# INCIDENCE AND PREDICTORS OF TOXICITY AMONG AIDS PATIENTS TREATED WITH NEVIRAPINE BASED REGIMEN AT BAMRASNARADURA INSTITUTE, NONTHABURI, THAILAND

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## ABSTRACT

Nevirapine-based regimens are commonly and widely used for treating HIV/AIDS-infected patients in resource-limited countries due to their affordability. Toxicity monitoring becomes more important as more people have access to it. Previous studies indicated that gender, CD4 count, ART status, BMI, concurrent medications, etc. were predictive of nevirapine toxicity. The purpose of this study was to determine the incidence of toxicity among Thai HIV/AIDS patients treated with nevirapine-based regimen and its predictors.

A total of 206 adult HIV/AIDS patients, of whom 105 (51%) were male and 101(49%), female; with a median age (IQR) at the start of the nevirapine-based regimen of 33 years (range 29-38 years), treated with the regimen during the period January 2004 to December 2005, were included in the study. It was found that, incidence of toxicity from nevirapine-based regimen at Bamrasnaradura Institute was 1.09/100 person-months. The median time to onset of toxicity was 4 weeks-- 2.57 weeks for skin toxicity and 12.43 weeks for hepatic toxicity.

There were statistically significant associations between history of drug allergy and development of toxicity (24.1 % vs 6.2%, p-value=0.006) and hepatic toxicity (37.5% vs 6.2%, p-value=0.016). Similarly, a statistically significant association was found between, sulfa drug allergy and development of toxicity from treatment with a nevirapine-based regimen (17.2% vs 4.0%, p-value=0.015). Concerning use of concurrent medication, a statistically significant association was found between concurrent treatment with anti-TB medication and development of hepatic toxicity (85.7% vs 22.0%, p-value=0.001).

It is important to closely monitor liver function tests for HIV/AIDS patients concurrently treated with anti-TB medication and those with a history of drug allergy especially to sulfa drugs, to provide prompt treatment in case of the development of toxicity from a nevirapine based regimen.

KEY WORDS: INCIDENCE/PREDICTORS/NEVIRAPINE/TOXICITY/ALLERGY

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| ABBREVIATION | TERM |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| ART | Antiretroviral Therapy |
| ARV | Antiretroviral drug |
| AST (SGOT) | Aspartate aminotransferase |
| ALT (SGPT) | Alanine aminotransferase |
| AZT | Zidovudine |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CCM | Cryptococcal meningitis |
| CDC | Centre for diseases control and prevention |
| Cr | Creatinine |
| CD4 | Cluster differentiation 4 |
| d4T | Stavudine |
| EFV | Efavirenz |
| GPO-vir | Trade name for a triple combination of anti-viral drugs (d4T, 3TC, NVP) |
| HIV | Human immunodeficiency virus |
| HAART | Highly active anti-retroviral therapy |
| IAS-USA | International AIDS Society-United State of America |
| IDV | Indinavir |
| IQR | Inter-quartile range |
| IVDU | Intravenous Drug User |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
| NRTI | Nucleoside reverse transcriptase Inhibitor |
| NVP | Nevirapine |
| RTV | Ritonavir |
| WBC | White blood cells |
| WHO | World Health Organization |

# CHAPTER I
# INTRODUCTION

Highly active antiretroviral therapy (HAART) has been widely used for the treatment of human immunodeficiency virus (HIV) infected patients with successful immune restoration and reductions in morbidity and mortality. However, access to antiretroviral therapy for HIV-infected patients in resource-limited countries is still a major obstacle. HIV-infected patients in these areas often presented with advanced HIV disease. Nevirapine was the first NNRTI to be approved by the Federal Drug Administration of United States for use in the combination therapy of HIV-1 infection in 1996.It has been approved for use in children of 2 months or older, and following the publication of the HIVNET 012 study in Uganda has been widely used as single-dose prophylaxis for prevention of mother-to-child transmission (MTCT) in resource-poor settings. NVP-based HAART has been widely used in the resource-limited countries because of its efficacy, relatively low cost, and availability. Additionally, NVP is part of two of the four World Health Organization- recommended generic combinations for the 3 × 5 program in resource-limited countries. (UNAIDS, Scaling up ARVs, 2003)

However, this useful life-prolonging drug is not without its limitations and toxicites. Major toxicities are life threatening cutaneous reactions and hepatotoxicity, usually during the initial 8 weeks of treatment. There are symptoms of hypersensitivity reactions like, fever, rash, arthralgia, or myalgias. Rash is seen in about 17%. It is usually maculopapular and erythematous with or without pruritus and is located on the trunk, face, and extremities. It was also associated with Steven Johnson syndrome and Toxic Epidermal Necrolysis. .Hepatotoxicity usually occurs in the first six weeks may be accompanied by drug rash, eosinophilia and systemic symptoms (DRESS). The major risk is a baseline CD4 count ≥ 250/mm³ in women; the rate of severe hepatotoxicity in this category is 11% compared to 0.9% in women with lower CD4 counts at baseline. Men also have increased risk with a CD4 count ≥ 400/mm³, but the rates are lower. Nevirapine recipients may also develop hepatotoxicity later in the course of treatment, a form of hepatitis that is more benign and similar to hepatitis seen with other anti-HIV

drugs. This hepatitis is characterized by an elevation in transaminases levels, it is usually asymptomatic, the rate is about 15% and is more frequent in those with chronic HBV of HCV.

In the global march to fight against HIV/AIDS, the importance of access to therapy for all people with AIDS, has been more and more emphasized, especially in the resource poor countries with resource limitation, where the need for low cost highly efficacious drug, is very urgent. Striding forward to WHO goal of providing 3 million people in the developing world with ARV therapy by the end of 2005 (WHO, the World Health Report, 2004) increasing number of people living with AIDS will have access to ARV therapy. However, in the developing countries, clinical research infrastructure is limited and we have to rely on current information of drug toxicities based from the findings of developed countries. The limited infrastructure for therapeutic monitoring in developing countries, make understanding of toxicities emerging from ARV therapies, very important. In Thailand, Government Pharmaceutical Organizations (GPO) has produced new formulation of ARV , a fixed dose combination of stavudine, lamivudine, and nevirapine (GPO-vir) as part of National Access to ARV for people living with AIDS, to accelerate the service extension to all medically eligible HIV/AIDS patients, as many AIDS patients in Thailand have economic limitation to access ARV. ( Thailand, Department of disease control, 2004). So, in Thailand , many more informations , are still needed to shed light on extent of toxicities emerging from the treatment with nevirapine based regimen and its predictors .

# CHAPTER II
# OBJECTIVES

**General objectives**

1. To determine the incidence of toxicities emerging from treatment with nevirapine based regimen.
2. To identify the predisposing factors associated with the emergence of toxicities from treatment with nevirapine based regimen.

**Specific objectives**

1. To describe the skin toxicity emerging from treatment with nevirapine based regimen.
2. To describe the hepatotoxicity emerging from treatment with nevirapine based regimen.

# CHAPTER III
# LITERATURE REVIEW

## 1. Global challenge to fight against HIV/AIDS

The most urgent public health concern for today is to fight against HIV/AIDS. Having claimed the lives of more than 20 million people in the world, an estimated 34- 46 million people are now currently infected with this deadly virus. As HIV-1 infection has turned into a chronic disease, more antiretroviral drugs will be needed in more patients for longer periods. (Carr et al, 2000).So far, in the developing countries, treatment has been the most neglected element and almost six million people in these countries will die in the future if they do not receive treatment. But only about 400, 000 of them were receiving it in 2003. (WHO, World Health Report, 2004). In Asia, Indonesia, Vietnam, Cambodia, Thailand and India are the five countries with the largest number of HIV infection according to the number of cases estimated by UNAIDS. (Ruxungtham et al ). In Thailand, in the year 2001, nearly 24, 000 Thai people developed acquired immunodeficiency syndrome (AIDS) and almost 7,000 have died. (Ministry of Public Health, Thailand, 2002). This situation reflects that if the HIV/AIDS problem in Thailand is not tackled early enough, it would create enormous burden to the Thai society as a whole. Despite the success in reducing new HIV infections in the recent years, it is estimated that the crisis of AIDS in Thailand will continue to grow up. (Department of Disease control, Thailand, 2004). All patients in Thailand who have contracted HIV infection will fall ill due to the disruption of the immune system during the natural course of HIV infection. The use of highly active antiretroviral therapy has dramatically decreased morbidity and mortality in patients with HIV infections. (Palella et al ). To reduce the losses of Thai people from AIDS and impact on the society, Thailand National Antiretroviral Program started in 1992 and has been continuously developed. (Department of Disease control, Thailand, 2004). The aim is to prevent HIV associated complications, to avoid the long term and short-term adverse drug reactions, to prevent HIV

transmission, to avoid HIV resistance, and to preserve HIV treatment options among the Thai populations. ( Department of Disease control, Thailand, 2004)

**2. Anti-retroviral drugs for resource limited countries.**

Over the recent years, with the urgent global concern to fight AIDS, the need for simplified, feasible, standardized, and potent ARV treatment guide-lines for the developing countries with the limited resources, have emerged. As there are limited resources in the developing countries, it is necessary that single first line anti-retroviral drugs are chosen first and a limited number of second line drugs are kept for large scale use. Those who failed both first line and second line drugs will thus be referred for individualized specialist care. Apart from cost, potential, side effect profile and potential for future treatment profile have to be taken into consideration. In the setting of limited resource, access to only a limited number of ARV drugs, a limited health service infra-structure, and the need to cover out-reach places as well, to population with high incidence of Hepatitis B and C become major concerns. All regimens consist of a dual nucleoside component and a potent third drug to complement it. But dual nucleoside drug regimen alone are no longer recommended as they do not adequately suppress HIV replication and are likely to lead to the rapid emergence of resistance. The advantage of the dual nucleoside plus non-nucleoside regimens are that the drugs are widely available at affordable cost, only reasonable pill count are needed and are still potent.

**3. HIV/AIDS in Thailand**

First case of AIDs in Thailand was reported in September 1984. Since then, many AIDS cases as well as people with HIV were reported throughout the coming years. Thailand has done a lot to fight this increasing burden. Due to a lot of work comprised in it, Thailand has succeeded only to a certain extent in coping with its HIV/AIDS epidemic. Not only Thailand has some accomplishment in HIV/AIDS prevention, but also has some progress towards National access to Ant-retroviral Program for People living with AIDS. (NAPHA). ( Department of disease control, Thailand, 2004). In Thailand with many AIDS patients having economic limitations to access ARV, treatment with a combination of three ARVs in HAART is a cost-

effective choice.( Freedberg et al). The 2001 British HIV association (BHIVA) guidelines for the treatment of HIV infected adults with ARV and the US Department of Health and Human Resources (DHHS) 2002 guidelines have recommended ARV treatment for patients with serious/ recurrent HIV related illnesses, or AIDS, and for HIV infected patients with CD4 count < 200/l regardless of HIV RNA concentrations. (British HIV association, 2001) (Henry J Kraiser Family Foundation, Guidelines for the use of ARV in HIV infected adults, 2002). The guidelines of the infectious disease association of Thailand 2001 for HIV infected patients concurred with one of the ARVs regimen recommended by BHIVA- nevirapine 200mg twice a day in combination with two NRTIs for treatment of AIDS.

**4.GPO vir (d4T+3TC+NVP) for HIV/AIDS patients in Thailand** .

In April, 2202, the Government Pharmaceutical organization (GPO) began producing a generic version of three ant-HIV drugs, 30-40 mg Stavudine (d4T), 150 mg Lamivudine (3TC), and 200 mg nevirapine- mixed together into one pill called GPO vir. Treatment requires only two pills a day, each of which costs only 50 cents. It has been available on the market since March 2002. (Science, special reprint, 2004). To meet the urgent need to treat the increasing number of AIDS cases, GPO Thailand has been granted special privilege not needing approval by Thai FDA for this type of new formula-according to Thai FDA formulations, this new drug has to go through various phases of clinical trial before becoming available at the market. (Anekthananon et al,2004). With current limited knowledge on the extent of toxicities of nevirapine in Thailand, studies need to be conducted to explore further the depth of toxicities of nevirapine, an essential NNRTI backbone of GPO vir.

**5.Toxicities of Antiretroviral drugs**

A standard of care therapy, Highly Active Anti-retroviral therapy (HAART) , has led to substantial reduction, in mortality and morbidity, and knowledge on toxicities of anti-retroviral drugs has become, very crucial indeed. For clinical benefit to be preserved, HAART will need to be given indefinite, accelerated

licensing of many ARVs to meet the need combat HIV/AIDS epidemic, all these have led to use of ARVs with insufficient knowledge about extent of their toxicities and their predictors. (Finzi et al, 1999) (Wong et al, 1997). With increasing number of ARVs and many possible combinations, switching to other possible combinations of second line ARV regimens, - a crucial part in patient's monitoring, has become increasingly dependent on the knowledge of toxicities of ARVs.( Carr and Cooper et al, 2000). Toxicities of ARVs can range from mild toxicities to more severe and even life threatening toxicities like, mitochondrial toxicity, hypersensitivity, lipodystrophy syndrome, etc. Since toxicities from ARVs can occur at any time after initiation, in the form of a number of short term or long term toxicities during treatment of varying severity, close clinical monitoring is essential. Sometimes diagnosis of ARVs toxicities can be difficult if patients are taking many concomitant drugs at the same time. Awareness of frequencies of and risk factors for the various ARVs drug related toxicities are important for development of effective toxicity management strategies and clinical screening of drug toxicities throughout the treatment course which is more or less indefinite.(Ho et al, 2003). However, a number of factors like, underlying diseases like chronic liver disease, neuropathy, treatment on prolong therapy, etc may complicate monitoring toxicity.

**6. Nonnucleotide Reverse transcriptase Inhibitors. (NNRTIs)**

NNRTIs are a group of highly specific inhibitors that bind to a hydrophobic pocket near the polymerase catalytic site of reverse transcriptase.( Wu et al, 1991 )( Ding J et al,1995). Their binding to HIV reverse transcriptase lower the catalytic rate of polymerization without effecting nucleotide binding or nucleotide induced conformational change. ( Spence et al, 1995). Binding of NNRTIs to HIV-1 reverse transcriptase had little effect on interactions with dideoxynucleotide inhibitors.( Rittinger et al,1995) (Gu et al, 1995). So, NNRTIs are non- competitive inhibitors of reverse transcriptase. As some NRTIs and NNRTIs combination have additive or synergistic effects, NNRTIs have now assumed an important role in treatment of HIV/AIDS ( Gu et al, 1995). Three NNRTIs are currently available, nevirapine,

delaviridine, efervirenz. They are a chemically diverse group of drugs. The main toxicities of NNRTIs are, rash, hypersensitivity, hepatotoxicity and mood alterations.

**7. Nevirapine and its pharmakokinetics**

Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds. They are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV-1 in drug combination regimens with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zidovudine (ZDV), and the protease inhibitors indinavir and saquinavir. Nevirapine is readily absorbed after oral administration.

With oral bioavalability more than 90%, its peak plasma concentration are attained by 4 hours following a single oral dose and its half life is 25-30 hours. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Nevirapine readily crosses the placenta and is also found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid were 45% of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein. Liver cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Its toxicity range from mild rash to severe Steven Johnson

Syndrome or Toxic Epidermal Necrolysis. Symptomatic hepatitis including fatal hepatic failure may also occur.( Boehringer Ingelheim Pharmaceuticals, 2005)

**8. Toxicity profile of nevirapine**

**Hypersensitivity reactions. (Skin toxicity)**

Rash is a functional class related adverse effect of NNRTIs and is the major clinical toxicity of nevirapine. Drug hypersensitivity typically manifests as an erythematous, maculopapular, pruritic, confluent rash with or without fever. The rash is most prominent on the body, arms, usually beginning after 1-3 weeks of therapy. Steven Johnson syndrome and Toxic Epidermal Necrolysis develop in less than 0.55 of patients. Patients with prior hypersensitivity exposure (including to a related drug) can develop reactivations within hours of the first dose. Diagnosis of hypersensitivity is mostly based on clinical criteria. Pathogenesis of hypersensitivity reaction, due to nevirapine, is largely unknown. But it is postulated that, the degree of immunodeficiency, or, immune activation, altered drug metabolism associated with glutathione deficiency or slow acetylating phenotype and co existing infection with cytomegalovirus of Epstein Barr virus, may contribute towards it. (Gu et al, 1995). Approximately, 50 % of ARVs hypersensitivity resolves spontaneously despite continuation of nevirapine based therapy. Rash, emerging from nevirapine based therapy, may range from mild, moderate reaction to severe and life threatening reactions. NNRTIs related rash are more common with nevirapine. But most patients with mild or moderate rash can continue nevirapine therapy under close supervision. The recommended 14 days lead in dose of 200 mg/day nevirapine prior to escalating to the maintainance dose of 200 mg twice daily has been shown to reduce frequency of rash. Rash may be associated with constitutional findings such as fever, blistering, oral lesions, facial oedema, myalgia/ arthralgia, significant elevations in hepatic transaminases levels or general malaise.

**Hepatotoxicity**

Rare cases of severe or fatal hepatitis, including fulminant hepatitis, have been observed among patients taking NNRTIs. (Carpenter , 2000) (Boehringer Ingelheim International, 2002) (Boehringer Ingelheim International,2000 (Clarke et al, 2000).In

clinical trials, the risk of clinical hepatic events at one year was approximately two fold higher in patients receiving nevirapine- based therapy than those receiving placebo.( Boehringer Ingelheim International,2002) .The risk of hepatic event at one year was less than 2% in nevirapine treated patients who were hepatitis B or C negative. During the first few weeks of therapy, patients treated with nevirapine have elevated alinine aminotransferases (AST/ALT). Factors which are known to be associated with hepatic events include increased baseline AST/ALT levels; coinfection with hepatitis B or C and CD cell count> 350 cells/mm3. Severe liver diseases occur most frequently during the first 12-16 weeks of nevirapine therapy. (Ho et al, 2003)

# CHAPTER IV
# MATERIALS AND METHODS

**Study site**

This study was conducted at the Bamrasnaradura Institute, Nonthaburi.

**Study period**

The data collection was performed during November to 2005 to January 2006. Data were extracted from medical records of HIV/AIDS patients who were treated with nevirapine based regimen from January 2004 to December 2005. Data analysis and interpretation were done at the Faculty of Tropical Medicine ,Mahidol University.

**Study design**

It was a retrospective cohort study.

**Study subjects**

All HIV/AIDS patients who were treated with nevirapine based regimen during January 2004 and December 2005.

**Inclusion criteria**

All medical records of HIV/AIDS patients who were treated with nevirapine based regimen during this period .

**Exclusion criteria**

All patients who stopped treatment without any medical reason (such as emergence of toxicities, failure to respond; etc.) and who were lost to follow up before six months of continuous treatment.

**Outcome of the study**

**Primary outcome**

1. Overall nevirapine toxicities - nevirapine toxicity is related to the inability to tolerate the side-effects of nevirapine and to the significant organ dysfunction (ie skin toxicity and hepatotoxicity) However, in this study, except those who developed toxicity within 6 months, the rest were presumed to have no toxicity at six months after treatment with nevirapine based HAAART. In grading the toxicities emerging from the treatment with nevirapine based regimen, the following guidelines were used.

   Grade1 (Mild) – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

   Grade 2 (Moderate) - Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

   Grade 3 (Severe) - Marked limitation in activity, some assistance usually required; significant medical intervention/therapy required, hospitalization possible.

   Grade 4: (Life threatening) - Extreme limitation in activity, significant assistance required; significant medical intervention / therapy required, hospitalization or hospice care probable. (AIDS clinical trial group, 2004)
2. Time to develop toxicities after treated with nevirapine based regimen

**Secondary outcome**

(1) Skin Toxicity - Medical record of clinically apparent skin reactions including diffuse erythematous or maculopapular rash, urticarial rash with serum sickness-like reaction, Stevens-Johnson Syndrome, and toxic epidermal necrolysis emerging within six months after initiation of nevirapine based regimen.

**Grading of skin toxicity**

Grade 1. Cutaneous reaction – Localized macular rash

Grade 2. Diffuse macular, maculopapular, or mobiliform rash or target lesion.

Grade3. Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site.

Grade 4. Extensive or generalized bullous lesions or Stevens-Johnson syndrome or ulceration of mucous membrane involving two or more distinct mucosal sites or Toxic epidermal necrolysis (TEN) (AIDS clinical trial group, 2004)

(2) Hepatotoxicity - Signs and symptoms consistent with clinical hepatitis such as anorexia, malaise, jaundice, nausea/vomiting, hepatomegaly, and hepatic tenderness concomitant with abnormal liver chemistry tests and without any other potential explanation, emerging within six months after initiation of nevirapine based regimen.

**Grading of Hepatotoxicity**.

Grade 1. Elevated serum transaminases level 1.25- 2.5 times the upper limit of normal .

Grade 2. Elevated serum transaminases level 2.6-5 times the upper limit of normal .

Grade 3. Elevated serum transaminases level of 5.1 – 10 times the upper limit of the normal.

Grade 4. Elevated serum transaminases level >10 times the upper limit of normal . (Division of AIDs table for grading the severity of adult and pediatric adverse events: December, 2004). Here we grade hepatotoxicity in terms of fold –change from upper limit of normal range regarding lab inference at Bamarasnaradura Institute. ( AIDS clinical trial group,2004)

**Sampling technique**

Samples were randomly collected by proportionate random sampling from all medical records of HIV/AIDS patients who met the inclusion criteria and were treated with the nevirapine based regimen (d4T/3TC/NVP) from January 2004 to December 2005. According to the hospital data record, there were about 3254 patients treated in

this period, 2378 in 2004 and 876 in 2005 .Using computer generated numbers, 72 % of the sample was randomly sampled from 2004 and 28% from 2005. As the source data for patients treated during 2004 and 2005 were mixed with the patients treated with nevirapine based regimen before this time and those being treated with efarvirenz based regimen, a total of 843 medical records were requested and reviewed , before the required sample was completed.

**Sample size**

Sample size was estimated using the following formula.

Sample size = $Z^2\ \alpha/2\ P\ (1-P)/\ d^2$

= $(1.96)^2\ (0.12)\ (1-0.12)/\ (0.05)^2$

= 162

Where,

P= Population proportion = Incidence of nevirapine toxicicity in Thailand = 0.12 (according to incidence of nevirapine toxicity 12 % ) (Anekthananon et al, 2004)

d=Maximum allowable error= 0.05

Z=1.96

So the minimal required sample size estimated was 162.

**Data collection**

Data collection was started from November 2005 to January 2006. Data from the medical records of HIV/AIDS patients who were treated with nevirapine based regimen during January 2004 to December 2005 at the Bamrasnaradura Institute and who met the inclusion criteria were collected. Medical records were reviewed and all necessary informations on demographic data, baseline laboratory investigations, occurrence of the opportunistic infections, concurrent medications, development of the toxicities, physicians' diagnosis of skin and hepatic toxicities, improvement and all other necessary informations were recorded on the case record forms. The data were then entered in the computer data file and analyzed later .

**Data analysis**

All continuous data were analyzed for comparison of median using Mann Whitney U test. All categorical data were compared and p value < 0.05 was considered as statistically significant, using Chi square or Fisher's exact test, as was appropriate. Survival analysis was used to estimate median time to onset of toxicity after treatment with nevirapine based regimen. In calculation of age at HIV diagnosis, for some patients with only the year of HIV diagnosis available, mid-year date of first July was used, and if that date was later than the date of start of nevirapine; the latter was presumed to be date of HIV diagnosis, for calculation.

# CHAPTER V
# RESULTS

**Demographic and baseline characteristics of 206 adult HIV positive patients.**

A total of 206 patients, both ART naïve and experienced, who were treated with nevirapine based regimen from January 2004 to December 2005, at the Bamrasnaradura Institute were included in the study. The median age of the patients at the start of the nevirapine based regimen, was 33 years (IQR, 29-38 years ). Among them, 51% were male and 49%, female - among whom only 7.9% were pregnant. Most of them, 45.6 % were single, 40.8% were married and only the rest 13.6% were, divorced, or separated from partners. Most of the patients 49.5% were from Bangkok, 20.9% from Nonthaburi itself, 18 % from central part and the rest from Northern, Northeastern and other places like Samut Sakorn, Chonburi Provinces, etc,. Regarding their occupations, majority (47.1%) were laborers, 19.4% were unemployed, 17.5% were business men, 1.9% came from each of agricultural workers and government employee and the rest were people with various backgrounds, like teachers, students, monks, health staffs, etc,. When their possible risks of getting infected with HIV were explored further, it was found that majority 93.2% were heterosexuals, 6.3% gave the history of injecting drug abuse and only one patient was a MSM.

The baseline characteristics of the patients were presented in the table 2. Their median age at HIV diagnosis was 31 years, with the IQR of 26 years to 36 years.
The median body weight at baseline was 54 kg in the IQR of 47kg to 60 kg. Majority, 90.8% were ART naïve and only the small number of 9.2% were ART experienced. Only 4.9 % of the patients had the history of alcohol abuse. When categorized according to the 1993 revised classification of HIV infection, 1.94 % of the patients were in the category A, 38.8 % in category B and majority, 59.2% were found in the category C at the start of nevirapine based regimen.

**Table 1: Demographic characteristics of 206 adult HIV positive patients starting nevirapine based regimen included in the study**

| Characteristics | Median (IQR) | Total (n=206) | % |
|---|---|---|---|
| Age (Years) | 33(29-38) | | |
| Gender | | | |
| Male | | 105 | 51.0 |
| Female | | 101 | 49.0 |
| Marital status | | | |
| Single | | 94 | 45.6 |
| Married | | 84 | 40.8 |
| Widow | | 19 | 9.2 |
| Divorced/Separated | | 9 | 4.4 |
| Pregnancy (n=101) | | | |
| Yes | | 8 | 7.9 |
| No | | 93 | 92.1 |
| Address | | | |
| Bangkok | | 102 | 49.5 |
| Nonthaburi | | 43 | 20.9 |
| Central | | 37 | 18.0 |
| Northeastern | | 8 | 3.9 |
| Northern | | 6 | 2.9 |
| Others | | 10 | 4.9 |
| Occupation | | | |
| Laborer | | 97 | 47.1 |
| Unemployed | | 40 | 19.4 |
| Business | | 36 | 17.5 |
| Government employee | | 4 | 1.9 |
| Agricultural worker | | 4 | 1.9 |
| Teacher | | 1 | 0.5 |
| Others | | 24 | 11.7 |
| Possible risks to get HIV infection | | | |
| MSM | | 1 | 0.5 |
| Heterosexual | | 192 | 93.2 |
| IVDU | | 13 | 6.3 |

**Table 2: Baseline characteristics of 206 adult HIV positive patients**

| Characteristics | Median (IQR) | Total (n=206) | % |
|---|---|---|---|
| Age at diagnosis of HIV infection | 31 (26-36) | | |
| ART status before nevirapine based regimen started | | | |
| Naïve | | 188 | 90.8 |
| Experienced | | 18 | 9.2 |
| Past history | | | |
| Poly -drug allergy | | 18 | 8.7 |
| Alcohol abuse | | 10 | 4.9 |
| IVDU | | 13 | 6.3 |
| Body weight at baseline(kg) | 54 (47-60) | | |
| Revised classification of HIV infection | | | |
| Category A | | 4 | 1.94 |
| A1 | | 0 | 0 |
| A2 | | 0 | 0 |
| A3 | | 4 | 1.94 |
| Category B | | 80 | 38.83 |
| B1 | | 2 | 0.9 |
| B2 | | 12 | 5.82 |
| B3 | | 66 | 32 |
| Category C | | 122 | 59.22 |
| C1 | | 0 | 0 |
| C2 | | 2 | 0.9 |
| C3 | | 120 | 58.2 |

**Previous ART regimens among experienced patients**

The experienced patients were previously treated with such ART regimens as EFV/d4T/3TC (31.57%), AZT/3TC/EFV (15.79%), NVP/d4T/3TC(10.52%), AZT/ddI (15.79%), AZT alone (10.52%) in the case of pregnant women or unknown ART regimens (15.79%).

**Table 3: Previous ARTs among experienced HIV positive patients currently treated with nevirapine based regimen**

| | Total | % |
|---|---|---|
| Experienced patients | 19 | |
| Previous ART regimens | | |
| EFV/d4T/3TC | 6 | 31.57% |
| AZT/3TC/EFV | 3 | 15.79% |
| AZT/ddI | 3 | 15.79% |
| AZT alone | 2 | 10.52% |
| NVP/d4T/3TC | 2 | 10.52% |
| Unknown | 3 | 15.79% |
| Course of treatment | | |
| Continuous with current regimen | 11 | 57.89% |
| Stopped the previous ART | 8 | 42.10% |
| Reasons of change to current regimen | | |
| Lactic acidosis | 1 | 5.26% |
| After delivery | 2 | 10.52% |
| Unknown | 16 | 84.21% |

**History of drug- allergy of 18 adult HIV positive patients treated with nevirapine based regimen.**

Among them, 8.7% (18/206) had the history of drug allergy. When the types of drugs, these patients had allergy to, were explored further, it was found that, among the 18 patients with history of drug allergy , it was found that, 66.6% had allergy to sulfa, 16.6% had allergy to rifampicin, 16.6% had allergy to ARVs(d4T & AZT), 16.6% had allergy to β lactams, 11.1% had allergy to dapsone, 11.1% had allergy to macrolides, 5.5% had allergy to quinolones, 5.5% had allergy to PZA and the rest 5.5% had allergy to metronidazole.

**Table 4: History of drug allergy among 18 adult HIV positive patients**

| | N | % |
|---|---|---|
| Overall | 18 | |
| Types of drugs | | |
| Sulfa | 12 | 66.6 |
| Rifampicin | 3 | 16.6 |
| ARV | 3 | 16.6 |
| β lactams | 3 | 16.6 |
| Dapsone | 2 | 11.1 |
| Macrolides | 2 | 11.1 |
| Quinolones | 1 | 5.5 |
| PZA | 1 | 5.5 |
| Metronidazole | 1 | 5.5 |
| Number of drugs | | |
| 1 | 14 | 77.7 |
| 2 | 1 | 5.5 |
| 3 | 1 | 5.5 |
| 4 | 1 | 5.5 |
| 5 | 1 | 5.5 |

**Baseline laboratory markers of the 206 adult HIV positive patients.**

Of 206 patients, the median CD4 T-cell at the start of the nevirapine based regimen was 40 cells/$mm^3$ with the IQR of 14 to 111cells/$mm^3$ (90.8% had CD4<200/$mm^3$ ). The median HIV-1 RNA (copies/ML), available for 82 patients was, 214,500 copies/ML with the IQR of 31,275 to 589,250 copies/ML (3.9% had viral load <50). Most of the median hematological values were found within the normal limits though their ranges were wide. The median value of hemoglobin (g/dl), available for 156 patients was 11.75 g/dl, with the IQR of 9.9 to 13.1g/dl (29.6% had hemoglobin<11g/dl). The median hematocrit (%) was 35 %, in the IQR of 30-39 % .The median lymphocyte count was closed to the lower limit of the normal range- available for 153 patients, 27 % with the IQR of 19-37 %.(75.7% had lymphocyte count>20%).

Most biochemical tests were done for patients as necessary in the course of treatment, but only a few results were available at baseline. Although most of the median biochemical values were found within the normal limits, median value of plasma lactate (mmol/L), available for only 3 patients, was higher than the upper limit of the normal- 4.1 mmol/L with the IQR of 1.1 to 9.5 mmol/L. The median value of, bilirubin (mg/dl), available for 70 patients, was 0.52 mg/dl with the range of 0.4 – 0.63 mg/dl (67.5% had total bilirubin >2mg/dl); alkaline phosphatase, available for 62 patients was 98.5 U/L with the IQR of 67-146 U/L (77.2% had alkaline phosphatase >150 U/L); aspartate aminotransferase, available for 146 patients, was 30 U/L with the IQR of 23-48 U/L(33.0% had AST>120U/L); and alanine amino transferase , available for 111 patients, was 27 U/L with the IQR of 17-44 U/L(47.6% had ALT>120U/L)

**Table 5: Baseline laboratory parameters in 206 adult HIV positive patients**

| Hematological findings | n | Median (IQR) |
|---|---|---|
| **Hematological values** | | |
| Hemoglobin (g/dl) | 156 | 11.75(9.9-13.1) |
| Hematocrit (%) | 161 | 35(30-39) |
| Platelet count ($10^9$/l) | 158 | 253(201-333) |
| WBC count($10^9$/l) | 160 | 5.03(3.8-6.8) |
| Neutrophil count % | 158 | 55(46-68) |
| Lymphocyte count % | 153 | 27(19-37) |
| **Virological and immunological values** | | |
| CD4 cell count(cells/$mm^3$) | 206 | 40(14-111) |
| CD4% | 196 | 4(1-8) |
| HIV-1 RNA (copies/ML) | 82 | 214,500(31,275-589,250) |
| HIV-1 RNA ($log_{10}$ copies/ML) | 82 | 5.33(4.5-5.7) |
| **Biochemical findings** | | |
| Bilirubin(mg/dl) | 70 | 0.52(.0.4-0.63) |
| Alkaline phosphatase(U/L) | 62 | 98.5(67-146) |
| AST(U/L) | 146 | 30.0(23-48) |
| ALT(U/L) | 111 | 27.0(17-44) |
| Urea (mg/dl) | 21 | 10(5.9-12) |
| Creatinine (mg/dl) | 36 | 0.79(0.6-0.9) |
| Lactate (mmol/L) | 3 | 4.1(1.1-9.5) |

**Occurrence of opportunistic infections among 206 adult HIV positive patients before and during treatment with nevirapine based regimen.**

It was found that most of the patients have one or more opportunistic infections at the start of the nevirapine based regimen and only very few patients developed opportunistic infections, in the course of the treatment. Majority of the patients, 34.5% (71/206) had tuberculosis at the start of the nevirapine based regimen, 17.0% (35/206) had oral candidiasis, 9.2 % (19/206) had pneumocystic carinii pneumonia, 5.3% (11/206) had cryptococcal meningitis, 4.8% (10/206) had herpes zoster, and those with esophageal candidiasis and cytomeglo virus infections was found to be, only 3.4 % (7/206) each. The opportunistic infections that developed during the course of the treatment, were tuberculosis, pneumocystic carinii pneumonia, herpes zoster and cytomeglo virus infections; and the number of patients, was found to be only one (0.5%) each. The durations from start of the nevirapine based regimen were found to be; 2 weeks, for development of tuberculosis; 11 weeks, for pneumocystic carinii pneumonia; 8 weeks, for herpes zoster; and 13 weeks, for cytomeglovirus infections. As a nature of retrospective study, for those patients who developed opportunistic infections after the initiation of nevirapine based regimen, it could not be ascertained whether it was due to immune reconstitution syndrome, due to unavailability of their immune status, like CD4 count at the time of occurrence.

**Table 6: Occurrence of opportunistic infections among 206 adult HIV positive patients before and during treatment with nevirapine based regimen**

| Opportunistic infections | No. of patients | |
|---|---|---|
| | Before treatment (n=206) | After treatment (n=206) |
| Tuberculosis | 71 | 1 |
| Cryptococcal meningitis | 11 | 0 |
| PCP | 19 | 1 |
| Herpes zoster | 10 | 1 |
| Oral candidiasis | 35 | 0 |
| Oesophageal candidiasis | 7 | 0 |
| CMV | 7 | 1 |

**Development of toxicites among 206 adult HIV positive patients from treatment with nevirapine based regimen.**

It was found that, 14.1% of patients developed toxicities from treatment with nevirapine based regimen and among them, 10.2 % developed skin toxicity and only 3.9% developed hepatic toxicity. Among those who developed skin toxicity, majority, 52.4% developed grade 2 skin rash, followed by; 23.8%- grade 3 skin rash; 14.3 % - grade 1 skin rash; and only 9.5% developed grade 4 skin rash- Steven Johnson Syndrome. Among those who developed hepatic toxicity, majority, 37.5% were found to develop, grade 2 hepatic toxicity, those who developed grade 3 and 4 hepatic toxicity were 25% each and only 12.5% developed grade 1 hepatic toxicity. When explored further into the median time to onset of toxicities, it was 4 weeks with the IQR of 1.79-16.7 weeks- 2.57 weeks with the IQR of 1.79-8.4 weeks for skin toxicity and 12.43 weeks with the IQR of 2.57-21.2 weeks for hepatic toxicity, from the start of the nevirapine based regimen.

**Table 7: Development of toxicities among 206 adult HIV patients from treatment with nevirapine based regimen**

| Toxicity | No.(%) | | |
|---|---|---|---|
| | Total | Skin toxicity | Hepatic toxicity |
| | 29(14.1%) | 21(10.2%) | 8(3.9%) |
| Toxicity grades | | | |
| Grade 1 | 4(13.8%) | 3(14.3%) | 1(12.5%) |
| Grade 2 | 14(48.2%) | 11(52.4%) | 3(37.5%) |
| Grade 3 | 7(24.1%) | 5(23.8%) | 2(25.0%) |
| Grade 4 | 4(13.8%) | 2(9.5%) | 2(25.0%) |
| Time to onset of toxicity since | | | |
| Start of nevirapine based regimen, weeks, median (IQR) | 4(1.79-16.7) | 2.57(1.79-8.4) | 12.43(2.57-21.2) |

**Table 8: Outcome and treatment intervention among 29 HIV positive patients who developed toxicities from treatment with nevirapine based regimen.**

| Toxicity | N | N(%) | | | |
|---|---|---|---|---|---|
| | Total | Grade1 | Grade 2 | Grade 3 | Grade 4 |
| Overall | 29 | 4(13.9%) | 14(48.2%) | 7(24.1%) | 4(13.8%) |
| Skin toxicity | 21 | | | | |
| Improved | | 3(14.3%) | 11(52.4%) | 5(23.8%) | 2(9.5%) |
| Resolved | | - | - | - | - |
| Death | | - | - | - | - |
| Resistance | | - | - | - | - |
| Intervention | | | | | |
| Stopped nevirapine and switched to other regimen | | 1(4.76%) | 10(47.6%) | 3(14.2%) | 2(9.5%) |
| Stopped nevirapine and rechallanged later | | - | - | 1(4.7%) | - |
| Continued nevirapine | | 2(9.5%) | 1(4.7%) | 1(4.7%) | - |
| Hepatic toxicity | 8 | | | | |
| Improved | | 1(12.5%) | 3(37.5%) | 2(25.0%) | 2(25.0%) |
| Resolved | | - | - | - | - |
| Death | | - | - | - | - |
| Resistance | | - | - | - | - |
| Intervention | | | | | |
| Stopped nevirapine and switched to other regimen | | 1(12.5%) | 3(37.5%) | 2(25.0%) | 2(25.0%) |
| Stopped nevirapine and rechallanged later | | - | - | - | - |
| Continued nevirapine | | - | - | - | - |

**Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of toxicities.**

When demographic and baseline characteristics of the patients who developed toxicities and patients who did not develop any toxicity were compared, no statistical significant associations were found between, age at the start of nevirapine based regimen (p-value = 0.52); gender (p-value=0.93); pregnancy status (p-value=1.0); body weight (p-value=0.51); ART status (p-value=0.32); of alcohol abuse (p-value=1.0); IVDU (p-value=0.69); clinical category before treatment (p-value=0.25); treatment with concurrent medications (p-value= 0.19);occurrence of opportunistic infections (p-value=0.446) and the development of toxicities.

However, there was a statistical significant association between history of drug allergy and the development of toxicity (24.1 % vs 6.2%; p-value=0.006) (RR=3.32, 95% CI=1.65<RR<6.69). HIV positive patients with drug allergy are three times more likely to develop toxicity, from treatment with nevirapine based regimen, than those without the drug allergy.

**Table 9:Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of toxicities**

| Variables | | Develop toxicities ( n=29) | | | Not Develop toxicities (n=177) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | Median (IQR) | N | % | Median (IQR) | |
| Age, years | | 29 | | 32 (27-39) | 177 | | 33 (30-38) | 0.52* |
| Gender | Male | 15 | 51.7 | | 90 | 50.8 | | 0.93*** |
| | Female | 14 | 48.3 | | 87 | 49.2 | | |
| Pregnancy | Yes | 1 | 7.1 | | 7 | 8.0 | | 1.0*** |
| | No | 13 | 92.9 | | 80 | 92.0 | | |
| Body weight, Kg | | 29 | | 52 (44-59) | 177 | | 54 (47-60) | 0.51* |
| ART status | | | | | | | | |
| | Naïve | 25 | 86.2 | | 162 | 91.5 | | 0.32*** |
| | Experienced | 4 | 13.8 | | 15 | 8.5 | | |
| Drug allergy | Yes | 7 | 24.1 | | 11 | 6.2 | | **0.006*** |
| | No | 22 | 75.9 | | 166 | 93.8 | | |
| Alcohol abuse | Yes | 1 | 3.4 | | 9 | 5.1 | | 1.0*** |
| | No | 28 | 96.6 | | 168 | 94.9 | | |
| IVDU | Yes | 1 | 3.4 | | 12 | 6.8 | | 0.69*** |
| | No | 28 | 96.6 | | 165 | 93.2 | | |
| Clinical category before treatment | | | | | | | | |
| | A &B | 9 | 31.0 | | 75 | 42.4 | | 0.25** |
| | C | 20 | 69.0 | | 102 | 57.6 | | |
| Opportunistic infections | | | | | | | | |
| | Yes | 20 | 69.0 | | 109 | 61.6 | | 0.446* |
| | No | 9 | 31.0 | | 68 | 38.4 | | |
| Concurrent Medication | Yes | 26 | 89.7 | | 169 | 95.5 | | 0.19*** |
| | No | 3 | 10.3 | | 8 | 4.5 | | |

*-Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Baseline laboratory parameters among 206 adult HIV positive patients with respect to development of toxicities**

When the baseline laboratory parameters of these two groups were compared, no statistical significant differences were found, between median CD4 T-cell count (p-value=0.237); median HIV-1 RNA copies/ml (p-value=0.956) those who developed toxicities, and those who did not. Similarly, no statistically significant differences were found between baseline biochemical parameters of these two groups.

**Table 10: Baseline laboratory parameters of 206 adult HIV positive patients with respect to development of toxicities.**

| Variable | Dev toxicities (n=29) | | Not develop toxicities (n=177) | | P-value |
|---|---|---|---|---|---|
| | N | Median(IQR) | n | Median (IQR) | |
| CD4 cell count,cells/$mm^3$ | 29 | 60(19-121) | 177 | 38(13-113) | 0.237* |
| CD4 % | 28 | 5(2-9) | 168 | 4(1-8) | 0.251* |
| HIV RNA copies/ml | 14 | 158,450(268,25-750,000) | 68 | 214,500(400,25-527,000) | 0.956* |
| HIV-1 RNA ($log_{10}$copies/ml) | 14 | 5.13(4.4-5.8) | 68 | 5.33(4.5-5.7) | 0.956* |
| ALP, U/L | 10 | 77(64-135) | 52 | 99(67-170) | 0.433* |
| ALT, U/L | 15 | 41(19-46) | 96 | 25(17-43) | 0.192 * |
| AST, U/L | 18 | 35(23-63) | 128 | 29(23-46) | 0.462* |
| Total bilirubin, U/L | 12 | 0.52(0.4-0.6) | 58 | 0.52(0.4-0.63) | 0.938* |

*-Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of skin toxicity.**

When demographic and baseline characteristics of the patients who developed skin toxicity and patients who did not develop any toxicity were compared, no statistically significant associations were found between, age at the start of nevirapine based regimen (p-value =0.302 ); gender (p-value=0.894); pregnancy status (p-value=1.0 ); body weight (p-value=0.633); ART status (p-value=0.698); history of drug allergy (p-value=0.059); of alcohol abuse (p-value=1.0); clinical category before treatment (p-value=0.96); treatment with concurrent medications (p-value=0.097) ;occurrence of opportunistic infections (p-value=0.693) and the development of skin toxicity.

**Table 11:Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of skin toxicity**

| Variables | | Skin toxicity (n=21) | | | Not Develop toxicities (n=177) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | Median (IQR) | N | % | Median (IQR) | |
| Age, years | | 21 | | 31 (27-38) | 177 | | 33 (30-38) | 0.302* |
| Gender | Male | 11 | 52.4 | | 90 | 50.8 | | 0.894** |
| | Female | 10 | 47.6 | | 87 | 49.2 | | |
| Pregnancy | Yes | 1 | 10.0 | | 7 | 8.0 | | 1.0*** |
| | No | 9 | 90.0 | | 80 | 92.0 | | |
| Body weight, kg | | 21 | | 52 (43-62) | 177 | | 54 (47-60) | 0.633* |
| ART status | | | | | | | | |
| | Naïve | 19 | 90.5 | | 162 | 91.5 | | 0.698*** |
| | Experience | 2 | 9.5 | | 15 | 8.5 | | |
| Drug allergy | Yes | 4 | 19.0 | | 11 | 6.2 | | 0.059*** |
| | No | 17 | 81.0 | | 166 | 93.8 | | |
| Alcohol abuse | Yes | 1 | 4.8 | | 9 | 5.1 | | 1.0*** |
| | No | 20 | 95.2 | | 168 | 94.9 | | |
| IVDU | Yes | 0 | 0 | | 12 | 6.8 | | |
| | No | 21 | 100 | | 165 | 93.2 | | |
| Clinical category before treatment | | | | | | | | |
| | A&B | 9 | 42.9 | | 75 | 42.4 | | 0.96 ** |
| | C | 12 | 57.1 | | 102 | 57.6 | | |
| Opportunistic infections | | | | | | | | |
| | Yes | 12 | 57.1 | | 109 | 61.6 | | 0.693** |
| | no | 9 | 42.9 | | 68 | 38.4 | | |
| Concurrent Medication | Yes | 18 | 85.7 | | 169 | 95.5 | | 0.097*** |
| | No | 3 | 14.3 | | 8 | 4.5 | | |

*- Mann-Whitney U test ** - Chi-square test ***- Fisher's exact test

**Baseline laboratory parameters of 206 adult HIV positive patients with respect to development of skin toxicity**

When the baseline laboratory parameters of these two groups were compared, no statistical significant differences were found, between median CD4 T-cell count (p-value=0.391); median HIV-1 RNA copies/ml (p-value=0.91) of those who developed skin toxicity and those who did not develop any toxicity. Similarly, no statistical significant differences were found between median values of baseline biochemical parameters of these two groups.

**Table 12: Baseline laboratory parameters of adult HIV positive patients with respect to development of skin toxicity.**

| Variable | Dev skin toxicity (n=21) | | Not develop toxicities (n=177) | | P-value |
|---|---|---|---|---|---|
| | N | Median(IQR) | n | Median (IQR) | |
| CD4 cell count,cells/$mm^3$ | 21 | 60(18-121) | 177 | 38(13-133) | 0.391* |
| CD4 % | 20 | 5(1.25-10.5) | 168 | 4(1-8) | 0.575* |
| HIV RNA copies/ml | 11 | 76,900(14,600-750,000) | 68 | 214,500(40,025-527,000) | 0.910* |
| HIV-1 RNA ($log_{10}$copies/ml) | 11 | 4.9(4.1-5.9) | 68 | 5.33(4.5-5.7) | 0.91* |
| ALP, U/L | 7 | 72(50-110) | 52 | 99(67-170) | 0.206* |
| ALT, U/L | 11 | 45(19-57) | 96 | 25(17-43) | 0.139* |
| AST, U/L | 13 | 34(23-59) | 128 | 29(23-46) | 0.679* |
| Total bilirubin, U/L | 10 | 0.52(0.38-0.62) | 58 | 0.52(0.4-0.63) | 0.917* |

*-Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of hepatic toxicity.**

When demographic and baseline characteristics of the patients who developed hepatic toxicity and patients who did not develop any toxicity were compared, no statistical significant associations were found between, age at the start of nevirapine based regimen (p-value =0.661); gender (p-value=1.0); body weight (p-value=0.601); ART status (p-value=0.16) and IVDU (p-value=0.44) .

However, a statistical significant association was found between, history of drug allergy and development of hepatic toxicity (37.5% vs 6.2%, p-value=0.016) (RR=7.33, 95%CI=1.95<RR<27.53). Those HIV/AIDS patients with history of drug allergy are 7 times more likely to develop hepatic toxicity, from nevirapine based regimen, than those without the drug allergy history.

**Table 13:Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of hepatic toxicity**

| Variables | | Hepatic toxicity (n=21) | | | Not Develop toxicities (n=177) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | Median (IQR) | N | % | Median (IQR) | |
| Age, years | | 8 | | 34 (30-43) | 177 | | 33 (30-38) | 0.661* |
| Gender | Male | 4 | 50.0 | | 90 | 50.8 | | 1.0*** |
| | Female | 4 | 50.0 | | 87 | 49.2 | | |
| Body weight, Kg | | 8 | | 53 (45-58) | 177 | | 54 (47-60) | 0.601* |
| Pregnancy | Yes | 0 | 0 | | 7 | 8.0 | | |
| | No | 4 | 100 | | 80 | 92.0 | | |
| ART status | Naïve | 6 | 75.0 | | 162 | 91.5 | | 0.16*** |
| | Experienced | 2 | 25.0 | | 15 | 8.5 | | |
| Drug allergy | Yes | 3 | 37.5 | | 11 | 6.2 | | **0.016*** |
| | No | 5 | 62.5 | | 166 | 93.8 | | |
| Alcohol abuse | Yes | 0 | 0 | | 9 | 5.1 | | |
| | No | 8 | 100 | | 168 | 94.9 | | |
| IVDU | Yes | 1 | 12.5 | | 12 | 6.8 | | 0.44*** |
| | No | 7 | 87.5 | | 165 | 93.2 | | |
| Clinical category before treatment | | | | | | | | |
| | A & B | 0 | 0 | | 75 | 42.4 | | 0.022*** |
| | C | 8 | 100 | | 102 | 57.6 | | |
| Opportunistic infections | | | | | | | | |
| | Yes | 8 | 100 | | 109 | 61.6 | | 0.028*** |
| | No | 0 | 0 | | 68 | 38.4 | | |
| Concurrent Medication | Yes | 8 | 100 | | 169 | 95.5 | | |
| | No | 0 | 0 | | 8 | 4.5 | | |

*- Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Baseline laboratory parameters of adult HIV positive patients with respect to development of hepatic toxicitiy**

When the baseline laboratory parameters of these two groups were compared, no statistically significant differences were found, between median CD4 T-cell count (p-value=0.348); median HIV-1 RNA copies/ml (p-value=0.720) of those who developed hepatic toxicity and who did not develop any toxicity. Similarly, no statistically significant differences were found between baseline biochemical parameters of these two groups.

**Table 14: Baseline laboratory parameters of adult HIV positive patients with respect to development of hepatic toxicitiy.**

| Variable | Dev hepatic toxicity (n=8) | | Not develop toxicities (n=177) | | P-value |
|---|---|---|---|---|---|
| | N | Median(IQR) | N | Median (IQR) | |
| CD4 cell count,cells/$mm^3$ | 8 | 57(26-139) | 177 | 38(13-133) | 0.348* |
| CD4 % | 8 | 7(3.2-8.7) | 168 | 4(1-8) | 0.177* |
| HIV RNA copies/ml | 3 | 240,000(43,900-750,000) | 68 | 214,500(40,025-527,000) | 0.720* |
| HIV-1 RNA ($log_{10}$copies/ml) | 3 | 5.4(4.6-5.8) | 68 | 5.33(4.5-5.7) | 0.720* |
| ALP, U/L | 3 | 133(77-142) | 52 | 99(67-170) | 0.604* |
| ALT, U/L | 4 | 34(12-43) | 96 | 25(17-43) | 0.902* |
| AST, U/L | 5 | 37(24-67) | 128 | 29(23-46) | 0.438* |
| Total bilirubin, U/L | 8 | 0.6(0.5-0.7) | 58 | 0.52(0.4-0.63) | 0.650* |

*-Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of skin toxicity and hepatic toxicity.**

When demographic and baseline characteristics of the patients who developed skin toxicity and those who developed hepatic toxicity were compared, no statistically significant differences were found between, age at the start of nevirapine (p-value =0.283 ); gender (p-value=1.0); body weight (p-value=0.788); ART status (p-value=0.3); history of drug allergy (p-value=0.36) and IVDU .

**Table 15:Demographic and baseline characteristics of 206 adult HIV positive patients with respect to development of skin toxicity and hepatic toxicity**

| Variables | | Skin toxicity (n=21) | | | Hepatic toxicity (n=8) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | N | % | Median (IQR) | N | % | Median (IQR) | |
| Age, years | | 21 | | 31 (27-38) | 8 | | 34 (30-43) | 0.283* |
| Gender | Male | 11 | 52.4 | | 4 | 50.0 | | 1.0*** |
| | Female | 10 | 47.6 | | 4 | 50.0 | | |
| Pregnancy | Yes | 1 | 10.0 | | 0 | 0 | | |
| | No | 9 | 90.0 | | 4 | 100 | | |
| Body weight, Kg | | 21 | | 52 (43-62) | 8 | | 53 (45-58) | 0.788* |
| ART status | Naïve | 19 | 90.5 | | 6 | 75.0 | | 0.30*** |
| | Experienced | 2 | 9.5 | | 2 | 25.0 | | |
| Poly- drug allergy | | | | | | | | |
| | Yes | 4 | 19.0 | | 3 | 37.5 | | 0.36*** |
| | No | 17 | 81.0 | | 5 | 62.5 | | |
| Alcohol abuse | Yes | 1 | 4.8 | | 0 | 0 | | |
| | No | 20 | 95.2 | | 8 | 100 | | |
| IVDU | Yes | 0 | 0 | | 1 | 12.5 | | 0.27*** |
| | No | 21 | 100 | | 7 | 87.5 | | |
| Clinical category before treatment | | | | | | | | |
| | A & B | 9 | 42.9 | | 0 | 0 | | 0.033 *** |
| | C | 12 | 57.1 | | 8 | 100 | | |
| Opportunistic infections | | | | | | | | |
| | Yes | 12 | 57.1 | | 8 | 100 | | 0.033*** |
| | No | 9 | 42.9 | | 0 | 0 | | |
| Concurrent Medication | | | | | | | | |
| | Yes | 18 | 85.7 | | 8 | 100 | | 0.54*** |
| | No | 3 | 14.3 | | 0 | 0 | | |

*- Mann-Whitney U test **- Chi-square test *** - Fisher's exact test

**Baseline laboratory parameters of 206 adult HIV positive patients with respect to development of skin toxicity and hepatic toxicity.**

. When the baseline laboratory parameters of these two groups were compared, no statistically significant differences were found, between median CD4 T-cell count (p-value=0.788); median HIV-1 RNA copies/ml (p-value=0.529) and the type of toxicity developed. Similarly, no statistically significant differences were found between baseline biochemical parameters of those who developed skin toxicity and those who developed hepatic toxicity.

**Table 16: Baseline laboratory parameters of adult HIV positive patients with respect to development of skin toxicitiy and hepatic toxicity.**

| Variable | Dev skin toxicity (n=21) | | Develop hepatic toxicity (n=8) | | P-value |
|---|---|---|---|---|---|
| | N | Median(IQR) | N | Median (IQR) | |
| CD4 cell count,cells/$mm^3$ | 21 | 60(18-121) | 8 | 57(26-139) | 0.788* |
| CD4 % | 20 | 5(1.25-10.5) | 8 | 7(3.2-8.7) | 0.491* |
| HIV RNA copies/ml | 11 | 76,900(14,600-750,000) | 3 | 240,000(43,900-750,000) | 0.529* |
| HIV-1 RNA ($log_{10}$copies/ml) | 11 | 4.9(4.1-5.9) | 3 | 5.4(4.6-5.8) | 0.529* |
| ALP, U/L | 7 | 72(50-110) | 3 | 133(77-142) | 0.170* |
| ALT, U/L | 11 | 45(19-57) | 4 | 34(12-43) | 0.240* |
| AST, U/L | 13 | 34(23-59) | 5 | 37(24-67) | 0.805* |
| Total bilirubin, U/L | 10 | 0.52(0.38-0.62) | 2 | 0.6(0.5-0.7) | 0.519* |

*-Mann-Whitney U test ** - Chi-square test *** - Fisher's exact test

**Use of concurrent medications among 206 adult HIV positive patients with respect to the development of toxicities from treatment with nevirapine based regimen.**

When type of concurrent medications used was compared between 29 patients who developed toxicities from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that, there were no statistical significant associations between exposure to anti-TB (p-value=0.43), number of concurrent drug (p-value=1.0), concurrent treatments with anti-TB (p-value=0.16) ; with bactrim (p-value=0.38);with fluconazole(p-value=0.6) and the development of toxicity from treatment with nevirapine based regimen.

Similarly, when type of concurrent medications used was compared between 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that , there were no statistically significant associations between exposure to anti-TB (p-value=0.35), number of concurrent drugs (p-value=0.47), concurrent treatment with anti-TB (p-value=0.77) ; with bactrim (p-value=0.73);with fluconazole(p-value=1.0) and the development of skin toxicity from treatment with nevirapine based regimen.

When type of concurrent medications used was compared between 8 patients who developed hepatic toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that , there were no statistical significant associations between number of concurrent drugs(p-value=0.27), concurrent treatment with bactrim (p-value=0.26);with fluconazole(p-value=0.301) and the development of hepatic toxicity from treatment with nevirapine based regimen.

However, there was a statistical significant association between treatment with anti-TB and development of hepatic toxicity (87.5% vs 33.9%, p-value=0.004). HIV patients who are treated with anti-TB are more likely to develop hepatic toxicity from taking nevirapine. Again with further analysis on anti-TB treatment, it was found that, concurrent anti-TB treatment had significant association with development of hepatic toxicity from treatment with nevirapine based regimen (85.7% vs 22.0%, p-value=0.001); (RR=18.15,95%CI=2.25<RR<146.17). HIV positive patients who are concurrently treated with anti-TB are 18 times more likely to develop hepatic toxicity

from treatment with nevirapine based regimen than those without any concurrent anti-TB treatment.

Accordingly, when type of concurrent medications used was compared between 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 8 patients who developed hepatic toxicity, it was found that, there were no significant associations between number of concurrent drugs given (p-value=0.2), concurrent treatment with bactrim (p-value=0.6);with fluconazole (p-value=0.43) and the type of toxicity developed from treatment with nevirapine based regimen.

However, there was a significant association between treatment with anti-TB and development of hepatic toxicity. (87.5% vs 23.8%, p-value=0.003). HIV positive patients who are treated with anti-TB are more likely to develop hepatic toxicity than skin toxicity from taking nevirapine. Again with further analysis on anti-TB treatment, it was found that, concurrent anti-TB treatment had statistical significant association with development of hepatic toxicity than skin toxicity from treatment with nevirapine based regimen (85.7% vs 15.8 %, p-value=0.002) (RR=11.33, 95%CI=1.6<RR<80.2).HIV positive patients who are concurrently treated with anti-TB are 11 times more likely to develop hepatic toxicity than skin toxicity from treatment with nevirapine based regimen.

**Table 17. A: Use of concurrent medications among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| Concurrent Medication | n(%) Dev toxi n=29 | No toxi n=177 | p-value | n(%) Skin toxi n=21 | No toxi n=177 | p-value |
|---|---|---|---|---|---|---|
| Number ≥ 3 drugs | 19(65.5%) | 116(65.55) | 1.0** | 12(57.1%) | 116(65.5%) | 0.47*** |
| All anti-TB | 12(41.4%) | 60(33.9%) | 0.43** | 5(23.8%) | 60(33.9%) | 0.35** |
| Concurrent | 9(34.6%) | 33(22.0%) | 0.16** | 3(15.8%) | 33(22.0%) | 0.77*** |
| Bactrim | 24(82.8%) | 156(88.1%) | 0.38*** | 18(85.7%) | 156(88.1%) | 0.73*** |
| Fluconazole | 15(51.7%) | 101(57.1%) | 0.6*** | 12(57.1%) | 101(57.1%) | 1.0** |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**Table 17. B: Use of concurrent medications among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| Concurrent Medication | n(%) Hep toxi N=8 | No toxi n=177 | p-value | n(%) Skin toxi n=21 | Hep toxi n=8 | p-value |
|---|---|---|---|---|---|---|
| Number ≥ 3 drugs | 7(87.5%) | 116(65.5%) | 0.27*** | 12(57.1%) | 7(87.5%) | 0.20*** |
| All anti -TB | 7(87.5%) | 60(33.9%) | **0.004**** | 5(23.8%) | 7(87.5%) | **0.003**** |
| Concurrent | 6(85.7%) | 33(22.0%) | **0.001**** | 3(15.8%) | 6(85.7%) | **0.002**** |
| Bactrim | 6(75.0%) | 156(88.1%) | 0.26*** | 18(85.7%) | 6(75.0%) | 0.6*** |
| Fluconazole | 3(37.5%) | 101(57.1%) | 0.301*** | 12(57.1%) | 3(37.5%) | 0.43*** |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**History of drug allergy of 206 adult HIV positive patients with respect to the development of toxicities.**

When type of allergic drug was compared between 29 patients who developed toxicities from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that, there were no statistical significant associations between allergy to rifampicin (p-value=0.37); allergy to penicillin (p-value=0.367); allergy to d4T (p-value=0.26); allergy to dapsone (p-value=0.26) and the development of toxicity. However, there were statistical significant associations between, drug allergy to sulfa and the development of toxicity (17.2% vs 4% p-value=0.015) (RR=3.37, 95%CI=1.56<RR<7.25). Adult HIV positive patients with history of drug allergy to sulfa are 3 times more likely to develop toxicity from treatment with nevirapine based regimen.

Similarly, when 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity were compared, it was found that, there were no statistical significant associations between allergy to sulfa (p-value=0.08); allergy to rifampicin (p-value=0.29); allergy to penicillin (p-value=0.29); allergy to dapsone (p-value=0.2) and the development of skin toxicity.

When type of allergic drug, was compared between 8 patients who developed hepatic toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that, there were no statistical significant associations between history of allergy to sulfa (p-value=0.051); to d4T (p-value=0.08) and the development of hepatic toxicity.

Accordingly, when 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 8 patients who developed hepatic toxicity, it was found that, there were no statistically significant associations between history of allergy to sulfa (p-value=0.59); and the type of toxicity developed.

**Table 18.A: History of drug allergy among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| | n(%) | | | n(%) | | |
|---|---|---|---|---|---|---|
| | Dev toxi | No toxi | p-value | Skin toxi | No toxi | p-value |
| Drug allergy | n=29 | n=177 | | n=21 | n=177 | |
| Sulfa | 5(17.2%) | 7(4.0%) | **0.015**$^{***}$ | 3(14.3%) | 7(4.0%) | 0.08$^{***}$ |
| Rifampicin | 1(3.4%) | 2(1.1%) | 0.37$^{***}$ | 1(4.8%) | 2(1.1%) | 0.29$^{***}$ |
| Penicillin | 1(3.4%) | 2(1.1%) | 0.367$^{***}$ | 1(4.8%) | 2(1.1%) | 0.29$^{***}$ |
| D4T | 1(3.4%) | 1(0.6%) | 0.26$^{***}$ | 0(0%) | 1(0.6%) | |
| Dapsone | 1(3.4%) | 1(0.6%) | 0.26$^{***}$ | 1(4.8%) | 1(0.6%) | 0.20$^{***}$ |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**Table 18.B: History of drug allergy among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| | n(%) | | | n(%) | | |
|---|---|---|---|---|---|---|
| | Hep toxi | No toxi | p-value | Skin toxi | Hep toxi | p-value |
| Drug allergy | n=8 | n=177 | | n=21 | n=8 | |
| Sulfa | 2(25.0%) | 7(4.0%) | 0.051$^{***}$ | 3(14.3%) | 2(25%) | 0.59$^{***}$ |
| Rifampicin | 0(0) | 2(1.1%) | | 1(4.8%) | 0(0%) | |
| Penicillin | 0(0) | 2(1.1%) | | 1(4.8%) | 0(0)% | |
| D4T | 1(12.5%) | 1(0.6%) | .08$^{***}$ | 0(0%) | 1(12.5%) | |
| Dapsone | 0(0%) | 1(0.6%) | | 1(4.8%) | 0(0%) | |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**Occurrence of opportunistic infections among 206 adult HIV positive patients with respect to development of toxicities.**

When occurrence of opportunistic infections was compared between 29 patients who developed toxicities from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that, there were no statistically significant associations between occurrence of tuberculosis (p-value=0.53); PCP (p-value=0.17); CMV(p-value=0.15); oral candidiasis (p-value=0.79); esophageal candidiasis(p-value=0.26); and the development of toxicity from treatment with nevirapine based regimen.

Similarly, when 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity were compared, it was found that ,there were no statistically significant associations between occurrence of tuberculosis (p-value=0.35); PCP (p-value=0.69); CMV(p-value=0.076); oral candidiasis (p-value=0.538); esophageal candidiasis(p-value=0.49); and the development of skin toxicity from treatment with nevirapine based regimen.

When occurrence of opportunistic infections, was compared between 8 patients who developed hepatic toxicity from the treatment with nevirapine based regimen and 177 patients who did not develop any toxicity, it was found that, there were no statistically significant associations between occurrence of oral candidiasis (p-value=0.63); esophageal candidiasis(p-value=0.236); and the development of hepatic toxicity from treatment with nevirapine based regimen. However, there were statistically significant associations between, presence of opportunistic infection TB (87.5% vs 33.9 %, p-value=0.004) (RR=12.33, 95%CI=1.55<RR<98.07); occurrence of PCP (37.5% vs 8.5%, p-value=0.032)(RR=5.57,95%CI=1.45<RR<21.39) and the development of hepatic toxicity from treatment with nevirapine based regimen. The HIV positive patients with opportunistic infections TB and PCP are 12 times and 5 times more likely to develop hepatic toxicity from treatment with nevitrapie based regimen respectively.

Accordingly, when 21 patients who developed skin toxicity from the treatment with nevirapine based regimen and 8 patients who developed hepatic toxicity were compared, it was found that, there were no statistical significant associations between occurrence of PCP (p-value=0.11); oral candidiasis (p-value=0.3); esophageal

candidiasis(p-value=0.48) and the type of toxicity developed However, significant association was found between, occurrence of TB and development hepatic toxicity. ( 23.8% vs 87.5%, p-value=0.003) (RR=9.92, 95%CI=1.4<RR<70.45). Patients with opportunistic infection, TB are 9 times more likely to develop hepatic toxicity than skin toxicity from treatment with nevirapine based regimen.

**Table 19.A: Occurrence of opportunistic infections among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| Opportunistic infections | n(%) Dev toxi n=29 | n(%) No toxicity n=177 | p-value | n(%) Skin toxi n=21 | n(%) No toxicity n=177 | p-value |
|---|---|---|---|---|---|---|
| TB | 12(41.4%) | 60(33.9%) | 0.53*** | 5(23.8%) | 60(33.9%) | 0.35*** |
| PCP | 5(17.2%) | 15(8.5%) | 0.17*** | 2(9.5%) | 15(8.5%) | 0.69** |
| CMV | 3(10.3%) | 7(4.0%) | 0.15*** | 3(14.3%) | 7(4.0%) | 0.076*** |
| Oral candidiasis | 4(13.8%) | 31(17.5%) | 0.79*** | 2(9.5%) | 31(17.5%) | 0.538*** |
| Esophageal candidiasis | 2(6.9%) | 5(2.8%) | 0.26*** | 1(4.8%) | 5(2.8%) | 0.49*** |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**Table 19.B: Occurrence of opportunistic infections among 206 adult HIV positive patients with respect to development of toxicities from nevirapine based regimen**

| Opportunistic infections | n(%) Hep toxi n=8 | n(%) No toxicity n=177 | p-value | n(%) Skin toxi n=21 | n(%) Hep toxi n=8 | p-value |
|---|---|---|---|---|---|---|
| TB | 7(87.5%) | 60(33.9%) | **0.004**** | 5(23.8%) | 7(87.5%) | **0.003**** |
| PCP | 3(37.5%) | 15(8.5%) | **0.032**** | 2(9.5%) | 3(37.5%) | 0.11*** |
| CMV | 0(0%) | 7(4.0%) | | 3(14.3%) | 0(0%) | |
| Oral candidiasis | 2(25.0%) | 31(17.5%) | 0.63*** | 2(9.5%) | 2(25%) | 0.3*** |
| Esophageal candidiasis | 1(12.5%) | 5(2.8%) | 0.236*** | 1(4.8%) | 1(12.5%) | 0.48*** |

*- Mann-Whitney U test ** - Chi-square test ***-Fisher's exact test

**Incidence rate and time to onset of toxicity from treatment with nevirapine based regimen in 206 adult HIV positive patients**

Among 206 adult HIV positive patients, although a total of 29 (14%) patients developed toxicities from treatment with nevirapine based regimen, Kaplan-Meier estimated incidence of toxicity was only 1.09/100 person- months.

Although higher incidence of toxicity, 3.7/100 person-months was found in those with drug allergy, much lower incidence, 0.9/100 person-months was found in those without history of drug allergy.

When incidence of toxicity was compared between those with sulfa allergy (3.3/ 100 person-months) and those without history of sulfa allergy, (0.9/100 person-months), a higher incidence of toxicity was found to be associated with history of sulfa allergy among HIV positive patients treated with nevirapine based regimen.

Among 206 adult HIV positive patients, although a total of 8 (3.88%) patients developed hepatic toxicity from treatment with nevirapine based regimen, Kaplan-Meier estimated incidence of hepatic toxicity was only 0.3/100 person- months.

When incidence of hepatic toxicity was compared between those with sulfa allergy (2.02/ 100 person-months) and those without history of sulfa allergy,(0.2/100 person-months), a higher incidence of hepatic toxicity was found to be associated with history of drug allergy among HIV positive patients treated with nevirapine based regimen.

**Table 20: Incidence rate and time to onset of toxicities from treatment with nevirapine based regimen in 206 adult HIV positive patients**

| Toxicity | No | Person-months | Incidence rate |
|---|---|---|---|
| General toxicity | | | |
| Overall | 29 | 2285.6 | 1.09/100 |
| Drug allergy | | | |
| Yes | 7 | 163.4 | 3.7/100 |
| No | 22 | 2122.2 | 0.9/100 |
| Sulfa allergy | | | |
| Yes | 5 | 117.9 | 3.3/100 |
| No | 24 | 2167.7 | 0.9/100 |
| Hepatic toxicity | | | |
| Overall | 8 | 2239.4 | 0.3/100 |
| Drug allergy | | | |
| Yes | 3 | 147.8 | 2.02/100 |
| No | 5 | 2091.6 | 0.2/100 |

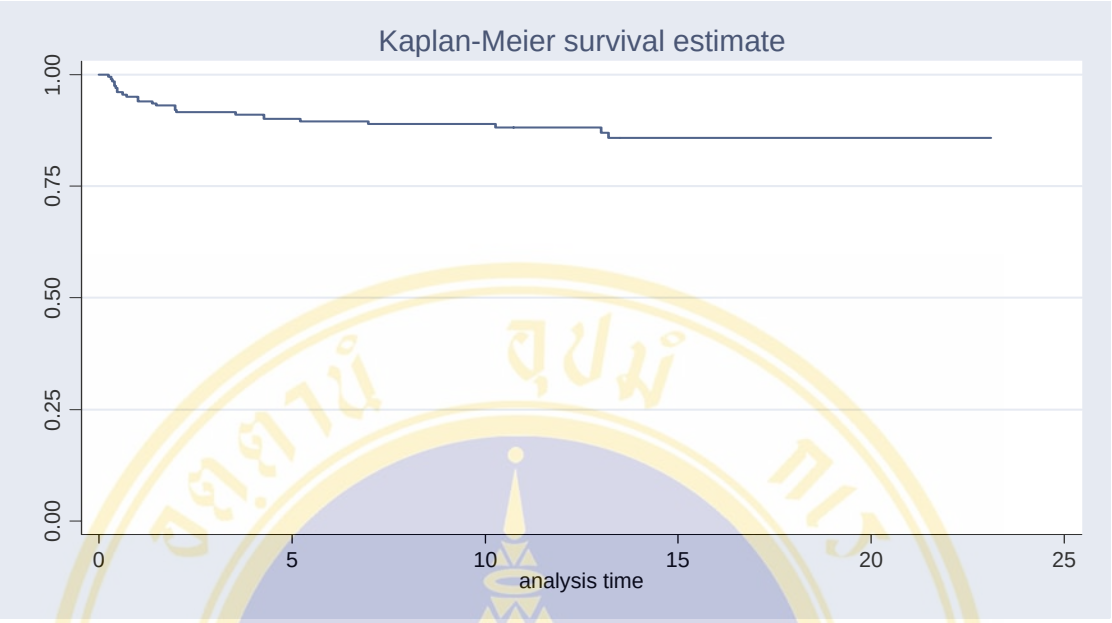


**Figure 1: Kaplan-Meier estimate of time to development of toxicities among 206 adult HIV positive patients treated with nevirapine based regimen.**

According to Kaplan-Meier estimated time to onset of toxicity, it was found that, among 206 HIV positive patients, majority, 89% of patients did not develop any toxicity and only 11% of HIV positive patients treated with nevirapine based regimen were found to develop toxicities within six months.

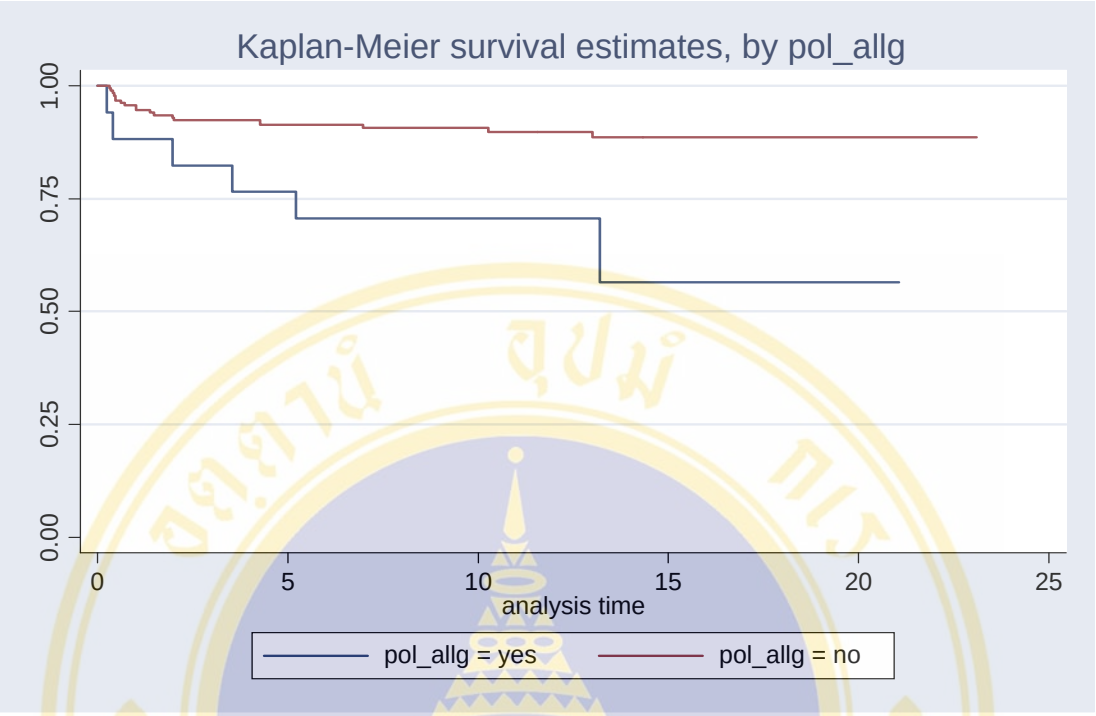


**Figure 2 : Comparison of time to onset of toxicities in 206 adult HIV positive patients with history of drug allergy and those without history of drug allergy taking nevirapine.**

With Kaplan-Meier comparison of time to onset of toxicity in those with history of drug allergy and without it, a higher incidence of toxicity was found in HIV positive patients with history of drug allergy. Among those patients with history of drug allergy, 70% did not develop any toxicity while 30% develop toxicities within six months. For those with no history of drug allergy, 91% did not develop any toxicity while only 9% developed toxicities within six months.

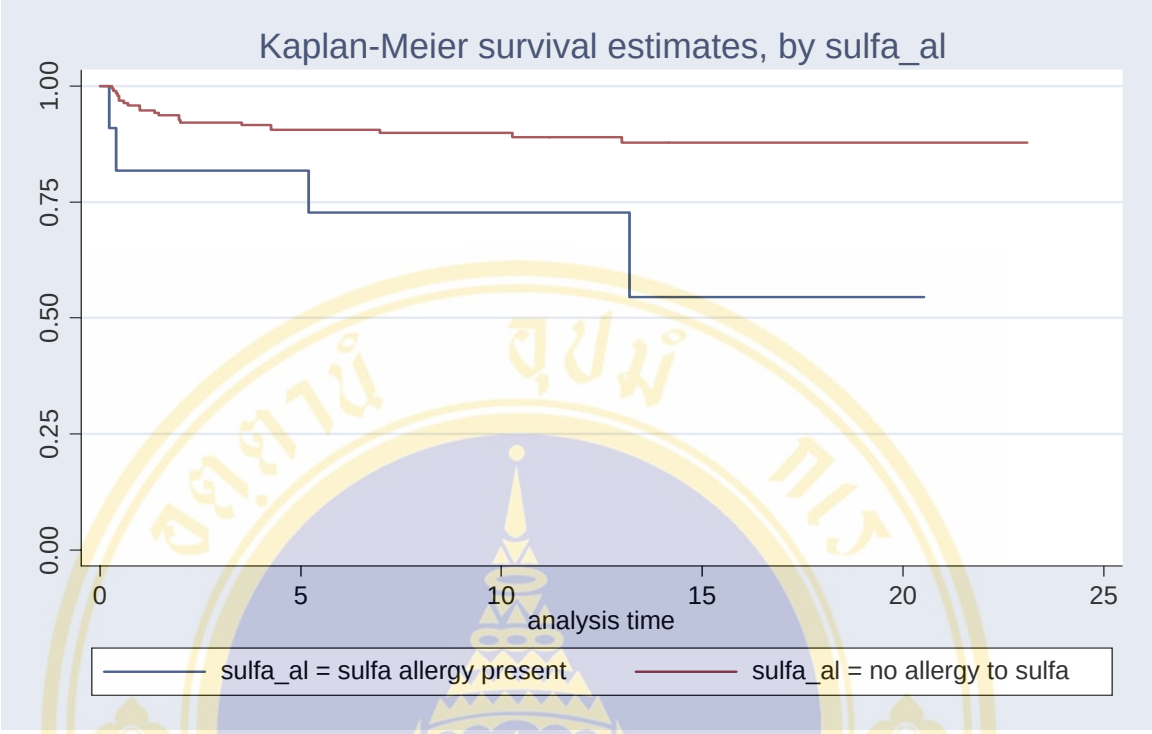


**Figure 3:Comparison of time to onset of toxicities in 206 adult HIV positive patients with history of sulfa allergy and those without history of sulfa allergy taking nevirapine.**

With Kaplan-Meier comparison of time to onset of toxicity in those with history of sulfa allergy and without it, a higher incidence of toxicity was found in HIV positive patients with history of sulfa allergy. Among those patients with history of sulfa allergy, 72% did not develop any toxicity while 28% developed toxicities within six months. For those with no history of sulfa allergy, 90% did not develop any toxicity while only 10% developed toxicity within six months.

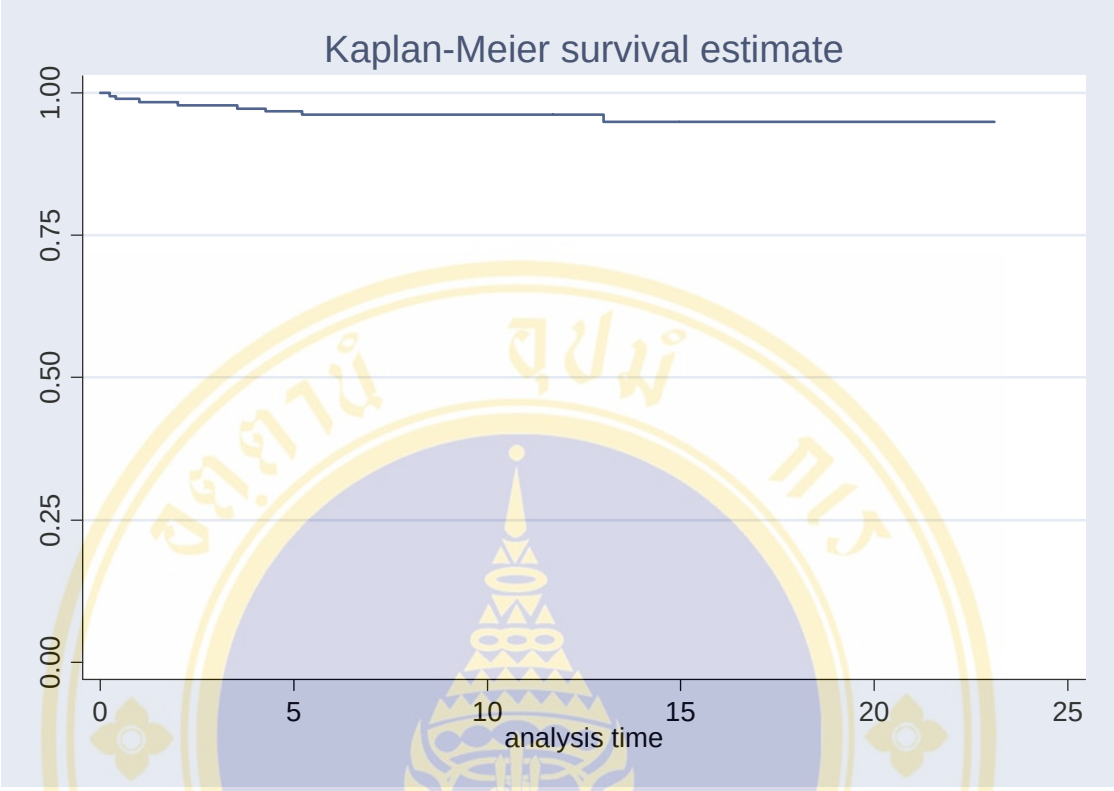


**Figure 4: Kaplan-Meier estimate of time to development of hepatic toxicity among 206 adult HIV positive patients treated with nevirapine based regimen.**

According to Kaplan-Meier estimated time to onset of toxicity, it was found that, among 206 HIV positive patients, majority, 96% of patients did not develop any toxicity and only 4% of HIV positive patients treated with nevirapine based regimen were found to develop hepatic toxicity, within six months.

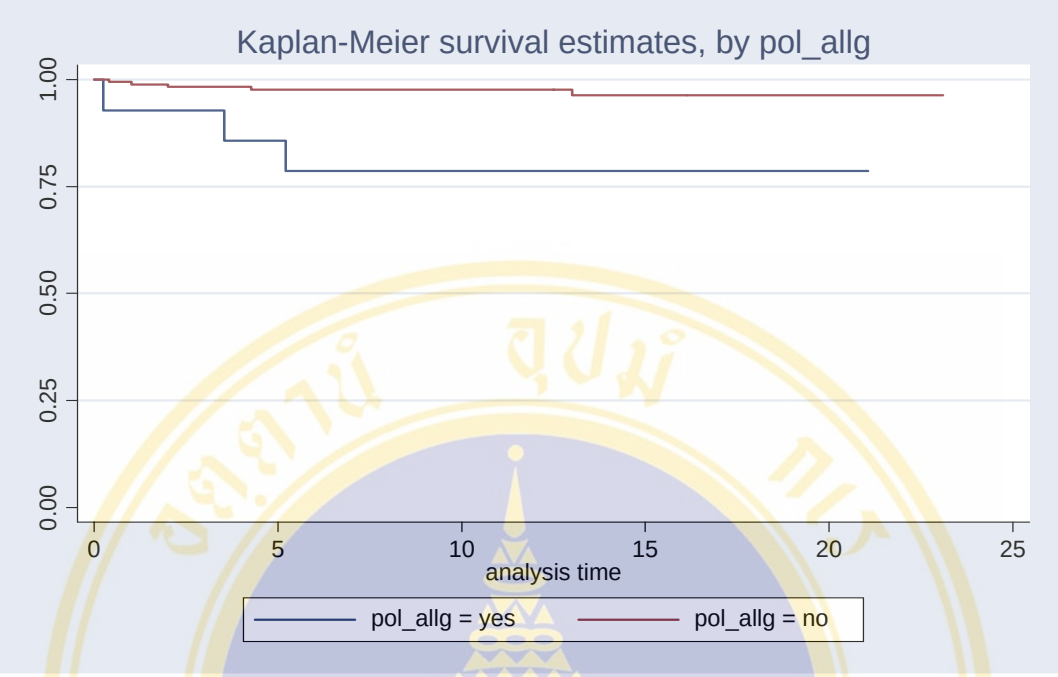


**Figure 5: Comparison of time to onset of hepatic toxicity in 206 adult HIV positive patients with history of drug allergy and those without history of drug allergy taking nevirapine.**

With Kaplan-Meier comparison of time to onset of hepatic toxicity in those with history of drug allergy and without it, a higher incidence of hepatic toxicity was found in HIV positive patients with history of drug allergy. Among those patients with history of drug allergy, 78% did not develop any toxicity while 22% developed toxicity within six months. For those with no history of drug allergy, 97% did not develop any toxicity while only 3% developed hepatic toxicity within six months.

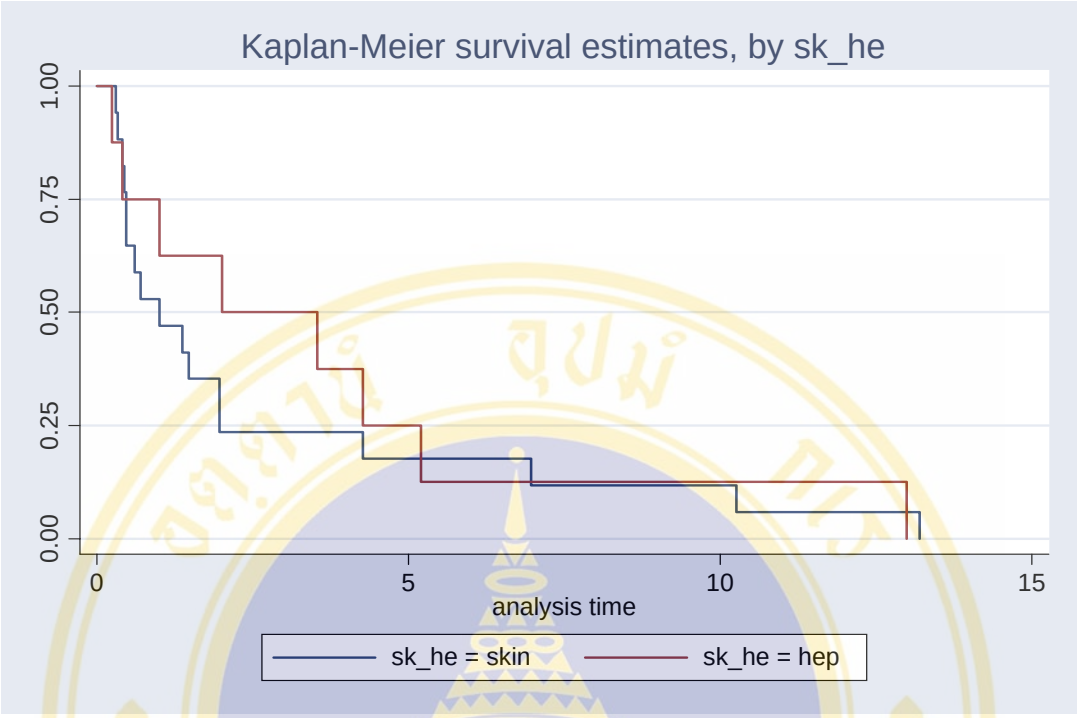


**Figure 6: Comparison of time to onset of skin toxicity and hepatic toxicity in 206 adult HIV positive patients taking nevirapine.**

With Kaplan-Meier comparison of estimated time to onset of skin toxicity and hepatic toxicity, a shorter median time to onset of toxicity was found in those who developed skin toxicity. While 50% of patients with skin toxicity developed toxicity within one month (95% CI for median 0,1), 50% of those with hepatic toxicity developed toxicity within 2 months (95% CI for median 0,6). There was no statistically significant difference in median time to onset of skin toxicity and hepatic toxicity (log-rank p=0.402).

# CHAPTER VI
# DISCUSSION

The findings from this study conducted among 206 adult HIV positive patients who were treated with nevirapine based regimen during January 2004 to December 2005 at the Bamrasnaradura Institute, has shown us the incidence of nevirapine toxicities, its predictors, and occurrence of opportunistic infections among the HIV positive patients.

Monitoring the development of the toxicities from the nevirapine based regimen over the course of the treatment is very useful to estimate the incidence and time to onset of nevirapine toxicities in HIV positive patients treated with nevirapine based regimen. The further analysis of the baseline demographic data, baseline laboratory parameters, and the baseline characteristics showed us the significant predictors towards the development of toxicities among HIV positive patients treated with nevirapine based regimen.

The present study found that, among 206 adult HIV positive patients, although a total of 29 (14%) patients developed toxicities from treatment with nevirapine based regimen, Kaplan-Meier estimated incidence of toxicity was only 1.09/100 person-months. According to Kaplan-Meier estimated time to onset of toxicities, it was found that, among 206 HIV positive patients, majority, 89% of patients did not develop any toxicity and only 11% of HIV positive patients treated with nevirapine based regimen were found to develop toxicities within six months.

Anekthananon et al (2004) from study among Thai patient previously reported that a total of 12% of the patients receiving d4T/3TC/NVP and 7% developed grade 3 and 4 hepatic toxicity.

Lower incidence of skin toxicity –10.2% and lower incidence of grade 3 and 4 hepatic toxicity – 1.94% was observed in the current study. It may be explained by the retrospective nature of the current study, baseline liver function tests not being available for all patients and less frequent monitoring of the liver function tests during

the course of treatment. When the medical records were requested, according to the random numbers from the data of patients presumed to be treated during 2004 and 2005, some records were reviewed and excluded as they were found to be patients treated before this period and some being treated with efavirenz based regimen. This may be a possible explanation why the skin toxicity rate in the current study (10.2%) is lower than the previously reported, 12 % among Thai patients.

The estimated median time to development of skin rash was 4 weeks which was comparable to the study by Martinez et al (2001) who reported that, nevirapine associated skin rashes usually appeared after one to four weeks of treatment. According to the finding from this study, the median time for hepatic toxicity development was 12 weeks which was similar to the finding reported by Stern et al (2003) that the risk for hepatotoxicity was greatest in the first six weeks of treatment and continued through 18 weeks of treatment. It is again supported by the point emphasized by the health authorities in the Europe and USA that critical period for intensive clinical and laboratory monitoring to detect potentially life-threatening hepatotoxicity should be the first 8-12 months.

When the baseline laboratory parameters of these two groups were compared, no statistical significant differences were found, between median CD4 T-cell count (p-value=0.237) and development of toxicities from nevirapine. This is comparable to the conclusions by Manosuthi et al (2005) in the study among Thai HIV patients at the Bamrasnaradura Institute that baseline CD4 count was not predictive of clinical hepatitis or skin rashes from taking nevirapine.

In the present study, majority (90.8%) of the patients were ART naïve -most of them (90.8%) had CD4 <200/ $mm^3$at the start and this may be the possible explanation for current result being uncomparable to the report by Barlett et al (2004) that nevirapine caused increased risk from toxicity in HIV patients with high CD4 counts- in ARV naïve women, CD4 count ≥ 250 cells/$mm^3$ and in men, CD4≥ 400/ $mm^3$.

No statistical significant associations were found between pregnancy status (p-value=1.0) and development of the toxicities from taking nevirapine. This is comparable to results from many studies done among the pregnant women taking nevirapine. One study by Thorne et al (2005), mentioned that HIV positive pregnant women did not have the increased risk of toxicities from taking nevirapine. These

findings are important as nevirapine is commonly used as a component of first-line therapy in resource-limited settings especially in women of reproductive age.

When demographic and baseline characteristics of the patients who developed skin rash and patients who did not develop any toxicity were compared, no statistical significant associations were found between, gender (p-value=0.894) and development of skin rash from nevirapine. This is different from the findings from the study on sex differences in nevirapine rash by Bersff-Matcha et al (2001), among AIDS patients in the States who reported that women had seven fold increase in risk for severe rash. The possible explanation may be the differences in the baseline characteristics between the two study populations like genetic predisposition.

In this study, there were statistically significant associations between history of drug allergy and the development of toxicity (24.1 % vs 6.2%; p-value=0.006) and development of hepatic toxicity ( 37.5% vs 6.2%, p-value=0.016).

There was one retrospective study by Derisi et al (2000) who reported that patients with a history of sulfa allergy were eight times more likely to experience NNRTI rash than patients who had taken sulfa drugs but had not developed rash. This may not be directly comparable as in the current study, statistically significant association with drug allergy to sulfa (17.2% vs 4.0%, p-value=0.015) was general toxicity rather than specifically skin rash from treatment with nevirapine based regimen.

Although Sanne et al (2005) reported from the study among South African patients, that women with BMI<18.5 had higher risk from hepatic toxicity from nevirapine, in this study, it was difficult to assess this as heights of all the patients were not available to record making it not possible to calculate BMI . However, there was no statistical significant difference between body weight (p-value=0.601) and development of the hepatic toxicity from nevirapine based regimen in this study.

In the current study, there was a significant association between treatment with anti-TB (87.5% vs 33.9%, p-value=0.004) and development of hepatic toxicity. HIV positive patients who are treated with anti-TB are more likely to develop hepatic toxicity from taking nevirapine. Again with further analysis on anti-TB treatment, it was found that, concurrent anti-TB treatment (85.7% vs 22.0%, p-value=0.001) had significant association with development of hepatic toxicity from treatment with nevirapine based regimen. This finding is similar to the finding reported by

Manosuthi et al (2005) in the study among the Thai patients that receiving anti-tuberculous drugs was significantly predictive for clinical hepatitis in HIV patients taking nevirapine.

Comparable to the finding reported by Bersoff-matcha et al (2001) in the study among patients in the States that there was no correlation between nevirapine rash and the use of cotrimoxazole, in this study, no statistically significant association was found between concurrent cotrimoxazole use and nevirapine skin rash.

Similar to the finding reported by Ruxrungtham et al (2004) from study among Thai patients that prior ART status was not associated with development of severe hepatotoxicity, current study did not find ART status as a predictor of hepatotoxicity among patients treated with nevirapine based regimen.

In this study, there were significant associations between, presence of opportunistic infection TB (87.5% vs 33.9 %, p-value=0.004); and the development of hepatic toxicity from treatment with nevirapine based regimen. Since most of the HIV patients (20.4%) in the study are concurrently treated with anti_TB, they had significantly higher chance to develop hepatic toxicity compared to HIV positive patients with no TB infections.

# CHAPTER VII
# CONCLUSION

Highly active antiretroviral therapy (HAART) has been widely used for the treatment of human immunodeficiency virus (HIV) infected patients with successful immune restoration and reduction in morbidity and mortality. With increased number of patients having access to ARVs, therapeutic monitoring of the side effects of the ARVs, especially toxicities from nevirapine-essential back-bone of GPO-vir, locally produced in Thailand- becomes more important.

This retrospective cohort study was conducted at Bamrasnaradura Institute, Nonthaburi, Thailand to determine the incidence of nevirapine toxicities among HIV positive patients and the predisposing factors towards it. The study was conducted among 206 adult HIV positive patients who were treated with nevirapine based regimen during January 2004 to December 2005.

The present study found that, among 206 adult HIV positive patients, although a total of 29 (14%) patients developed toxicities from treatment with nevirapine based regimen, Kaplan-Meier estimated incidence of toxicity was only 1.09/100 person-months. According to Kaplan-Meier estimated time to onset of toxicities, it was found that, among 206 HIV positive patients, majority, 89% of patients did not develop any toxicity and only 11% of HIV positive patients treated with nevirapine based regimen were found to develop toxicities within six months.

Regarding the predisposing factors towards it, there were statistically significant associations between history of drug allergy and the development of toxicities (24.1 % vs 6.2%; p-value=0.006) and hepatic toxicity ( 37.5% vs 6.2%, p-value=0.016). Similarly, statistically significant associations were found between, history of drug allergy to sulfa (17.2%, vs, 4.0%, p-value=0.015); and development of toxicity from treatment with nevirapine based regimen.

Concerning with the use of concurrent medications, the statistically significant associations were found between concurrent treatment with anti-TB (85.7% vs 22.0%, p-value=0.001) and development of hepatic toxicity.

As a nature of the retrospective study, there were some unavailable data like heights of the patients, so it was not possible to calculate BMI. Some of the baseline investigations were also not available for all patients to make comparison.

As the concurrent use of anti-TB was significantly predictive of development of hepatic toxicity, close monitoring of liver function tests should be done for these patients . Findings from this study also showed that history of drug allergy especially allergy to sulfa was a risk factor towards development of toxicities in patients taking nevirapine. HIV patients with history of drug allergy especially sulfa should be closely monitored during the first month after the initiation of nevirapine to give prompt management in case of toxicity development.

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# APPENDIX

# APPENDIX A

## 1993 Revised classification System for HIV-1 Infection and Expended AIDS Surveillance Case Definition for Adolescent and Adult

| CD4+ T cell ctegory | (A) Asymptomatic acute (primary) HIV or PGL | (B) Symptomatic,not (A) or (C) conditions | (C) AIDS indicator conditions |
|---|---|---|---|
| ≥ 500 cell/ ul | A1 | B1 | C1 |
| 200- 499 cell/ul | A2 | B2 | C2 |
| <200 cell/ul | A3 | B3 | C3 |

**Category A**

Asymptomatic HIV infection

Persistent generalized lympadenopathy

Acute (primary ) HIV infection with accompanying illness or history of acute HIV infection

**Category B**

Bacillary angiomatosis

Oropharyngeal candidiasis (thrush)

Vulvovaginal candidiasis (persistent, frequent, and poorly responsive)

Cervical dysplasia; cervical carcinoma in situ

Constitutional symptoms lasting >1 month

Oral hairy Leucoplakia

Herpes Zoster (Shingles) in 2 episodesor > 1 dermatome

Idiopathic throbocytopenic purpura

Listeriosis

Pelvic Inflammatory disease

Peripheral neuropathy

**Category C (AIDS defining conditions)**

Candidiasis of brochi, trachea, or lungs

Esophageal candidiasis

Cervical cancer, invasive

Coccidiodomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal

Cytomeglovirus infection

HIV related encephalopathy

Herpes Simplex with esophageal, pulmonary, or mucocutaneous involvement of > 1 month

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal

Kaposi's sarcoma

Lymphoma

*Mycoacterium Avium complex* or *M.kansasii* infection, Disseminated or Extrapulmonary

*M.tuberculosis,* any site

*Pneumocystic carinii* pneumonia

Penumonia recurrrent with more than two episodes in 12 months

Progressive multifocal encephalopathy

*Salmonella* species, recurrent

Brain toxoplasmosis

Wasting Syndrome due to HIV

# APPENDIX B
# Subject case record form

**Date of data entry** _____ **Serial number**_____

Year of admission _____ Date of admission _____

**I. Demographic Data**

1. Patient initials _____

Hospital Number (H.N) _____

2. Age _____years Date of birth _____

3. Gender
   Male □ female □
4. Marital status
   Married □ Single □ Divorced/separated □ widow □
5. Pregnancy
   Yes □ No □
6. Address
   Nonthaburi □ Northern □ Northeastern □
   Bangkok □ Central □ Others □
7. Occupation
   Laborer □ Business □ Governmental employee/State enterprise □
   Agriworker □ Unemployed □ Teacher □

   Others (in detail) _____
8. Risk factors to get HIV /AIDS
   MSM □ Heterosexual □ Injection drug use □
   Unknown □

**II. History of ART**

9.1: Date of diagnosis of AIDS_____ (if not possible, month)
9.2: Age when diagnosed with AIDS _____
9.3: Age when NVP-based HAART started _____
9.4: ART status before treatment with Nevirapine based HAART
Naïve □ Experienced □
9.5: If Experienced, Describe the previous regimens

| Duration | Regimen | Remarks |
|---|---|---|
| | | |
| | | |
| | | |

9.6: Reason for changing to Nevirapine based regimen _____

**III. Nevirapine-based HAART**

10.1: Date of initiation of Nevirapine based HAART _____
10.2: Types of Nevirapine based HAART

| BASE | DOSE | OTHER COMBINING DRUGS | DOSE | DURATION | | REMARK |
|---|---|---|---|---|---|---|
| | | | | Start | End | |
| NVP | | 3TC | | | | |
| | | d4T | | | | |
| | | AZT | | | | |
| | | RTV | | | | |
| | | IDV | | | | |
| | | | | | | |
| NVP | | 3TC | | | | |
| | | d4T | | | | |
| | | AZT | | | | |
| | | RTV | | | | |
| | | IDV | | | | |
| | | | | | | |

10.3: Adherence to the treatment (compliance)
Yes □ No □

**IV. Body composition and Past medical history**

11. Body Composition

Body weight _____ Height _____cm

12. Historiy of Drug Allergy and Substance use before NVP-based HAART / ART

| Item | Yes | No | Not described | Remarks |
|---|---|---|---|---|
| Drug allergy/poly-drug allergy | | | | |
| Alcohol use | | | | |
| Drug abuse | | | | |

13. History of prior medication

1. Yes □ 2. No □
If Yes, please describe … … … … … and duration of use: ---------- (months or years)

**V. Adverse effects, Laboratory data and Opportunistic infections**

14. Adverse effects

| **Con-committant OIs** | **Baseline before the start of NVP-Based HAART** | | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** | **Remarks** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Yes** | **No** | **Date** | **Date** | **Date** | **Date** | **Date** | **Date** | **Date** | |
| Fever | | | | | | | | | | |
| Rash (Grade) | | | | | | | | | | |
| Anorexia / Nausea | | | | | | | | | | |
| Vomiting | | | | | | | | | | |
| Jaundice | | | | | | | | | | |
| Hepatomegaly | | | | | | | | | | |
| Hepatic tenderness | | | | | | | | | | |
| Immune restoration syndrome | | | | | | | | | | |
| Lipodystrophy | | | | | | | | | | |
| Neuropathy | | | | | | | | | | |
| Myalgia | | | | | | | | | | |
| Breathlessness | | | | | | | | | | |
| Sleep disturbance | | | | | | | | | | |
| Others: ---------- | | | | | | | | | | |

*****Please grade: Rash**

**Grade 1** Cutaneous reaction – Localized macular rash

**Grade 2** Diffuse macular, maculopapular, or mobiliform rash or target lesion

**Grade 3** Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site

**Grade 4** Extensive or generalized bullous lesions or Stevens-Johnson syndrome or ulceration of mucous membrane involving two or more distinct mucosal sites or Toxic epidermal necrolysis (TEN)

15. Basic Laboratory Data

| **Basic Laboratory Data** | | **Baseline before the start of NVP-Based HAART** | | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** | **Remarks** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Yes** | **No** | **Date** | **Date** | **Date** | **Date** | **Date** | **Date** | **Date** | |
| CD4 cells Count (μ / L) | | | | | | | | | | | |
| CD4 % | | | | | | | | | | | |
| Viral load (copies / ml) | | | | | | | | | | | |
| Viral load (log ) | | | | | | | | | | | |
| CD4 : CD8 | | | | | | | | | | | |
| Bilirubin (mg/dL) | | | | | | | | | | | |
| GGT | | | | | | | | | | | |
| AST (SGOT) | Exact (μ /L) | | | | | | | | | | |
| | Grade | | | | | | | | | | |
| ALT (SGPT) | Exact (μ /L) | | | | | | | | | | |
| | Grade | | | | | | | | | | |
| Hepatitis A | | | | | | | | | | | |
| Hepatitis B | | | | | | | | | | | |
| Hepatitis C | | | | | | | | | | | |
| Cryptococcal Ag | | | | | | | | | | | |

*****Please Note: SGPT and SGOT**

**Grade 1** Elevated serum transaminases level 1.25- 2.5 times the upper limit of normal.
**Grade 2**. Elevated serum transaminases level 2.6-5 times the upper limit of normal.
**Grade 3** Elevated serum transaminases level of 5.1 – 10 times the upper limit of the normal.
**Grade 4** Elevated serum transaminases level >10 times the upper limit of normal.
(Division of AIDS table for grading the severity of adult and pediatric adverse events:December, 2004)

16. Other Laboratory Data

| Other Laboratory Data | | Baseline before the start of NVP-Based HAART | | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Yes | No | Date | Date | Date | Date | Date | Date | Date | |
| Hb (g / L) | | | | | | | | | | | |
| Hct (%) | | | | | | | | | | | |
| Platelet | | | | | | | | | | | |
| WBC | Exact | | | | | | | | | | |
| | Grade | | | | | | | | | | |
| Neutrophil % | | | | | | | | | | | |
| Lymphocyte% | | | | | | | | | | | |
| Total Lymphocytes count | | | | | | | | | | | |
| Blood Urea | | | | | | | | | | | |
| Creatinine | | | | | | | | | | | |
| Lactate (mmol/L) | | | | | | | | | | | |
| Others: --- --- --- --- --- | | | | | | | | | | | |

17. Opportunistic infections before and after the use of NVP-based HAART

| Con-committant OIs | Baseline before the start of NVP-Based HAART | | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | Date | Date | Date | Date | Date | Date | Date | |
| Tuberculosis (T.B) | | | | | | | | | | |
| Cryptococcal meningitis | | | | | | | | | | |
| PCP | | | | | | | | | | |
| Herpes Zoster | | | | | | | | | | |
| Oral candidiasis | | | | | | | | | | |
| Esophagial candidiasis | | | | | | | | | | |
| Others: ---------- | | | | | | | | | | |

18. HIV clinical status **before NVP-based HAART** (FYI: Please check CD$ and OIs before the start of NVP-based regimens)

HIV clinical status before NVP-based HAART _____

Please Use the table below,
AIDS Surveillance Case Definition for Adolescent and Adults:1993

| CD4+ T cell ctegory | (A) Asymptomatic acute (primary) HIV or PGL | (B) Symptomatic,not (B) or (C) conditions | (C) AIDS indicator conditions |
|---|---|---|---|
| ≥ 500 cell/ ul | A1 | B1 | C1 |
| 200- 499 cell/ul | A2 | B2 | C2 |
| <200 cell/ul | A3 | B3 | C3 |

All patients in categories A3,B3, and C1-3 are defined as having AIDS based on the presence of an AIDS indicator condition and/or a CD4 count < 200 /mm3
19. Any Concurrent drug use with NVP-based HAART

1. Yes □ 2. No □

If Yes, please describe the name, dose and duration of use in the table below.

| **No** | **Drug** | **Indication** | **From** | **To** | **Duration Received** | **Remark** |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |

***** Please check!!!!**

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| | |
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