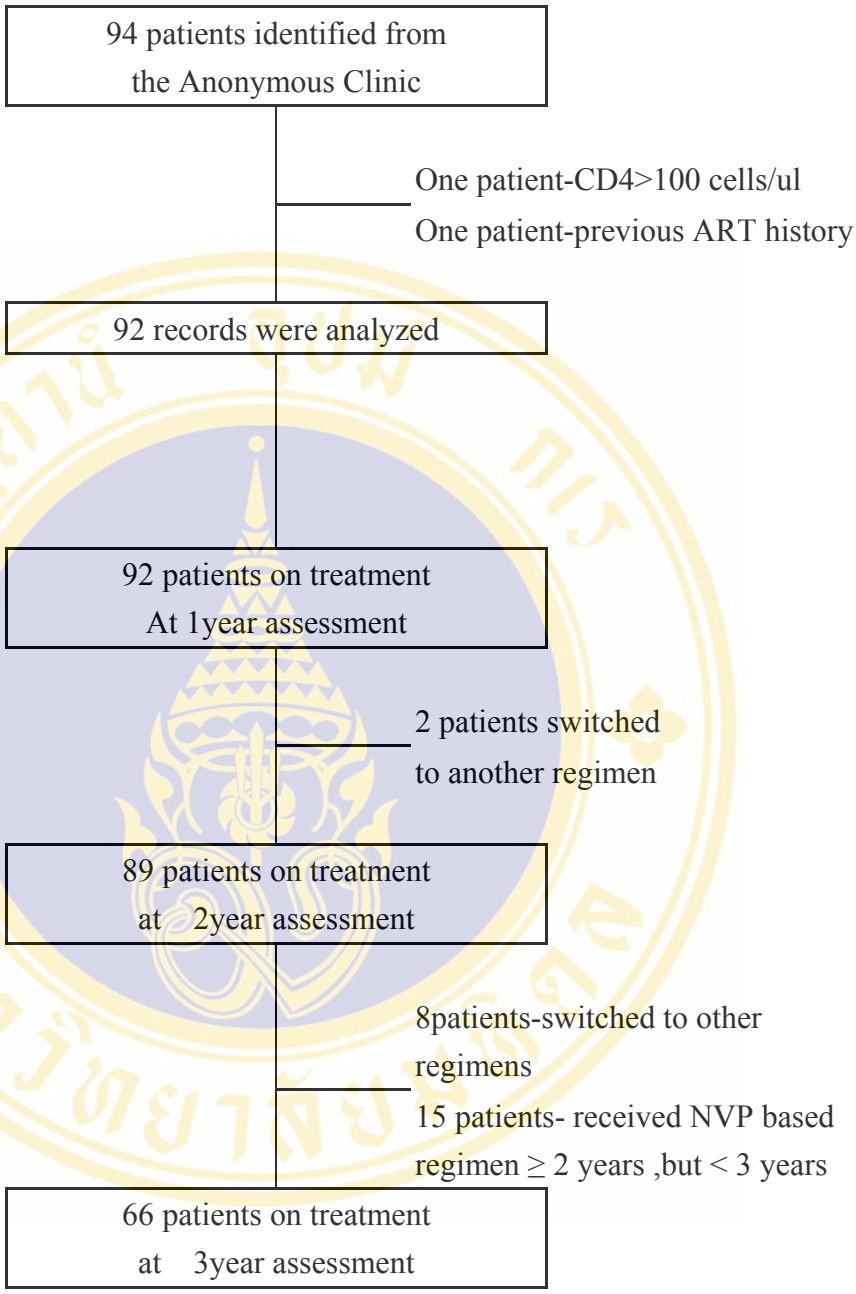


Figure 1: Study profile of the 92 studied patients received NVP based regimen

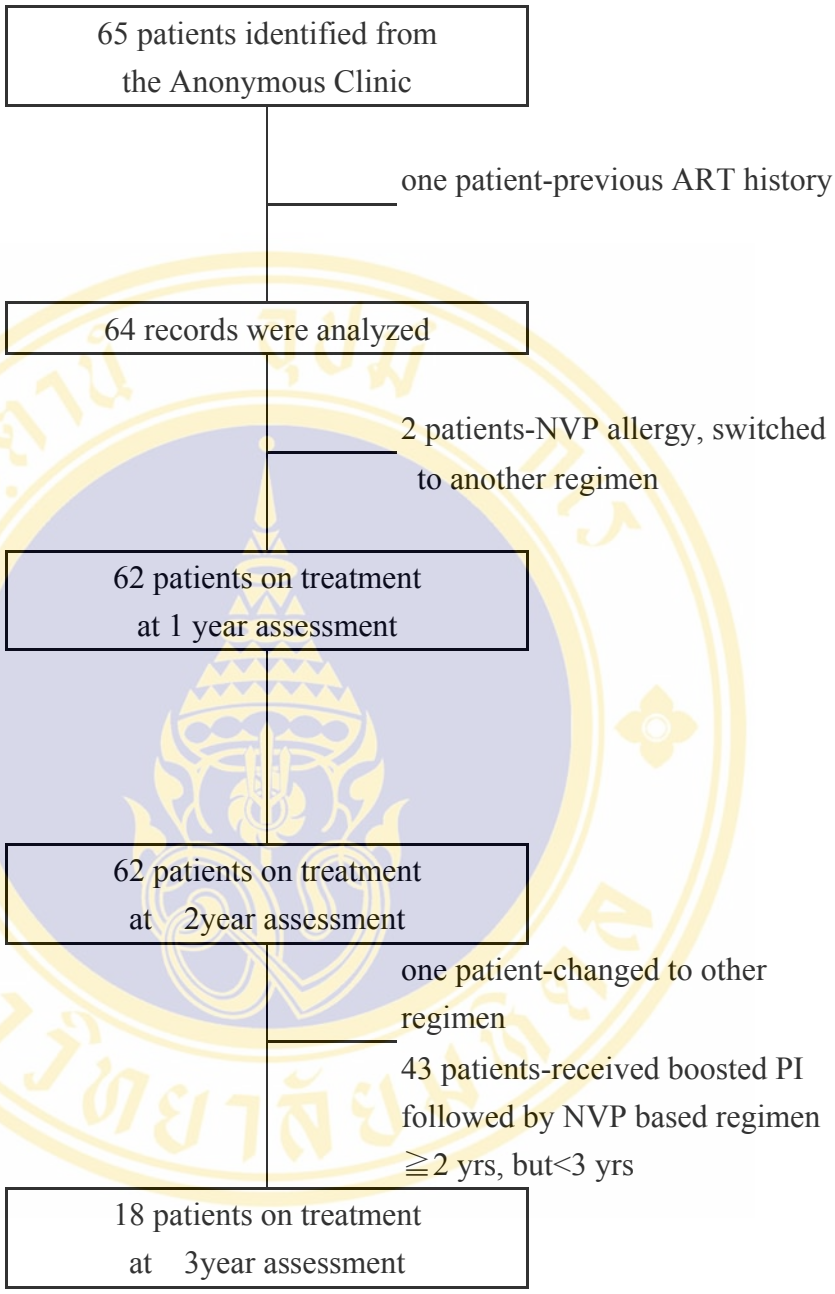


Figure 2:Study profile of the 62 studied patients received boosted PI based regimen followed by NVP based regimen

Demographic characteristic of 92 patients receiving NVP based regimen and 64 patients receiving boosted PI based regimen followed by NVP based regimen

The demographic characteristics of 92 patients in NVP based regimen and 64 patients in boosted PI based regimen were presented in Table 1.The median age of patient was 33 years with range of 28-39 years for NVP based regimen and 32 years with range of 30-38 years for boosted PI based regimen .The study group consisted of 59.8% male and 40.2% female in NVP based regimen whilst 56.3% males and 43.7 % female were accounted for boosted PI base regimen .The majority of patients were married 62% and 59.9%, in NVP based regimen and boosted PI based regimen, respectively.

Most of the patients, 78.3% in NVP based regimen and 81.3% in boosted PI based regimen, were from Chonburi province. Minority of patients (others) were from Rayon, Pattaya,Pitsanalope,Chachoengsao,Trat. The majority of patients were employees (84.8%) in NVP based group and 90.6% in boosted PI based regimen,

Baseline characteristic of 92 patients receiving NVP based regimen and 64 patients receiving boosted PI based regimen followed by NVP based regimen

Baseline characteristics of 92 patients in NVP and 64 patients in boosted PI based groups were shown in table 2. Majority of patients had at least one opportunistic infection before starting HAART treatment. The common opportunistic infection before treatment were tuberculosis (30.4%) and (26.6%), Cryptococcus (17.4%) and (7.8%), Candidasis (14.1%) and (9.4%), PCP (10.9%) and (6.3%), CMV retinitis (8.7%) and (4.7%) in NVP based and boosted PI based regimen, respectively.

The median (range) pre-treatment $CD4^+$T-cell count was 41cell/mm^3 (15-62) and 32cell/mm^3 (9-53), in NVP based regimen and boosted PI regimen, respectively. The patients were categorized into groups according to their pre-treatment $CD4^+$T-cell count of less than $50x10^6$ cells/l,$50-100x10^6$ cells/l .As for NVP based regimen, 65.1% of patients had less than 50 cells/ul of pre-treatment $CD4^+$ T-cell count whereas 34.9%

had 50-100 cells/ul.74.2% of patients who receiving boosted PI based regimen had less than 50 cells/ul pre-treatment $CD4^+$ T-cell count, 25.8% was accounted for 50-100 cell/ul of pre-treatment $CD4^+$ count.

The median pre-treatment body weight were 52 Kg with range of 45-57 Kg in 92 studied patients receiving NVP based regimen and 54 Kg with the range of 48-61 in 62 studied patients receiving boosted PI based regimen. The patients were divided into groups according to the pre-treatment body weight (≤50 kg, 51-60 kg, and >60 kg). About 42.9% of patients were ≤50 kg in NVP based regimen where 34.4% of patients were accounted for boosted PI based regimen. For pre-treatment body weight of 51-60 kg group, 38.5% of patients were for NVP based regimen while 40.6% of patients present for boosted PI based regimen. The rest was 18.6% and 25% of patients, in NVP group and boosted PI based group, respectively, had pre-treatment body weight of >60 kg group.

Table 1:Demographic characteristics of 156 adult HIV positive patients

Characteristics	Patients receiving NVP based regimen (n=92)		Patients receiving boosted PI based regimen (n=64)	
	No (%)	**median (Range)**	**No (%)**	**median (Range)**
Age(years)		**33(28-39)**		**32(30-38))**
15-24	**10(10.9)**		**2(3.1)**	
25-34	**45(48.9)**		**41(64.1)**	
35-44	**25(27.1)**		**15(7.8)**	
45-54	**11(12.0)**		**5(7.8)**	
55-64	**1(1.1)**		**1(1.6)**	
Sex				
male	**55(59.8)**		**36(56.3)**	
female	**37(40.2)**		**28(43.7)**	
Marital status				
single	**31(33.7)**		**15(23.4)**	
married	**57(62.0)**		**38(59.4)**	
widow/divorce	**4(4.3)**		**11(17.2)**	
Residence				
Chonburi province	**72(78.3)**		**52(81.3)**	
Other province	**20(21.7)**		**12(18.7)**	
Occupation				
employed	**78(84.8)**		**58(90.6)**	
unemployed	**14(15.2)**		**6(9.4)**	

Table 2:Baseline characteristics of 92 patients receiving NVP based regimen and 64 patients receiving boosted PI based regimen followed by NVP based regimen

Characteristics	Patients receiving NVP based regimen			Patients receiving boosted PI based regimen		
	n	No (%)	median (range)	n	No (%)	median (range)
OI prior to HAART	**92**	**63(68.5)**		**64**	**36(56.3)**	
Tuberculosis		**28(30.4)**			**17(26.7)**	
PCP		**10(10.9)**			**4(6.3)**	
Cryptococcus		**16(17.4)**			**5(7.8)**	
Herpes Zoster		**2(2.1)**			**4(6.3)**	
CMV retinitis		**8(8.6)**			**3(4.6)**	
Candidiasis		**13(14.1)**			**6(9.3)**	
Other infections		**4(4.3)**			**4(6.3)**	
Chronic illness	**92**	**9(9.8)**		**64**	**11(17.2)**	
Heart disease		**1(1.1)**			**1(1.6)**	
Hypertension		**2(2.2)**			**4(6.3)**	
Diabetic mellitus		**1(1.1)**			**1(1.6)**	
Hepatitis B		**1(1.1)**			**3(4.7)**	
Hepatitis C		**1(1.1)**			**0(0)**	
Renal disease		**1(1.1)**			**0(0)**	
Other chronic diseases		**2(2.2)**			**2(3.1)**	
Pre-treatment $CD4^+$ T-cell count (10^6cells/l)	**86**		**41(15-62)**	**62**		**25(9-53)**
<50		**56(65.1)**			**46(74.2)**	
50-100		**30(34.9)**			**16(25.8)**	
Pre-treatment body Weight (Kg)	**91**		**52(45-57)**	**64**		**54(48-61)**
≤50		**39(42.9)**			**22(34.4)**	
51-60		**35(38.5)**			**26(40.6)**	
>60		**17(18.6)**			**16(25.0)**	

Body weight change among 92 patients during treatment with NVP based regimen

Percentage of body weight change from baseline after treatment with NVP based regimen at 1 year,2 year, and 3 year among 92 patients were demonstrated in figure 3.Percentage of body weight gain at 1 year, 2 year and 3 year were calculated based on pre-treatment body weight .More than 50% of patients had weight gain >10% from baseline body weight at 1 year, 2 year and 3year of treatment interval while 10-20% of patients experienced increment in bodyweight ranging from 1% to 10% of pre-treatment body weight over same study period. Only less than 10 % of patients had no weight gain or loss their body weight at 1 year, 2 year and 3 year of treatment.

The relation of three monthly median body weight change(%) from baseline during NVP treatment with respect to pre-treatment $CD4^+$ T-cell count was shown in figure 4.Patients were classified into two groups according to their pre-treatment $CD4^+$ T-cell count of less than $50x10^6$ cells/l and $50\text{-}100x10^6$ cells/l .It was shown that there was no significant difference in median body weight change(%) between pre-treatment $CD4^+$ T-cell count of less than $50x10^6$ cells/l and $50\text{-}100x10^6$ cells/l at the baseline and over 3 years of treatment except at time point of 21 months (P=0.046) and 36 months.(P=0.005)

The relation of three monthly median percentage of body weight change from baseline during NVP regimen with respect to pre-treatment body weight was shown in figure 5.In this figure, patients were categorized into 3 groups according to their pre-treatment body weight of less than or equal to 50 Kg,51-60 Kg ,and more than 60 Kg. There was no significant difference in median body weight change (%) over 3year of treatment among three groups mentioned except at the time point of 12 months(P=0.014) and 21 months (P= 0.043) . Subgroup analysis in 12 months presented that there was significant difference in percentage of median body weight change between pre-treatment body weight of less than or equal to 50 Kg and 51-60 Kg (P=0.011), again between pre-treatment bodyweight ≤50 Kg and >60(P=<0.001).

At 21 months of treatment, there was also significant difference in median body weight change (%) between pre-treatment body weight of less than or equal to 50 Kg and 51-60 Kg (P=0.022), and between pre-treatment bodyweight ≤50 Kg and >60 Kg (P=0.008).

Frequency distribution of body weight changes at 1 year, 2 years and 3 years of treatment with respect to pre-treatment body weight by NVP based regimen can be seen in table 3.It was found that patients with pre-treatment body weight of less than or equal to 50 Kg of patients had higher percentage of weight gain ≥10% from baseline than other two groups during 3 years treatment.

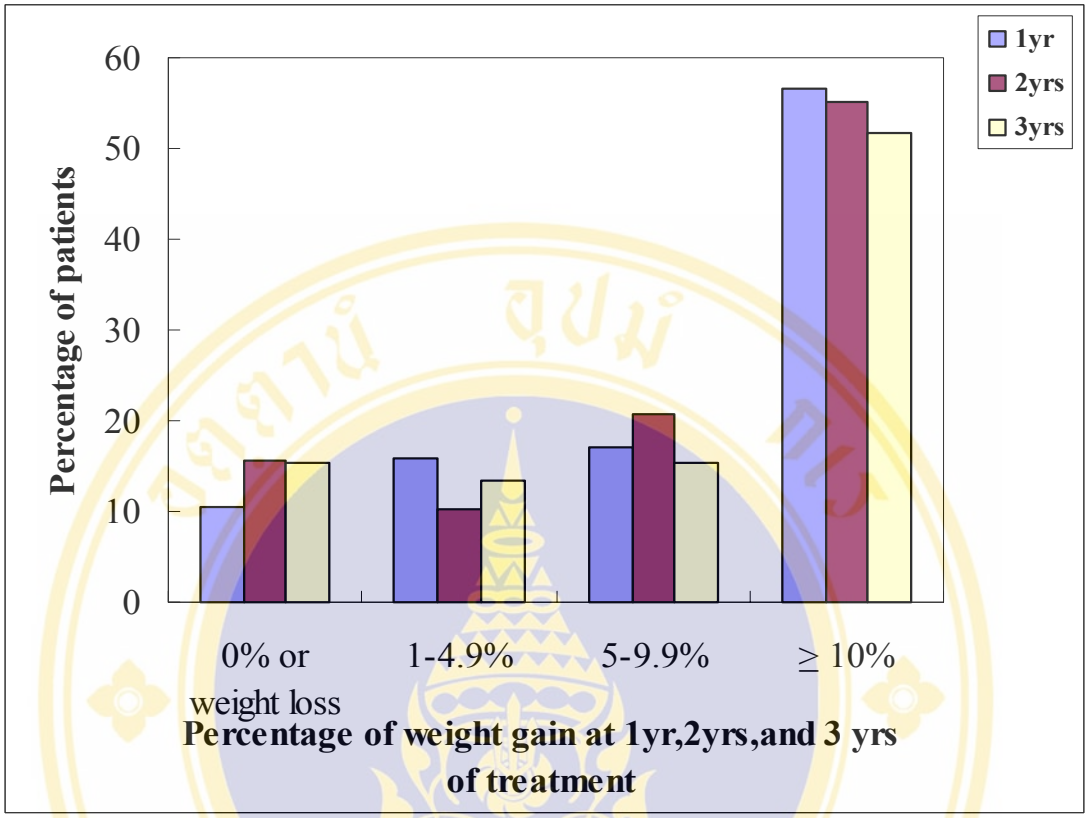
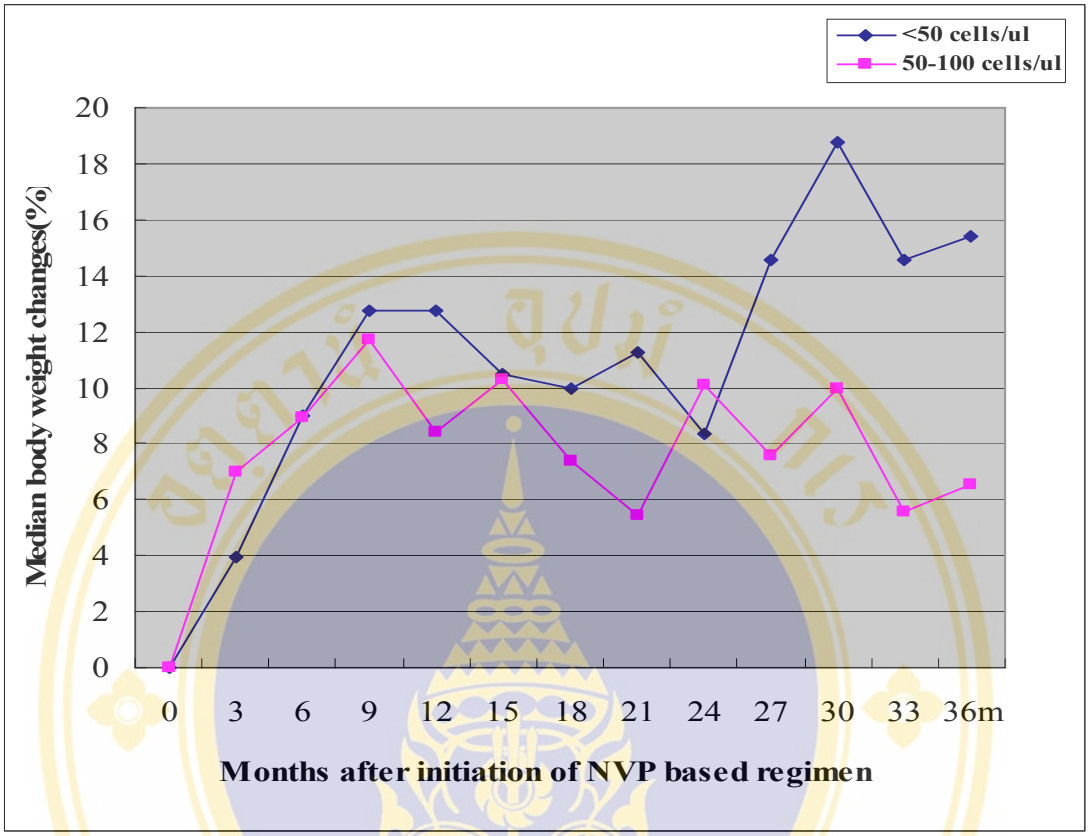


Figure 3: Percentage of body weight change from baseline after treatment with Boosted PI based regimen at 1 yr (n=76), 2 yrs (n=59), 3 yrs (n=53)



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of patients at each time point												
<50	0	48	49	47	44	32	41	38	35	33	27	27	31
50-100	0	27	27	20	28	20	17	19	18	16	14	13	18

Figure 4: :The relation of three-monthly median percentage of body weight change from baseline during NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count.

Table 3:Frequency distribution of body weight changes at(a) 1yr,(b)2yrs,and(c) 3 yrs with respect to pre-treatment body weight at NVP based regimen

(a)

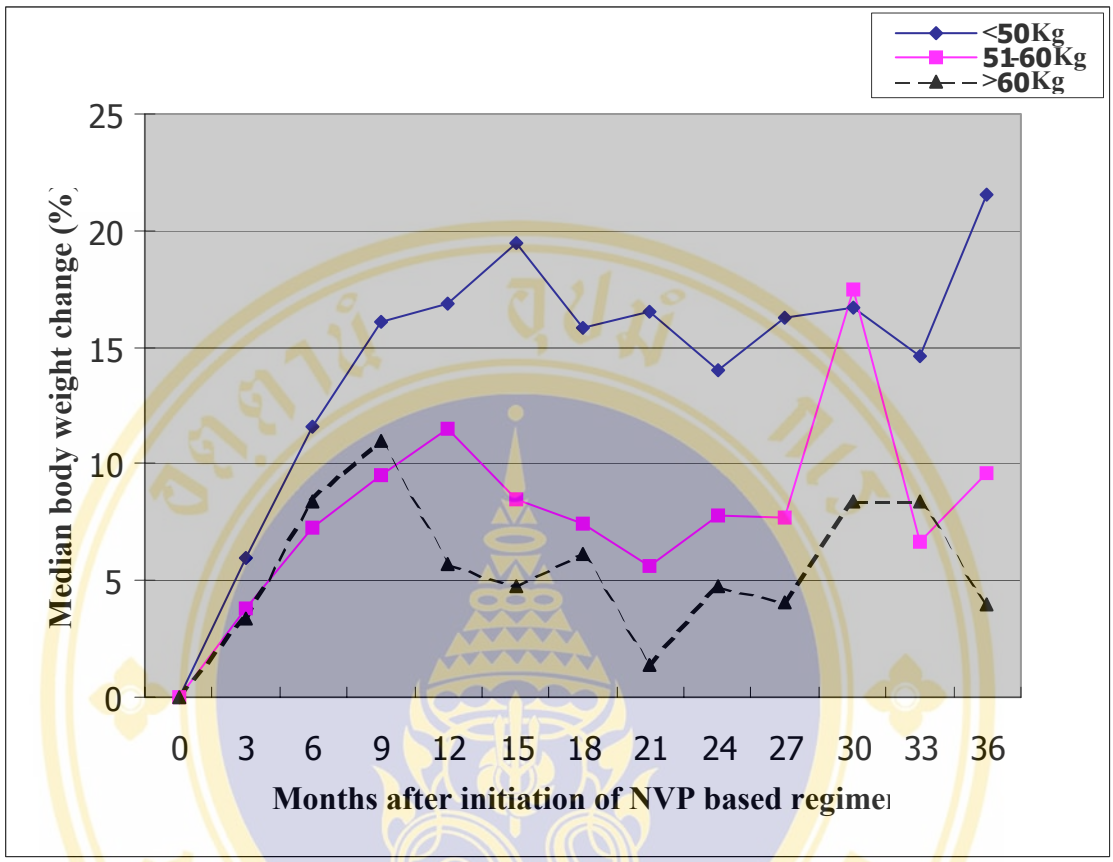
Pre-treatment body weight (kg)	**No (%) of patients with weight changes from baseline at 1 year**				**Total**
	≤0% **(n=8)**	1-4.9% **(n=12)**	5-9.9% **(n=13)**	≥10% **(n=43)**	**(n=76)**
≤50	0(0)	5(15.6)	4(12.5)	23(71.9)	32
51-60	7(24.1)	2(6.9)	5(17.3)	15(51.7)	29
>60	1(6.7)	5(33.3)	4(26.7)	5(33.3)	15

(b)

Pre-treatment bodyweight (Kg)	**No (%) of patients with weight changes from baseline at 2 year**				**Total**
	≤0% **(n=9)**	1-4.9% **(n=6)**	5-9.9% **(n=12)**	≥10% **(n=32)**	**(n=59)**
≤50	2(6.9)	2(6.9)	4(13.8)	21(72.4)	29
51-60	4(20)	1(5)	6(30)	9(45)	20
>60	3(30)	3(30)	2(20)	2(20)	10

(C)

Pre-treatment bodyweight (Kg)	**No (%) of patients with weight changes from baseline at 3 year**				**Total**
	≤0% **(n=8)**	1-4.9% **(n=7)**	5-9.9% **(n=8)**	≥10% **(n=30)**	**(n=53)**
≤50	0(0)	1(5)	3(15)	16(80)	20
51-60	4(17.4)	4(17.4)	4(17.4)	11(47.8)	23
>60	4(40)	2(20)	1(10)	3(30)	10



Pre-treatment Body weight (Kg)	No of patients at each time point												
≤50	**0**	**36**	**35**	**32**	**32**	**24**	**26**	**28**	**29**	**23**	**21**	**17**	**20**
51-60	**0**	**30**	**31**	**28**	**29**	**20**	**23**	**25**	**20**	**21**	**17**	**20**	**23**
>60	**0**	**14**	**14**	**12**	**15**	**13**	**12**	**6**	**10**	**9**	**6**	**6**	**10**

Figure 5: The relation of three- monthly median percentage of body weight change from baseline during NVP based regimen with respect to pre-treatment body weight.

Body weight change among 62 patients during treatment with boosted PI base regimen followed by NVP based regimen

Percentage of body weight change from baseline after treatment with boosted PI based regimen followed by NVP based regimen among 62 patients at 1 year, 2 year, and 3 year of treatment among 62 patients were presented in figure 6. Approximately 50% of patients had weight gain more than 10% of pre-treatment body weight at 1 year, 2year and 3 year of treatment while 20% or more of patients encountered weight gain 5-9.9% of pre-treatment body weight within same studied period. Only 10% of patients gained weight ranging from 1% to 4.99% from the baseline body weight over 1 year, 2 year and 3 year of treatment.

The relation of three monthly percentage of median body weight change from baseline during boosted PI based regimen followed by NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count was shown in figure 7.62 patients were split into two groups according to their pre-treatment $CD4^+$ T-cell count of $< 50x10^6$ cells/l and $50\text{-}100x10^6$ cells/l. It was found that no significant difference in median body weight change (%) was observed between two groups at the baseline and over three years of treatment except at time point of 24 months. [P=0.019]

The relation of three monthly median percentage of body weight change from baseline during boosted PI based regimen followed by NVP based regimen with respect to pre-treatment body weight was indicated in figure 8. Patients were classified into 3 groups according to their pre-treatment body weight of less than or equal to 50 Kg, 51-60 Kg, and more than 60 Kg. There was no significant difference in percentage of median body weight change from baseline among three groups during 3 years of treatment.

Frequency distribution of body weight changes at 1 year, 2 year and 3 year of treatment by boosted PI based regimen followed by NVP based regimen with respect to pre-treatment body weight was shown in table 4.It was found that patients with pre-treatment body weight less than or equal to 50 Kg of patients had higher

percentage of weight gain ≥10% from baseline than other two groups within 3 years of treatment.

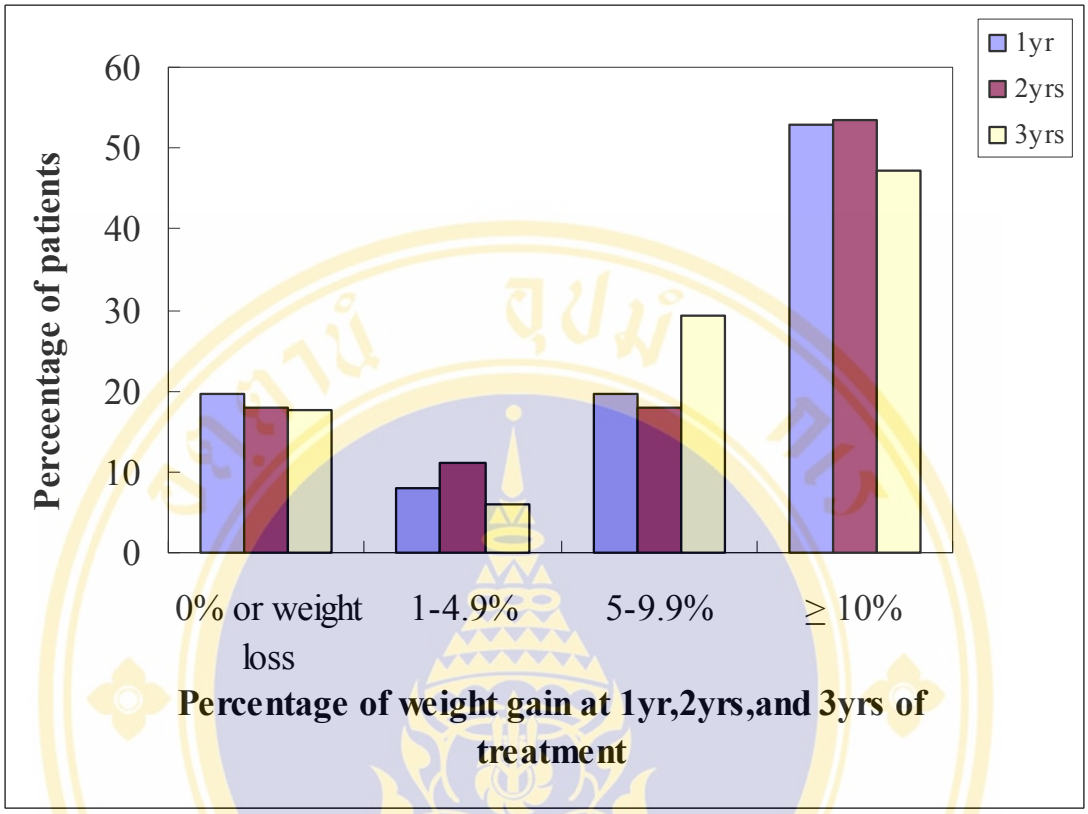
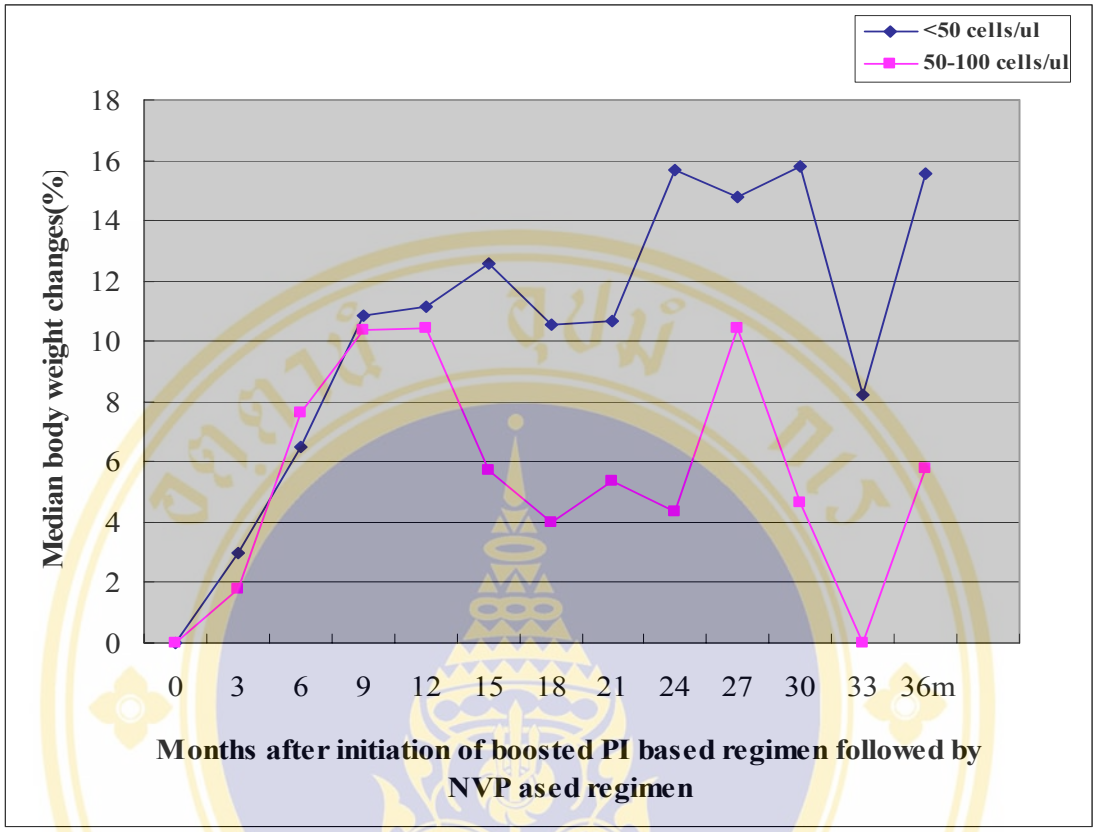


Figure 6: Percentage of body weight change from baseline after treatment with boosted PI based regimen followed by NVP based regimen at 1 yr (n=51), 2 yrs (n=45), 3 yrs (n=17)



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of pts at each time point											
<50	**0**	**43**	**41**	**35**	**38**	**38**	**34**	**26**	**31**	**26**	**22**	**15**	**13**
50-100	**0**	**16**	**16**	**11**	**13**	**12**	**9**	**12**	**12**	**9**	**8**	**5**	**3**

Figure 7:The relation of three-monthly median body weight change during boosted PI base regimen followed by NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count.

Table 4: Frequency distribution of body weight change at (a) 1 yr,(b) 2 yrs ,and (c) 3 yrs with respect to pre-treatment body weight at boosted PI regimen followed by NVP based regimen

(a)

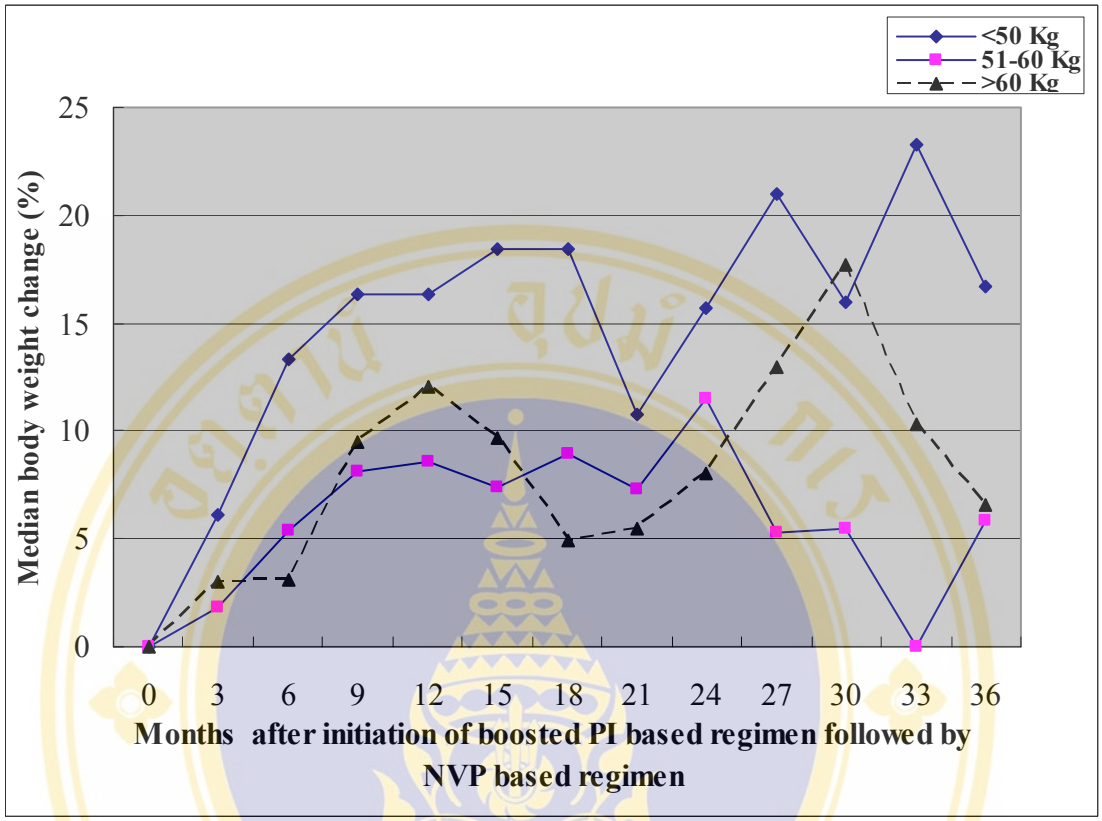
Pre-treatment body weight (Kg)	**No (%) of patients with weight changes from baseline at 1 year**				**Total (n=51)**
	≤0% **(n=10)**	1-4.9% **(n=4)**	5-9.9% **(n=10)**	≥10% **(n=27)**	
≤50	3(15.8)	0	2(10.5)	14(73.7)	19
51-60	3(15.8)	3(15.8)	7(36.8)	6(31.6)	19
>60	4(30.8)	1(7.7)	1(7.7)	7(53.8)	13

(b)

Pre-treatment bodyweight (Kg)	**No (%) of patients with weight changes from baseline at 2 year**				**Total (n=45)**
	≤0% **(n=8)**	1-4.9% **(n=5)**	5-9.9% **(n=8)**	≥10% **(n=24)**	
≤50	1(5.9)	4(23.5)	2(11.8)	10(58.8)	17
51-60	6(33.3)	0	2(11.1)	10(55.6)	18
>60	1(10)	1(10)	4(40)	4(40)	10

(C)

Pre-treatment bodyweight (Kg)	**No (%) of patients with weight changes from baseline at 3year**				**Total (n=17)**
	≤0% **(n=3)**	1-4.9% **(n=1)**	5-9.9% **(n=5)**	≥10% **(n=8)**	
≤50	1(14.3)	0	0	6(85.7)	7
51-60	1(33.3)	0	1(33.3)	1(33.3)	3
>60	1(14.3)	1(14.3)	4(57.1)	1(14.3)	7



Pre-treatment Body weight (Kg)	No of patients at each time point											
≤50	**0**	**21**	**21**	**17**	**19**	**19**	**17**	**15**	**17**	**12**	**11**	**7**	**7**
51-60	**0**	**25**	**24**	**18**	**19**	**19**	**16**	**13**	**18**	**15**	**15**	**6**	**3**
>50	**0**	**15**	**14**	**12**	**13**	**13**	**11**	**10**	**10**	**8**	**5**	**7**	**7**

Figure 8: The relation of three-monthly median body weight changes from baseline after initiation of boosted PI base regimen followed by NVP based regimen with respect to pre-treatment body weight.

Median CD4T- cell count after NVP based regimen

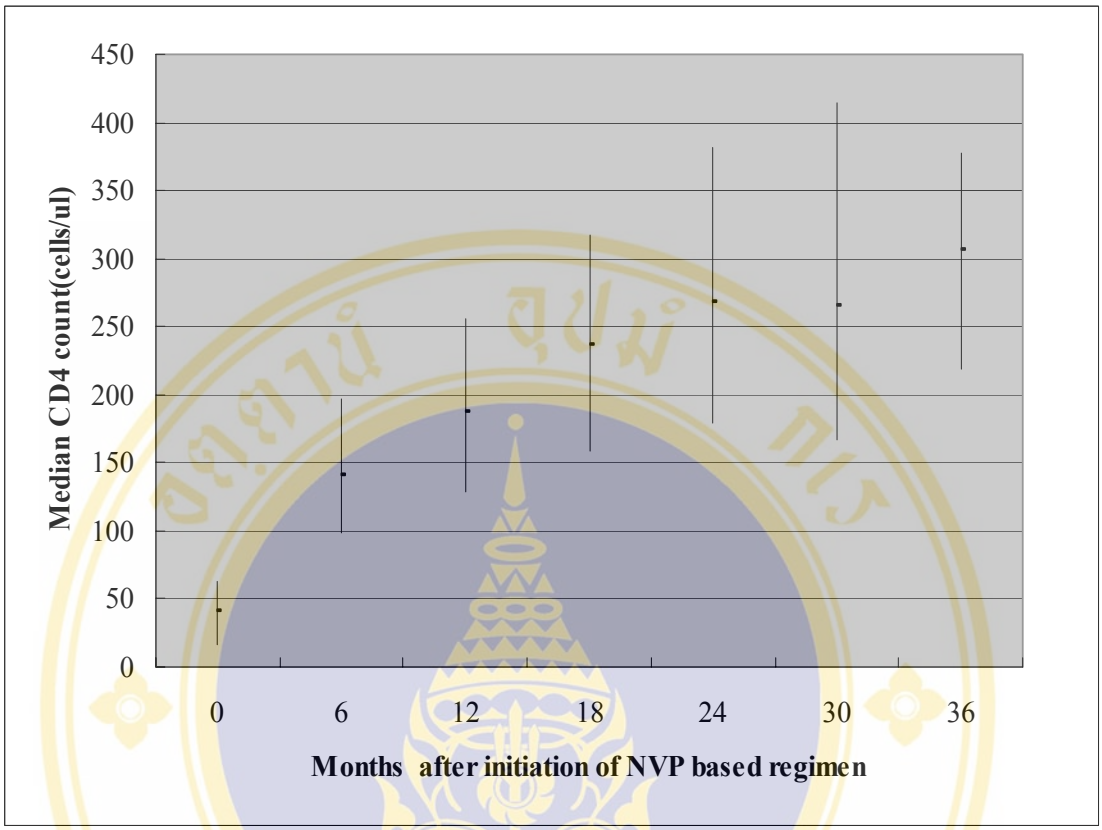
A summary of absolute median $CD4^+$T-cell count increment after the treatment with NVP based regimen among 86 patients was presented in figure 9.Generally, median $CD4^+$ T-cell count reached to nearly $200x10^6$ cells/l at first 12 months of treatment. Afterward, median $CD4^+$ T-cell/l count was gradually increased up to $306x10^6$ cells/l at 36 months of treatment.

After 1 year of treatment with NVP based regimen, 46.2 %(36/78) of patients had $CD4^+$T-cell count of $>200x10^6$ cells/l. At 2 years of treatment interval, 55.4 %(41/74) achieved $CD4^+$ T-cell count of more than 200 $x10^6$ cells/l and 9.5 %(7/74) had $CD4^+$ T-cell of > $500x10^6$ cells/l. About 67.9 %(36/53) had $CD4^+$ $>200x10^6$ cells/l at 3 year of therapy, where 13.2% of patients had $CD4^+$ $>500x10^6$ cells/l within same year of treatment.

Median $CD4^+$count change from the baseline after initiation of NVP based regimen was illustrated in figure 10. Median $CD4^+$ T-cell count changes increased gradually during 3 years of treatment.

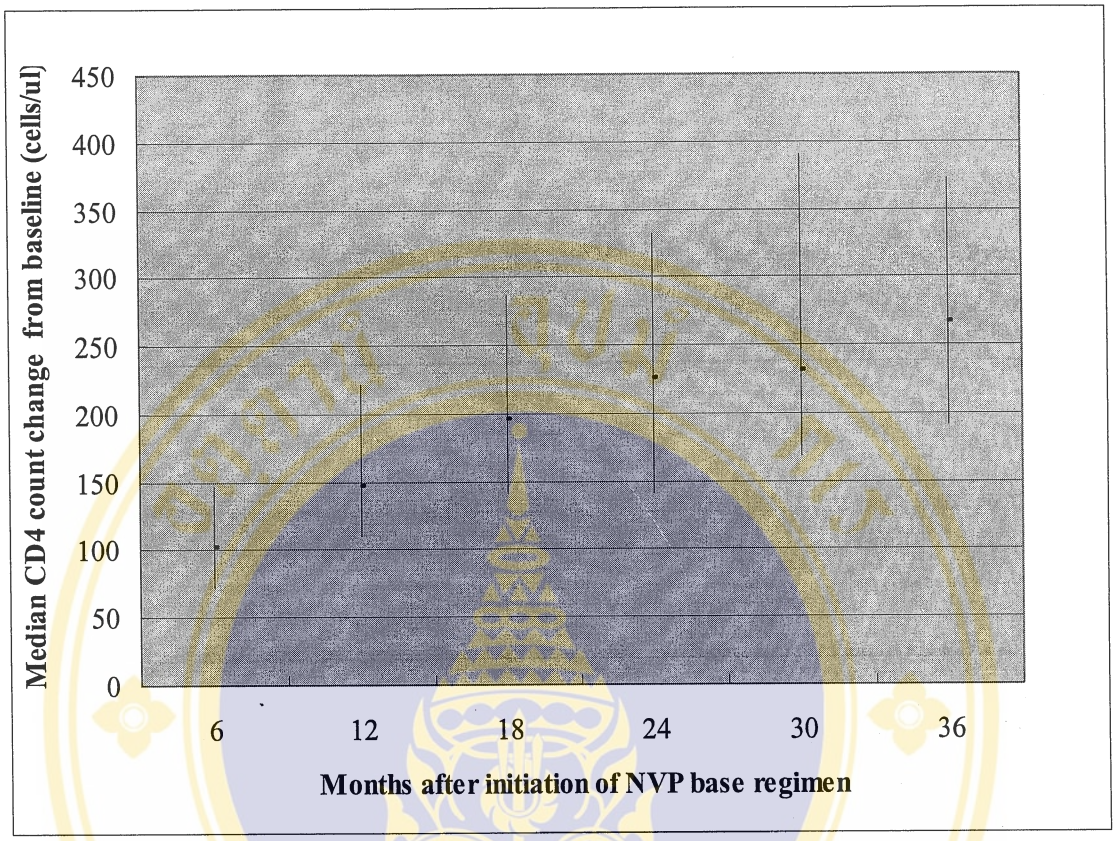
The relation of six-monthly median $CD4^+$ T-cell count changes from baseline during NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count

The patients were categorized into two groups according their pre-treatment $CD4^+$ T-cell count of less than or equal to $50x10^6$ cells/l and 50-100 $x10^6$ cells/l. The relation of six-monthly median $CD4^+$count change from the baseline during NVP treatment with respect to pre-treatment $CD4^+$ count was presented in figure 11. The two groups had increment of median $CD4^+$ count over 3year of treatment period. There was no significant difference in median $CD4^+$T-cell count change from baseline between two groups except at 18 months (P=0.001)



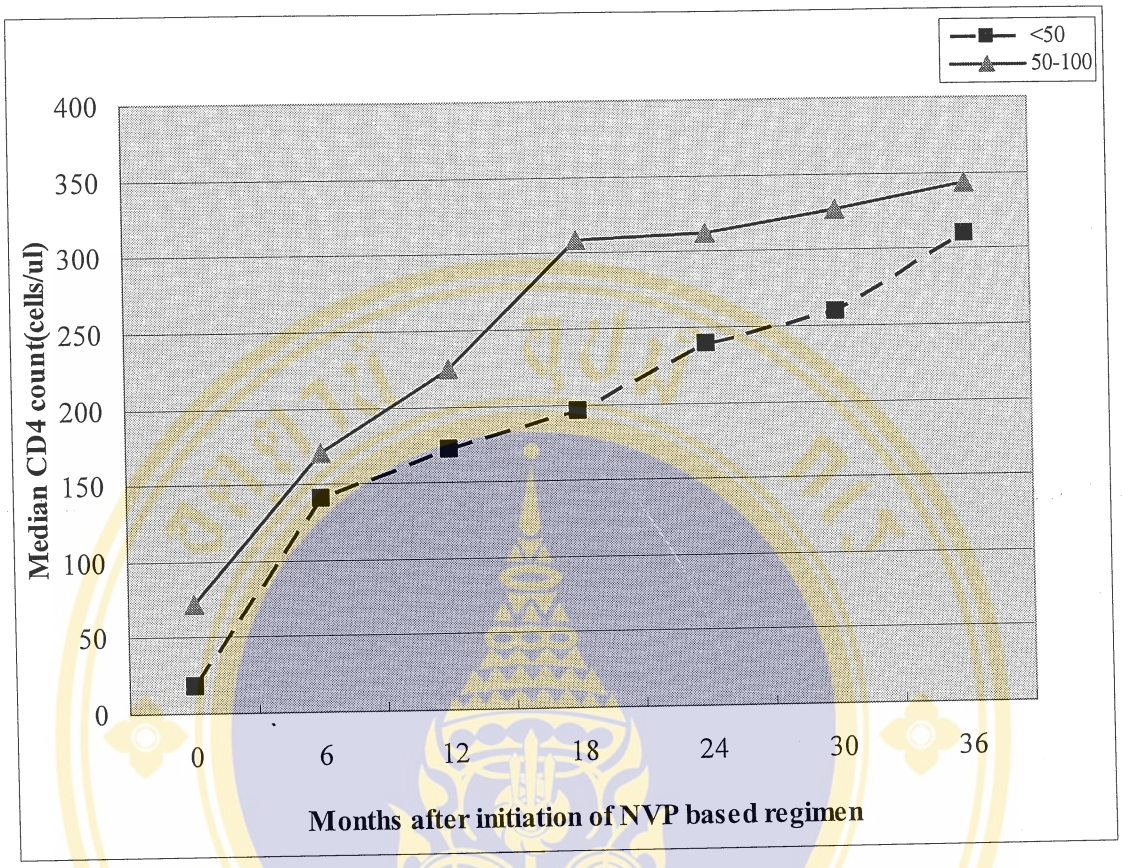
No of Patients	86	70	78	63	74	59	53

Figure 9: Median $CD4^{+}$T-cell count increment after starting NVP based regimen among 86 advance HIV patients.



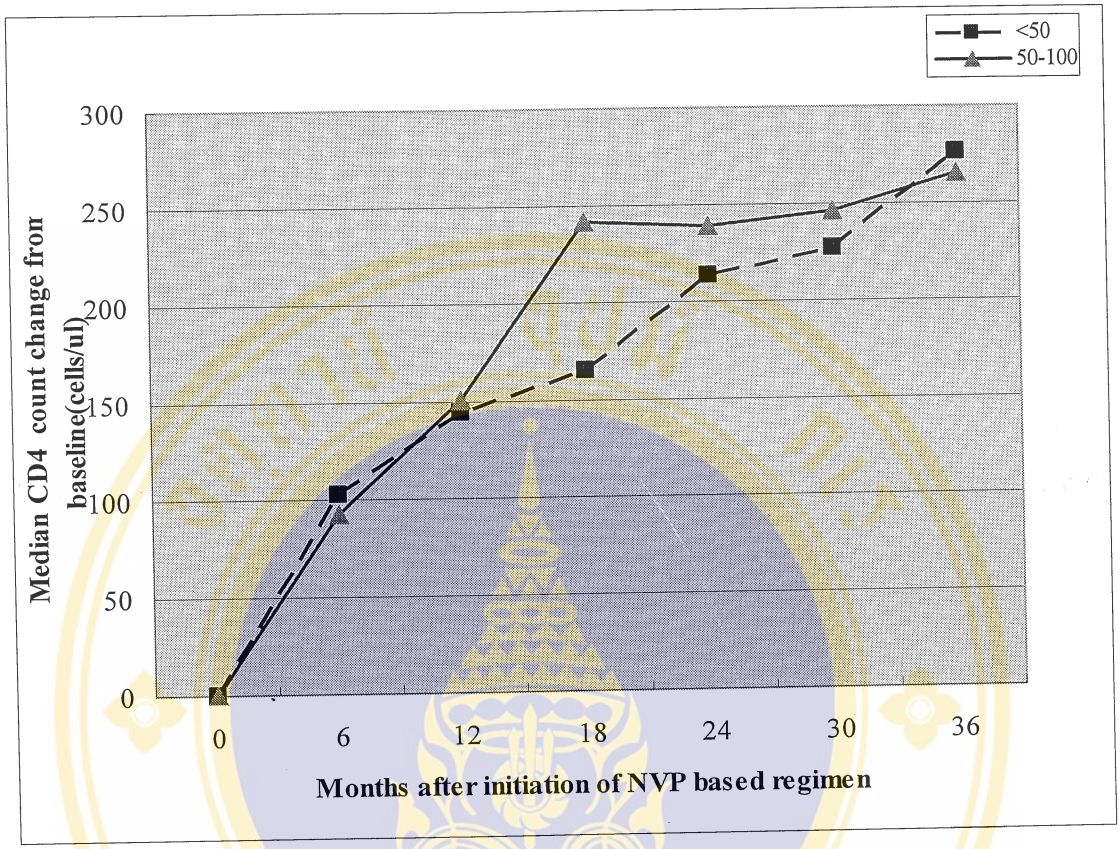
No of Patients	65	72	58	68	54	48

Figure 10: Median (interquartile) change in $CD4^+$ T-cell count from the baseline after starting NVP based regimen among 86 advance HIV patients.



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of patients at each time point						
<50	56	45	46	43	44	38	28
50-100	30	20	26	15	24	16	20

Figure 11: The relation of six- monthly median $CD4^+$ T-cell count increase time after initiation of NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count.



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of patients at each time point						
<50	0	45	46	43	44	38	28
50-100	0	20	26	15	24	16	20

Figure 12: The relation of six- monthly median $CD4^+$count change from baseline during NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count.

Median $CD4^+$T- cell count after initiation of boosted PI based regimen followed by NVP based regimen

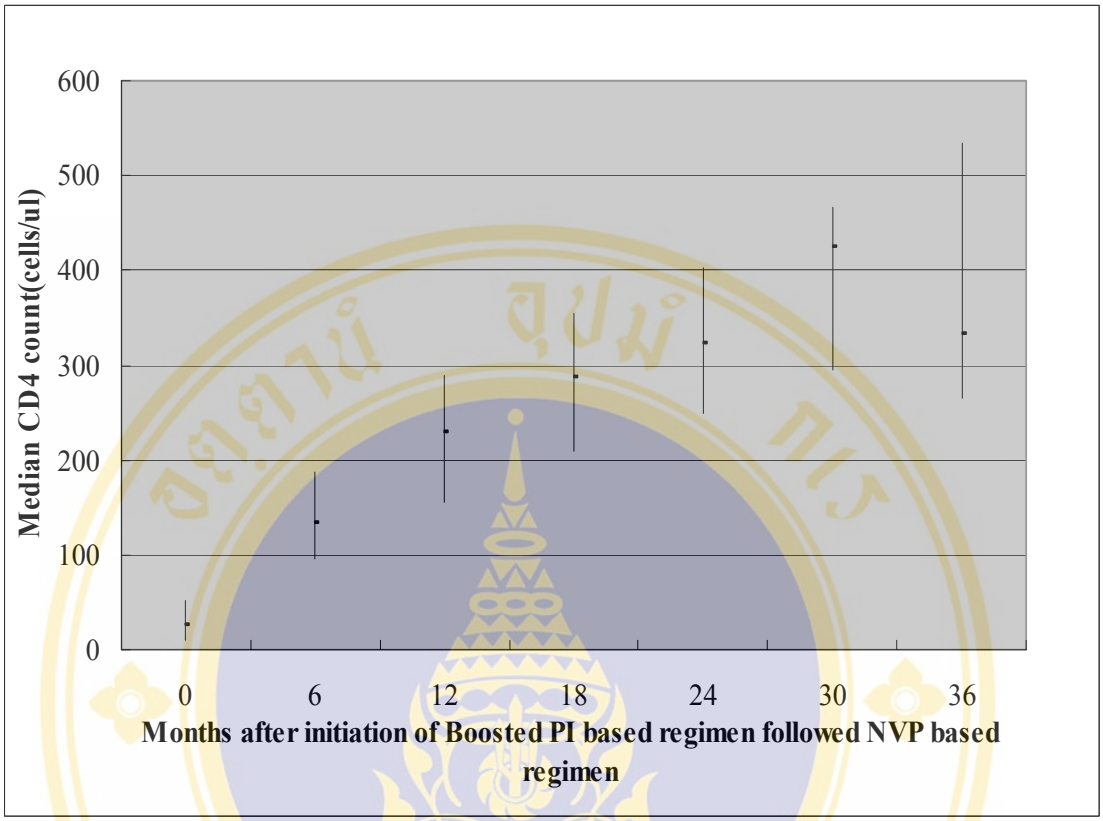
The increment of median $CD4^+$ T-cell count after initiation of boosted PI based regimen followed by NVP based regimen was shown in figure 13.The median $CD4^+$ T-cells count increased dramatically after starting of treatment and reached to $424x10^6$ cells/l at 30 months of treatment .From this time onward, median $CD4^+$ T-cell count reduced slightly to $333x10^6$ cells/l at 36 months of treatment.

After 1 year of treatment, 57.7 %(30/52) of patients had $CD4^+$ T-cell count of $>200x10^6$ cells/l. At 2 year of treatment, 85.4 %(41/48) of patients had $CD4^+$T-cell count of > 200 $x10^6$ cell/l while 6.3 %(3/48) of patients had $CD4^+$ T-cell count $>500x10^6$ cells/l. At 3 years of treatment, 62.5 %(10/16) and 31.3 %(5/16) of patients attained $CD4^+$ >200cells/ul and >500cells/ul, respectively.

Median $CD4^+$ T-cell count change from baseline in boosted PI based regimen was shown in figure14. The median $CD4^+$ T-cell count increased gradually during three years of treatment.

The relation of six-monthly median $CD4^+$count change from baseline during boosted PI based regimen followed by NVP based regimen with respect to re-treatment $CD4^+$count

The patients were divided into two groups according to their pre-treatment $CD4^+$ T- cells count of $<50x10^6$ cells/l and $50\text{-}100x10^6$ cells/l. The relation of six monthly median $CD4^+$ T-cells increment from initiation of boosted PI base regimen with respect to pre-treatment $CD4^+$ T- ell count was shown in figure 15.There was no significant difference in median $CD4^+$ T-cell count over of 3 year period of treatment between two groups.



No of Patients	62	49	52	37	48	27	16

Figure 13: Median $CD4^+$ T-cell count increment after starting boosted PI based regimen followed by NVP based regimen among 62 advanced HIV patients

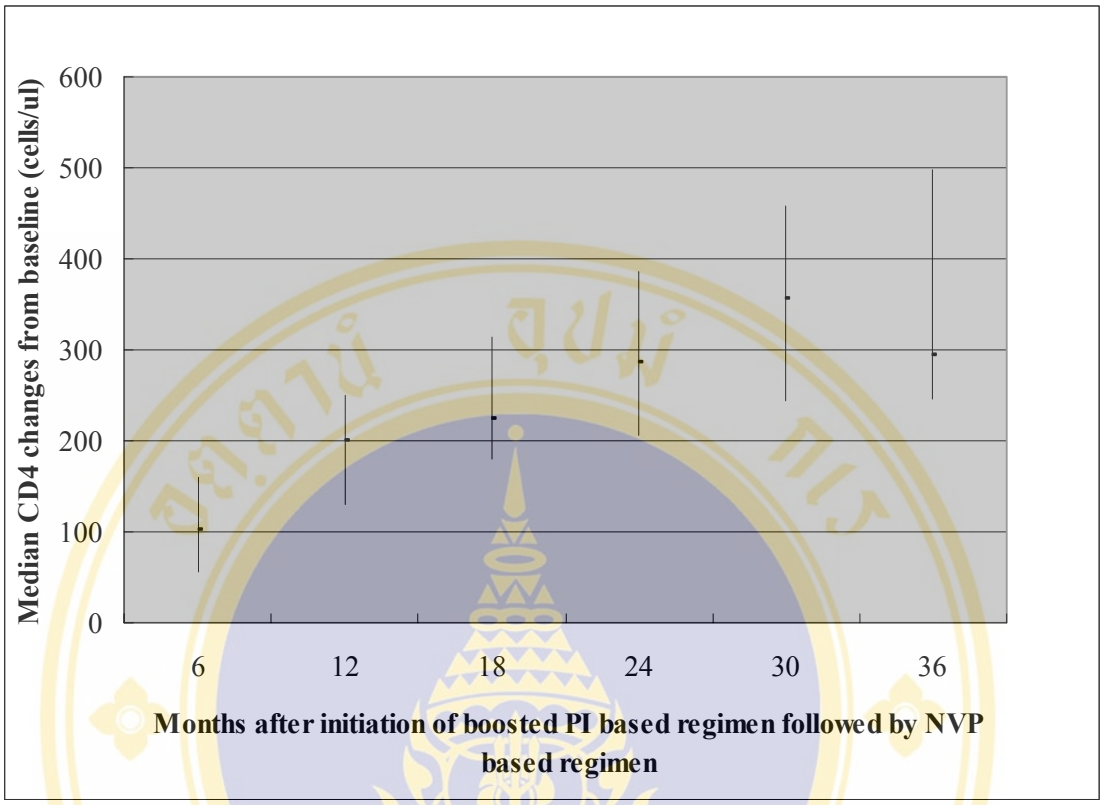
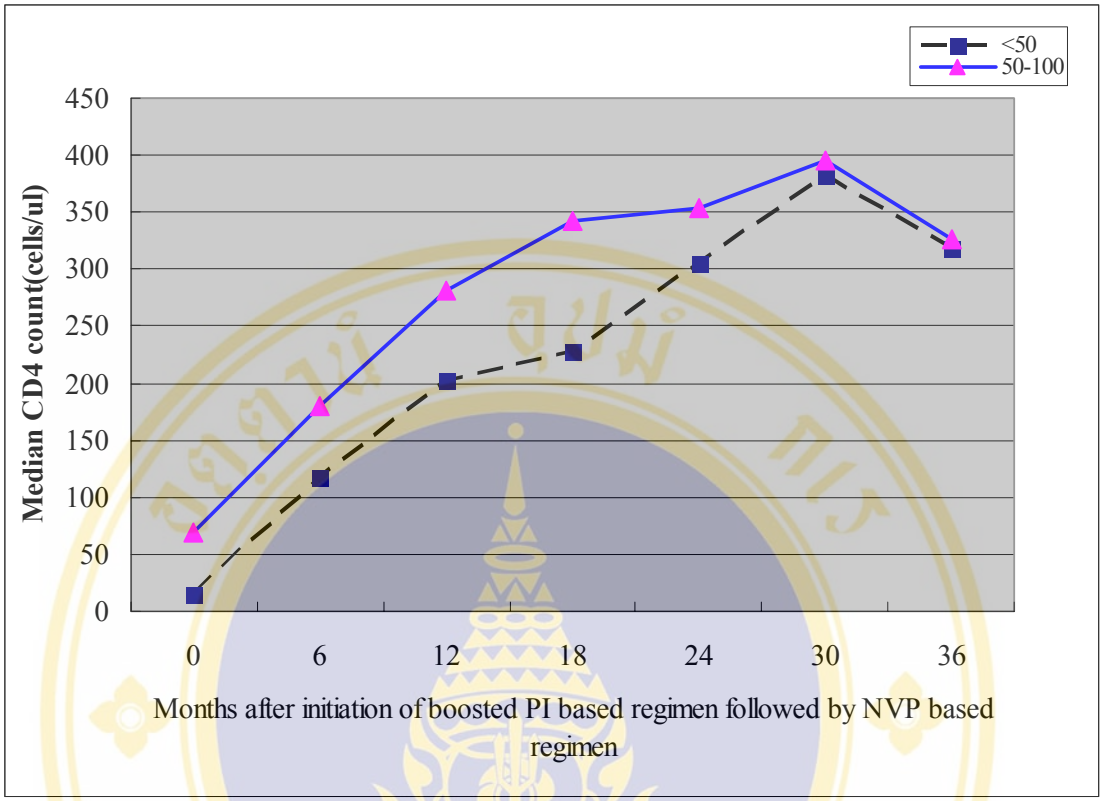
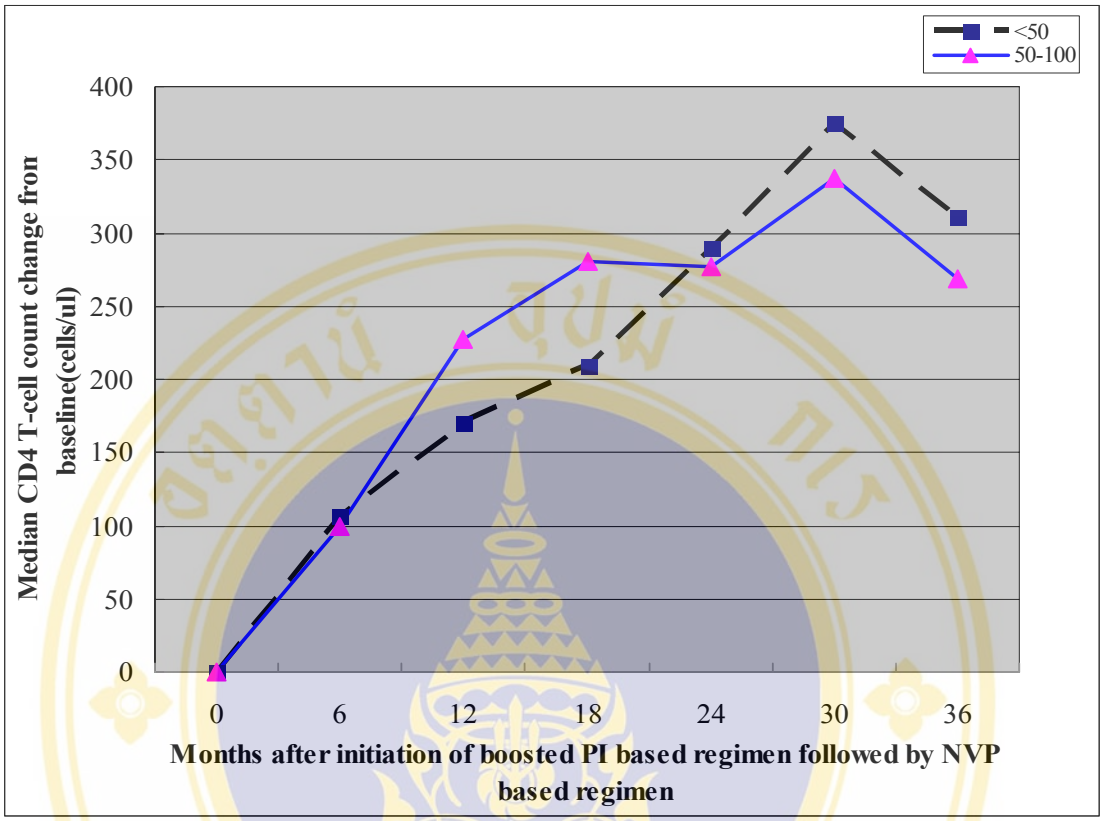


Figure 14:Median(interquartile) change in $CD4^+$ T-cell count after starting boosted PI based regimen followed by NVP based regimen among 62 advanced HIV patients



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of patients at each time point						
<50	46	33	39	22	34	21	12
50-100	16	14	11	13	12	5	3

Figure 15: The relation of six- monthly median $CD4^+$ T- cell count increase time after initiation of boosted PI based regimen followed by NVP based regimen with respect to pre-treatment $CD4^+$ count.



Pre-treatment $CD4^+$ count (10^6 cells/l)	No of patients at each time point						
<50	0	33	39	22	34	21	12
50-100	0	14	11	13	12	5	3

Figure 16: The relation of six- monthly median $CD4^+$ T-cell count change from baseline during boosted PI based regimen followed by NVP based regimen with respect to pre-treatment $CD4^+$ T-cell count

Virological response in NVP based regimen

Majority of the patients could not assess for baseline viral load. Therefore, only frequency distribution of viral load response was shown in table 5. Only one patient had baseline pVL<400 copies/ml and achieved pVL below detectable level at 1 year of treatment. There were 2 patients, 11 patients and 27 patients having pVL test done at 1year, 2 year, and 3 year of therapy, respectively. At 1 year of treatment, two patients had less than 50 copies /ml of viral load. At 2 year of treatment, there were 8 patients who achieve viral load below detectable level. At 3 year of treatment, 15 patients had pVL <50 copies/ml.

Virological response in boosted PI based regimen

All patients who received boosted PI based regimen could not assess for baseline viral load. Virological response of patients receiving boosted PI based regimen was illustrated in table 6. About 86.1 %(31/36) of patients had HIV viral load < 50 copies/ml within 1 year of treatment. Boosted PI was usually changed to NVP based regimen at the median time of 9 months with range from 6-12 months. Thereafter, patients continued their treatment with NVP based regimen. There were total 17 patients having viral load test done during 2 year and 3 year of treatment. 8 patients and 6 patients had viral load below detectable level at 2year and 3 year of therapy, respectively. This group is not found virological failure.

Table 5:Frequency distribution of CD4 + T-cell count, viral load and body weight after receiving NVP based regimen at 1 year,2 year and 3 year among advanced HIV patients

Characteristic	Base-line		NVP based regimen treatment after					
			1yr		2yrs		3yrs	
	n	No	n	No	n	No	n	No
CD4 count (106 cells/ul)	86		78		74		53	
<200		86		42		26		10
200-499				36		41		36
≥500				0		7		7
Viral load(copies/l)	1		2		11		7	
<50				2		8		18
>50-<400		1		0		1		2
>400				0		2		7
bodyweight(kg)	91		76		60		53	
≤50		39		13		14		9
51-60		35		30		24		18
>60		17		33		22		26

Table 6:Frequency distribution of CD4 + T-cell count, viral load and body weight after receiving boosted PI based regimen followed by NVP based regimen at 1 year,2 year and 3 year among advanced HIV patients

Characteristic	Base-line		boosted PI base regimen followed By NVP based regimen treatment after					
			1yr		2yrs		3yrs	
	n	No	n	No	n	No	n	No
CD4 count (106 cells/ul)	62		52		48		16	
<200		62		22		4		1
200-499				30		41		10
≥500				0		3		5
Viral load(copies/l)			36		10		7	
<50				31		8		6
>50-<400				2		2		0
>400				3				1
bodyweight(kg)	64		51		45		17	
≤50		22		8		10		2
51-60		26		21		15		8
>60		16		22		20		7

Occurrence of complication other infection due to immune reconstitution syndrome

Two Candidiasis, one CMV retinitis, and one Herpes Zoster occurred due to IRS during treatment with a median 4.5 months, range 2.25-8.25 months in NVP based regimen. Only one Herpes zoster developed after 3 months of boosted PI based therapy. The $CD4^+$ T-cell count change of patients who had complication or other infection due to IRS was shown in table 7.

Table 7:The $CD4^+$ T-cell count change of patients who had complication or other infection due to immune reconstitution syndrome

patients No	other infections due to IRS	CD4 count at different time point (106 cell/l)			Months of occurrence
		1st	2nd	3rd	
(a)NVP based regimen					
83	CMV retinitis	28	130	103	3
51	Herpes Zoster	14	196	270	2
13	Candidasis	12	190	129	6
47	Candidasis	45	86	167	9
(b)boosted PI based regimen followed by NVP based regimen					
3	Herpes Zoster	13	90	not done	3

Outcome of treatment

In NVP based regimen

Outcome of NVP based regimen treatment was shown in table 8.It was found that 43(56.6%) of patients had weight gain ≥ 10% from baseline at 1 year. The $CD4^+$ T-cell count increase >150 cell/ul from baseline at 1 year was 47.2%.Ten patients switched to other regimen (mostly boosted PI based regimen). The main reason to switch to other regimen among 9 patients was development of drug resistance to NVP after a median 32 months with rage of 26-40 months. One patient with severe hepatitis due to NVP was changed to efavirenz based regimen at 24 months of treatment.

In boosted PI base regimen

Outcome of boosted PI based regimen followed by NVP based regimen treatment was presented in table 9.It was shown that weight gain≥10% from baseline at 1 year was 52.9%.$CD4^+$ T-cell count increase >150 cell/ul from baseline at 1 year was 68%.The outcome of viral load <50 copies/ul at 1 year was 86.1%.There was no drug resistance in boosted PI based regimen followed by NVP based regimen over 3 year of treatment. Two patients developed drug allergy at 1month, 2 months after changing from boosted PI based regimen to NVP based regimen. They discontinued NVP based regimen, and start again with efavirenz based regimen.

Compliance of patient

More than 90% of compliance was found in patients receiving NVP based regimen and boosted PI based regimen followed by NVP based regimen.

Table 8:Outcome after treatment with NVP based regimen

	n	Frequency	Percentage
Weight gain ≥10% from baseline at 1 year	76	43	56.6
$CD4^+$T-cell count increase >150 cell/ul from baseline at 1 year	72	34	47.2
Viral load <50 copies/ul at 1 year	2	2	
Drug resistance within 3 year of treatment	9	9	

Table 9:Outcome after treatment with boosted PI based regimen followed by NVP based regimen

	n	Frequency	Percentage
Weight gain ≥10% from baseline at 1 year	51	27	52.9
$CD4^+$T-cell count increase >150 cell/ul from baseline at 1 year	50	34	68
Viral load <50 copies/ul at 1 year	36	31	86.1

CHAPTER VI
DISCUSSION

We conducted a retrospective descriptive study to assess the efficacy of NVP based and boosted PI based HAART regimen in patients with advanced HIV infection in Chonburi hospital. Our study evaluated NVP based regimen efficacy and boosted PI based regimen followed by NVP regimen efficacy by analysing $CD4^+$ T-cells count changes, body weight changes, virological response and occurrence of opportunistic infections during treatment .The study also analysed occurrence of drug resistance.

We found that patients in NVP based and boosted PI based regimen groups took about 9 months and 12 months, respectively, after initiation of treatment to achieve median $CD4^+$ T-cell count $>200x10^6$ cells/l. We observed significantly increase in absolute number of median $CD4^+$ T-cell count in patients receiving NVP based regimen and boosted PI based regimen followed by NVP based regimen over a period of 2 years. Tin Ei EI et al (2005) study showed that 39.5% of patients attained median CD4 T-cell count of >200cell/l after 2 years of treatment with GPO-vir.It is comparable to our study .In our present study, the immunological success rate ($CD4^+$ $>200x10^6$cell/l) was 53.4%for NVP based regimen and 82% for boosted PI based regimen followed by NVP based regimen groups at 2 years of treatment time frame.

In NVP and boosted PI group, lower pre-treatment $CD4^+$ T-cell count was associated with lower increment of median $CD4^+$ count change up to 3 years of treatment interval.(P=0.049 for NVP groupat18 months).But some studies demonstrated that low pre-treatment $CD4^+$ count are associated with grater $CD4^+$ cells gain and rapid immunological response(Peter W Hunt et al,2003).In addition ,our study is differ from finding of TinEiEi et al(2005).It was a retrospective study of on 83 HIV patients with median $CD4^+$ T-cells count $69x10^6$ cells/l and received GPO-vir for

at least 1 year. They found that $CD4^+$ count increase overtime during treatment, but there was no association of pre-treatment $CD4^+$ count.

In van lenth et al, (2004) study, mean $CD4^+$ T-cell count increase from baseline was 212cells/ul in the NVP and 310 cells/ul in the PI group. In addition, Sven A et al (1995) study reported that the median increase from baseline in CD4+lymphocyte count was 230cells/ul. These studies were comparable to our study where median $CD4^+$ T-cell count increase from baseline was 226 cells/ul for NVP based regimen group and 287cells/ul for boosted PI based regimen over 2 years on treatment.

The study illustrated that majority of patients in NVP based and boosted PI based groups attained more than 10% of body weight from baseline after initiation of treatment at 1year, 2years, and 3years. Our finding are similar to those often Tin ei ei et al (2005).This study explained that median percentage of body weight from baseline increased gradually overtime through out the treatment .Of 83 patients,52.3% of patients gain more than 10% of pre-treatment body weight after taking GPO-vir for 1 year.

In our NVP based group, not in boosted PI based regimen group, there was significant association with pre-treatment body weight and percentage of median body weight change from baseline at 12 months and 21months of therapy. (P=0.014, P=0.043)The significant association occurred at pre-treatment body weight <50 Kg vs. 51-60 Kg (P=0.011) and <50 Kg vs. >60 Kg (P<0.000). In boosted PI based regimen group, there was no significant association between pre-treatment body weight and median body weight change (%) from baseline. Our study in boosted PI based regimen is comparable to Cabonnel Frank et al, 1998, study. This study demonstrated that body weight gain did not differ between patients with >90% of usual body weight and patient with<90% of usual body weight before receiving protease inhibitor treatment.

It is also observed that lower pre-treatment CD4 T cell count was

associated with more increment of median body weight change from the baseline in both regimen groups..A previous study (Tin Ei Ei ,et al 2005) reported that changes of median percentage of body weight of the patients with lower pre-treatment CD4 count (≤50 cell/ul) was significantly higher than change of those with pre-treatment CD4+count more than 50 cells/ul during 4-15 months of therapy. Therefore, it was comparable to our recent study.

As majority of patients could not assess baseline pVL, virologic success rate could not calculate from our study. However, outcome of virological response after initiation of boosted PI based regimen was satisfactory. Most of patients (83.3%) with boosted PI based regimen had HIV RNA <50 copies/ul at median 9months of therapy with range of 6-12 months. Regarding to virologicaal response, our study is similar to Konopnicki D et al (2005) study. It was reported that a viral load of <50 HIV-1 RNA copies/mL was achieved by 64% of the patients treating with IDV/RTV based regimen at 48 weeks. In NVP based group, only 2 patients did pVL test at 1 year of therapy. Therefore, outcome of virological response in NVP group could not assess.

Occurrence of new opportunistic was common in patients with lower $CD4^+$ T-cell count(10 -199x10^6cell/l) .The study also showed that the occurrence of opportunistic infection was significantly lower during treatment .This may due to sharply increase in $CD4^+$T-cell count in response to antiretroviral drug. Most of patients had opportunistic infection before receiving HAART and majority of patients with opportunistic infection had already received prophylaxis drug for OI before they took ART. Therefore, it caused lower the occurrence of opportunistic infections.

The limitation of our study are small sample size .As it is retrospective study, it has some extent of weakness and some valuable clinical data might loss .Data were not collected based on randomization method due to not sufficient clinical records Therefore, our study have selection bias at time of data collection. There were no baseline test results of HIV RNA because of patient's financial status.

Majority of patients could not test $CD4^+$ T-cell count at every 3 months of follow-up.

During treatment with NVP based regimen, nine patients (9.8%) developed drug resistance to NVP (confirmed by viral genotype testing) and no case was reported in boosted PI based regimen. With reference to drug resistance, Chaix et al (1999) study presented that 4%of patients had drug resistance in NNRTI and 3% in PI.Little et al (2001) study reported that rate of drug resistance in newly infected patients, were 7.1% in NNRTI and 8.2%in PI. These studies were comparable to our study. But, the finding in boosted PI based regimen was different, compare to these two studies.

CHAPTER VII
CONCLUSION

More than 10% of body weight change from baseline in patients with NVP based regimen and boosted PI based regimen groups were 54.2% and 53.3%, respectively, at 2 years of treatment time scale. We found no difference in percentage of median body weight changes between NVP based regimen and boosted based regimen followed by NVP based regimen groups.

The immunological response rate at 2 years of therapy ($CD4^+$T-celll count $>200x10^6$cells/ul) was 55.4% and 85.4 % in NVP and boosted PI based groups respectively. The outcome of NVP based regimen and boosted PI based regimen followed by NVP based regimen group, in term of immunological response, were similar. Our study showed that NVP based regimen and boosted PI based regimen followed by NVP based regimen caused significant and sustained increase in $CD4^+$ T-cell count in advance HIV patients.

The virological success rate could not figure out due to lack of baseline pVL in our study. However, the outcome of virologic response in boosted PI based regimen was satisfactory. Majority of patients (86.1%) had un-detectable level of pVL in boosted PI group within median 9.5 months with range of 6.5-12 months. Only two patients did pVL investigation, one achieved viral load undetectable level and other one had pVL>400 copies/l in NVP group. A large scale randomized controlled clinical trail in a group of patient with advance HIV infection is needed to assess the virologic success rate.

During treatment with NVP based regimen, drug resistance to NVP occurred in 9 patients whilst no patient had drug resistance to boosted PI based

regimen. Therefore, boosted PI based regimen is least likely to develop drug resistance, compare to NVP based regimen.

In summary, our study found that both 2NRTI+NVP based regimen and, 2NRTI+boosted PI (IDV/RTV) based regimen followed by NVP based regimen, were effective in increment of body weight, $CD4^+$ T-cell count in advance HIV patients for the follow up 2 years time frame.

Finally, we recommended that a large scale randomized, prospective, controlled clinical trail in a group of patients with advance HIV infection is needed in order to assess the virologic and immunologic efficacy of NVP based regimen and boosted PI based regimen followed by NVP based regimen.

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APPENDIX

APPENDIX A

TREATMENT FAILURE

Treatment failure is defined by the DHHS guideline as virologic, immunologic or clinical by the following criteria;

Virologic failure

VL> 400 c/ml at 24 weeks
VL> 50 c/ml at 48 weeks
VL rebound to .400c/ml after viral suppression

Note: Blips, defined as single level to 50 to 1000 c/ml, are not considered failure, but levels that are higher or occur more frequently are. There is no consensus on the management of persistent low level viremia(1000 to 5000 c/ml) in terms of implication for changing therapy.

Immunological failure

Failure of CD4 count to increase by >25 to50/mm^3

Note: Average increase with virologic suppression is an increase of about 150/mm^3

Clinical failure

Occurrence or recurrence of an HIV related event after >3 month therapy

Note: Must exclude the immune reconstitution syndrome.

APPENDIX B

CLINICAL DATA COLLECTION FORM

Date …….. H.N…….. Case#.....

Part 1. General information

1. Age……

2. Gender

F□ M□

3. Marital status

1. Married□ 2. Separated □ 3. Single□ 4.Widow□
5. Divorce□

4. Occupation

Specify……

5. Address

1. Chonburi□ 2. other (specify)

Part 2. Past medical history

6. Anti HIV positive since……

7. Starting Date of ART

…….

8. OI prior to ART initiation

1Yes□ 2. no□ 9. unknown□

OI	when	treatment	outcome
1……			
2……..			
3……..			
4……..			
5……			
6……			
7……			

9. History of chronic illness

1. Yes□ 2. No□ 9. Unknown□

If yes

1. Hypertension yes□ no□
2. Diabetes yes□ no□
3. Renal diseases yes□ no□
4. Liver disease yes □ no□
5. Drug allergy yes□ no□
6. Hepatitis B yes□ no□
7. Hepatitis C yes□ no□

Part 3. Present medical history

SYMPTOMS	**At time of Enrollment**	**1mo**	**2mo**	**3mo**	**4mo**	**5mo**	**6mo**	**9mo**	**12 mo**
Fever									
Cough									
Weakness									
Loss of Appetite									
Diarrhea									
Skin Rash									
Loin/groin pain									
Dyspnoea									
Nausea									
SIGNS									
Temperature									
Body weight									
Blood pressure									
Lymphadenopathy									
Anemia									
Jaundice									
Oral thrush/ Oral hairy leucoplakia									
Organomegaly									
Skin lesion									

Part 3. Present medical history(cont.)

SYMPTOMS	15mo	18mo	21mo	24mo	27mo	30mo	33mo	36mo
Fever								
Cough								
Weakness								
Loss of Appetite								
Diarrhea								
Skin Rash								
Loin/groin pain								
Dyspnoea								
Nausea								
SIGNS								
Temperature								
Body weight								
Blood pressure								
Lymphadenopathy								
Anemia								
Jaundice								
Oral thrush/ Oral hairy leucoplakia								
Organomegaly								
Skin lesion								

Part 4. Antiretroviral treatment

NVP based regimen

Regimen	Duration	Change	Cause to change
1.d4T, 3TC,NVP			
2.AZT, 3TC,NVP			
3.ddI, 3TC,NVP			

IDV/RTV based regimen

Regimen	Duration	Change	Cause to change
1.d4T, 3TC,IDV/RTV			
2.AZT, 3TC,IDV/RTV			
3.ddI, 3TC,IDV/RTV			

Regimen	Duration	Change	Cause to change

Part 5. Outcome of treatment

	Yes/No
Weight gain	
Viral load<50c/ul at 24 wks	
CD4 count increase >50 cell/ml at 16 wks	
Treatment failure	
Death	

Part 6. Adverse effect from HAART

ADR	drug	duration	drug change
1……			
2……			
3……			
4……			
5……			

Part 7. Compliance ……%

Part 8.CD4^{+} count ,CD8^{+} count investigation

	baseline	follow up					remark
	month 0	6 mo ±3	12mo ±3	18mo ± 3	24mo ±3	30mo ±3	36mo ± 3	
CD4 (cell/μL)%								
CD8 (cell/ul)%								

Part 9. Viral load investigation

	baseline	1 year±6months	2 years±6months	3 years ±6months	remark
viral load					
(copies/ul)					

Part 10. Laboratory investigation

	Month 0	6 mo±3	12mo±3	18mo±3	24mo±3	30mo±3	36mo±3
Hct							
Hemoglobin							
WBC							
neutrophil%							
Lymphocyte%							
eosinophil%							
monocyte							
Platelets							
BUN							
Creatinine							
Uric Acid							
Total Bilirubin							
conjugate bilirubin							
alkaline phosphate							
AST							
ALT							
FBS							
Total cholesterol							
Triglyceride							
HDL							
LDL							
Urine rbc/wbc							
Urine crystal							
Urine cast							

BIOGRAPHY

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