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Predisposing Factors for Nevirapine Toxicity among AIDS Patients with Low Baseline CD4 Count

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SUMMARY The objective of the study was to determine the predisposing factors and incidence of toxicity among AIDS patients treated with a nevirapine (NVP)-based regimen in clinical practice. A retrospective cohort study of representative samples of AIDS patients treated with a NVP-based regimen was performed. A total of 206 adult HIV/AIDS cases with median age (IQR) 33 years (range, 29-38 years), 51% male, treated between January 2004-December 2005, were included. Most (92.2%) of the patients were naïve to antiretroviral drug. The incidence of NVP toxicity was 1.09/100 person-months. The median onset time was 4 weeks post NVP initiation (2.57 weeks for skin toxicity and 12.43 weeks for hepatic toxicity). History of drug allergy and NVP toxicity were significantly associated (p = 0.006), as were sulfamethoxazole allergy and toxicity (p = 0.015). Regarding concomitant medication, concurrent anti-tuberculosis drugs significantly increased the risk of NVP associated liver toxicity (p = 0.001). Therefore, it is important to monitor adverse events from NVP, including liver function tests among HIV/AIDS patients with history of drug allergy, especially against sulfamethoxazole, and those concurrently treated with anti-tuberculosis drugs

The efficacy of highly active antiretroviral therapy (HAART) in immune restoration and reduction of morbidity and mortality among HIV/AIDS patients has been successfully proven, and has led to its recommendation as a standard treatment for HIV/AIDS nowadays.[1] However, access to antiretroviral therapy in resource-limited countries is still a major obstacle for all HIV-infected patients due to economic impediments. Nevirapine (NVP)-based regimens of HAART have been widely used in resource-limited countries because of their efficacy, availability and relatively low cost.[2] In Thailand, the local made fixed-dose combination of antiretroviral drugs; stavudine, lamivudine, and NVP, is named GPO-Vir™. The NVP content was randomly determined by high performance liquid chromatography and confirmed to comply within international and manufacturer's standard concentrations.[3]

NVP, one of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), binds directly to reverse transcriptase (RT) and blocks RNA-dependent and DNA-dependent DNA polymerase activity causing disruption to the enzyme's catalytic site. With oral bioavailability of 93%, its peak plasma concentration is attained by 4 hours following

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a single oral dose and its half-life is 25-30 hours.[4] Liver cytochrome P450 metabolism and urinary excretion of hydroxylated metabolites represent the primary route of NVP biotransformation and elimination in humans. Common toxicity includes mild rash to severe life-threatening Steven Johnson syndrome or toxic epidermal necrolysis (TEN), and symptomatic hepatitis to fatal hepatic failure.[5] This study was aimed to identify the predisposing factors associated with emergence of toxicity from NVP-based HAART regimens among AIDS patients with low baseline CD4 counts.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Bamrasnaradura Infectious Disease Institute, Nonthaburi, Thailand and approved by the Institutional Review Board of the institute. All HIV/AIDS patients treated with any NVP-based regimen including the antiretroviral drug (ARV) experienced patients during the period January 2004-December 2005 were enrolled into this study. Any patients who discontinued NVP without medical reason (such as emergence of toxicity, treatment failure, development of viral resistance, etc.), and who were lost to follow-up before six months' continuous treatment, were excluded. The outcome of the study was overall NVP toxicity related to intolerability of NVP, including skin toxicity and hepatotoxicity. However, at the end of the study, those who did not develop toxicity and had been treated with NVP-based HAART for at least 6 months were presumed to have no NVP induced toxicity. In grading toxicity emerging from treatment with a NVP-based regimen within six months' post-initiation of the NVP-based regimen, the guidelines of the AIDS Clinical Trial Group 2004 were used.[6]

Proportionate random sampling from all medical records of HIV/AIDS patients was used as the sampling technique. According to hospital data records, 3254 HIV/AIDS patients were treated with the NVP-based regimen (GPO-Vir™), 2378 and 876 initiated in the years 2004 and 2005, respectively. Using computer-generated numbers, proportionally, 72% of the sample size was randomly sampled from the year 2004 and 28% from year 2005. Sample size was estimated as at least 162 medical records to be retrieved for the study. Thirty percent was added for extra-number of the reviewed medical files regarding possible unavailability of the files. However, only 4 files were not available.

Medical records were reviewed and all necessary information on demographic data, baseline laboratory investigations, occurrence of opportunistic infections, concurrent medications, development of toxicity, physicians' diagnosis of skin and hepatic toxicity and outcomes, were collected and recorded on case-record forms. 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 statistically significant, using Chi square or Fisher's exact tests, as appropriate. Survival analysis was used to estimate the median time to onset of toxicity post-treatment with the NVP-based regimen.

RESULTS

Two hundred and six ART-naïve and experienced HIV/AIDS cases with the median age (IQR) of the patients was 33 years (29-38) were included in this study. Among them, 49% were female, of whom 7.9% were pregnant. The baseline characteristics of the patients are presented in Table 1. When categorized according to the 1993 revised classification of HIV infection, 59.2% were category C at HAART initiation. 92.2% of 206 were naïve to ARV and GPOVir™. The lead-in dose of 200 mg NVP once daily was used for initial two weeks. Among ARV experienced patients, the previous regimens were zidovudine/lamivudine/efavirenz (31.25%), stavudine/lamivudine/efavirenz (25%), zidovudine/didanosine (25%), zidovudine alone (12.5%) during pregnancy to prevent mother-to-child transmission (PMTCT), or unknown antiretroviral regimens (6.25%). However, 75% of them were initially given the lead-in dose of NVP.

Of the 206 patients, 18 (8.7%) had a history of drug allergy documented in their medical records by physician. The median (IQR) CD4 T-cell count at start of GPOVir™ was 40 (14-111) cells/mm^3 and 90.8% had CD4 < 200/mm^3. The median baseline HIV-1 RNA (IQR) was 214,500 (31,275-589,250) copies/µl (n = 82) and 9.8% had viral load < 50. The median (IQR) hemoglobin value was 11.75 (9.9-13.1). The median (IQR) alkaline phosphatase value

Table 1 Demographic and baseline characteristics of 206 adult HIV-positive patients with comparison between the groups regarding development of nevirapine associated toxicity

Variables	Toxicity (n = 29)		No toxicity (n = 177)		*P*-value
	%	Median (IQR)	%	Median (IQR)	
Age (years)		32 (27-39)		33 (30-38)	0.52*
Gender: male	51.7		50.8		0.93**
Pregnancy	7.1		8.0		1.0**
Body weight (Kgs)		52 (44-59)		54 (47-60)	0.51*
ART status: Naïve	86.2		91.5		0.32**
Drug allergy	24.1		6.2		**0.006****
Alcohol abuse	3.4		5.1		1.0**
IVDU	3.4		6.8		0.69
Clinical category pre-treatment: C stage					
	69.0		57.6		0.25
Concurrent medication	89.7		95.5		0.19**
CD4 cell count (cells/mm^3)		60 (19-121)		38 (13-113)	
					0.237*
HIV-1 RNA (log_{10} copies/ml)		5.13 (4.4-5.8)		5.33 (4.5-5.7)	0.956*

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

was 98.5 (67-146) U/l and 24.2% had levels above ULN (>150 U/l) (n = 62); aspartate aminotransferase was 30 (23-48) U/l and 19.1% had AST > 1.5 times the upper limit of normal (ULN) (n = 146); alanine amino transferase was 27 (17-44) U/l and 14.4% had ALT > 1.5 ULN (n = 111).

Regarding opportunistic infections, 35.9% had tuberculosis (TB) at the start of the NVP-based regimen, 17% had oral candidiasis, 9.2% had *Pneumocystis jiroveci* pneumonia (formerly known as PCP), 5.8% had cryptococcal meningitis, 4.9% (10/206) had herpes zoster (HZV), 4.4% had cytomegalovirus (CMV) infections and 3.4% had esophageal candidiasis. After ARV initiation, the opportunistic infections that developed were tuberculosis, PCP, HZV and CMV infections, with one patient each (0.5%). Onset was 2 weeks for tuberculosis, 11 weeks for PCP, 8 weeks for HZV, and 13 weeks for CMV infections after starting the NVP-based regimen.

Development of NVP toxicity and predisposing factors for the toxicity development

Twenty-nine (14.1%) patients developed toxicity related to NVP and the incidence of toxicity was 1.09/100 person-months. Among them, 21 (10.2%) and 8 (3.9%) developed skin and liver toxicity, respectively. The incidence of liver toxicity was 0.3/100 person-months. The grading of skin and liver toxicity in detail is described in Table 2. However, 5/21 who developed skin rash continued NVP without interruption but none continued NVP when liver toxicity of NVP detected.

To find out the association factor of NVP, no statistically significant association was found between development of NVP toxicity and age at start of NVP-based regimen ($p = 0.52$); gender ($p = 0.93$); pregnancy ($p = 1.0$); body weight ($p = 0.51$); CDC classification category ($p = 0.36$); naïve or experienced to ARV ($p = 0.57$); concomitant medication ($p = 0.19$); occurrence of opportunistic infections ($p = 0.45$), baseline CD4 T-cell count ($p = 0.24$) or HIV-1 RNA copies/ml ($p = 0.96$). Similarly, no statistically significant differences were found between any of the baseline biochemical parameters of the two groups including ALT ($p = 0.36$) and AST ($p = 0.34$). However, there were statistically significant associations between presence of TB (87.5% *vs*. 33.9%, $p = 0.004$), with a relative risk of 12.33, 95% $CI = 1.55 < RR < 98.07$; occurrence of PCP (37.5% *vs*.

Table 2 Characters of nevirapine toxicity among 29 adult HIV patients

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 post-NVP based regimen initiation Median (IQR): weeks	4 (1.79-16.7)	2.57 (1.79-8.4)	12.43 (2.57-21.2)
Intervention			
Switched to other regimens	24 (82.76%)	16 (76.2%)	8 (100%)
Re-challenge NVP	1 (3.45%)	1 (4.8%)	-
Continued nevirapine	4 (13.8%)	4 (19.0%)	-

The adverse event guidelines of the AIDS Clinical Trial Group, 2004[6];

Skin toxicity 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.

Hepatic toxicity comprising clinical hepatitis with abnormal liver chemistry: Grade 1: elevated serum transaminase level 1.25- 2.5 times the upper limit of normal; Grade 2: elevated serum transaminase level 2.6-5 times the upper limit of normal; Grade 3: elevated serum transaminase level of 5.1-10 times the upper limit of normal; Grade 4: elevated serum transaminase level >10 times the upper limit of normal.

8.5%, $p = 0.032$), with a relative risk of 5.57, 95% $CI = 1.45<RR<21.39$; and development of hepatic toxicity from the NVP-based regimen. When comparing skin toxicity and hepatic toxicity, only TB was found among the opportunistic infections to be significantly higher for hepatic than skin toxicity (87.5% *vs.* 23.8%, $p = 0.003$), with a relative risk of 9.92, 95% $CI = 1.4<RR<70.45$.

There was a statistically significantly higher proportion of NVP toxicity among those with history of drug allergy (24.1% *vs.* 6.2%; $p = 0.006$), with a relative risk of 3.32, 95% $CI = 1.65<RR<6.69$. AIDS patients with history of drug allergy were 3 times more likely to develop toxicity from treatment with the NVP-based regimen than those without any history of drug allergy. History of sulfamethoxazole allergy and NVP toxicity development showed a significant association (17.2% *vs.* 4%, $P = 0.015$) with a relative risk of 3.37, 95% $CI = 1.56<RR<7.25$). There were no statistically significant associations between allergy to rifampicin ($p = 0.37$), penicillin ($p = 0.367$), stavudine ($p = 0.26$), dapsone ($p = 0.26$) and development of NVP toxicity (Table 3).

Regarding skin toxicity development, no statistically significant association was found among baseline demographic, clinical, and laboratory parameters. However, in the group who developed hepatic toxicity, history of drug allergy was significantly associated (37.5% *vs.* 6.2%, $p = 0.016$) and relative risk was 7.33, 95% $CI = 1.95<RR<27.53$). AIDS patients with history of drug allergy were 7 times more likely to develop hepatic toxicity from the NVP-based regimen than those without any history of drug allergy. The incidence of NVP toxicity was 3.7/100 person-months in those with history of drug allergy and 0.9/100 person-months in those without. When the incidence of overall toxicity was compared between those with sulfamethoxazole allergy (3.3/100 person-months) and those without history of sulfamethoxazole allergy (0.9/100 person-months) and the incidence of hepatic toxicity was compared between those with sulfamethoxazole al-

Table 3 Factors predicting development of nevirapine toxicity among 206 adult HIV patients

Factors	All NVP toxicity N (%)			Skin toxicity N (%)			Hepatotoxicity N (%)			Toxicity N (%)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Skin	Hepatic	*p*-value
	N = 29	N = 177		N = 21	N = 177		N = 8	N = 177		N = 21	N = 8	
Drug allergy	7 (24.1%)	11 (6.2%)	0.006**	4 (19%)	11 (6.2%)	0.059**	3 (37.5%)	11 (6.2%)	0.016**	4 (19%)	3 (37.5%)	0.356**
Sulfonamide allergy	5 (17.2%)	7 (4.0%)	0.015**	3 (14.3%)	7 (4.0%)	0.08**	2 (25.0%)	7 (4.0%)	0.051**	3 (14.3%)	2 (25%)	0.59**
History of anti-TB drugs	12 (41.4%)	60 (33.9%)	0.43*	5 (23.8%)	60 (33.9%)	0.35*	7 (87.5%)	60 (33.9%)	0.004**	5 (23.8%)	7 (87.5%)	0.003**
Concurrent anti-TB drugs	9 (34.6%)	33 (22.0%)	0.16*	3 (15.8%)	33 (22.0%)	0.77**	6 (85.7%)	33 (22.0%)	0.001**	3 (15.8%)	6 (85.7%)	0.002**
Concurrent Sulfonamide	24 (82.8%)	156 (88.1%)	0.38**	18 (85.7%)	156 (88.1%)	0.73**	6 (75.0%)	156 (88.1%)	0.26**	18 (85.7%)	6 (75.0%)	0.6**
Concurrent Fluconazole	15 (51.7%)	101 (57.1%)	0.6**	12 (57.1%)	101 (57.1%)	1.0*	3 (37.5%)	101 (57.1%)	0.301**	12 (57.1%)	3 (37.5%)	0.43**

* - Chi-square test ** - Fisher's exact test

lergy (2.02/100 person-months) and those without history of sulfamethoxazole allergy (0.2/100 person-months), a higher incidence of toxicity was associated with history of sulfamethoxazole allergy among AIDS patients treated with the NVP-based regimen (Fig. 1).

When types of concomitant medications used were compared between 29 patients who developed overall NVP toxicity and 177 patients who did not develop any toxicity, no statistical significant association was found between exposure history to anti-TB drugs (p = 0.43), number of concurrent drugs (p = 1.0), concurrent use of anti-TB drugs (p = 0.16); trimethroprim/sulfamethoxazole (p = 0.38); fluconazole (p = 0.6) and development of toxicity from the NVP-based regimen. Also there was no significant association for the development of skin toxicity from the NVP-based regimen. However, history of anti-TB treatment had a statistically significant association with development of hepatic toxicity (87.5% *vs.* 33.9%, p = 0.004). Moreover, concomitant anti-TB treatment was significantly associated with development of hepatic toxicity from NVP (85.7% *vs.* 22.0%, p = 0.001), with a relative risk of 18.15, 95% CI = 2.25<RR<146.17. AIDS patients on anti-TB treatment were more likely to develop hepatic toxicity than skin toxicity from NVP (85.7% *vs.* 15.8%, p = 0.002), with a relative risk of 11.33, 95% CI =1.6<RR<80.2 (Table 3).

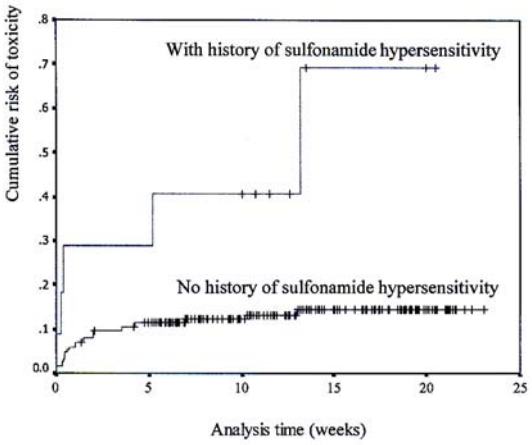

Fig. 1 Time to onset of nevirapine associated toxicity among 206 adult HIV patients with history of sulfonamide hypersensitivity and those without history of sulfonamide hypersensitivity. With Kaplan-Meier comparison, 72% of the patients with history of sulfonamide hypersensitivity did not develop any toxicity within six months of post-nevirapine initiation. Among those without history of sulfonamide hypersensitivity, 90% did not develop any toxicity and 10% developed toxicity within six months of post-nevirapine initiation.

DISCUSSION

The major NVP toxicity referred to cutaneous reactions and liver toxicity, was usually reported during the initial 8 weeks' treatment exposure.[5,7,8] All documented cases in this study presented NVP toxicity with clinical suspicion by physician in real clinical practice setting, in which series of investigations were not well organized as a good prospective research. A lower incidence of NVP toxicity especially liver toxicity with less severity in this study might be due to the limitation of our study in terms of the study design and use of a half-dose NVP lead-in period[9,10] in all ARV naïve and most of ARV experienced patients as well. NVP-associated rash and liver toxicity usually appears in the first 1-4 weeks and 6-18 weeks' post-treatment, respectively.[7,11,12] The median onset time to development of NVP toxicity was 4 weeks, which again support the point emphasized by the US health authorities, that the first 8-12 months is the critical period for intensive clinical and laboratory monitoring to detect potentially life-threatening hepatic toxicity.[13] A 6-month period was sufficient to reach toxicity peak for NVP-treated patients, who had well adhered to the regimen and lost to follow up afterwards.[14] However, patients lost to follow-up within the first 6 months after initiation were not counted for this study, and may have included ones who developed severe or life-threatening conditions.

The incidence of NVP liver toxicity was comparable to the previous study of GPO-Vir™ but with less grade 3 and 4 hepatotoxicity (2%) than previously reported (7%).[15] Pathogenesis of hypersensitivity reaction due to NVP is still unknown, but it is postulated that the degree of immunodeficiency or immune activation altering the drug metabolism associated with glutathione deficiency, or slow acetylating phenotype may contribute towards it.[16] The lower risk of toxicity among the patients with low CD4 cell count may relate to a state of immunodeficiency. However, in this study, we did not routinely perform liver function test and viral hepatitis serology to detect early possible asymptomatic hepatitis (transaminasemia) and co-infection of chronic hepatitis C/B/D viruses in which the NVP associated hepatotoxicity was reported more frequently.[11,17-19] The implementation of the investigation requirement in clinical settings needs to be verified by the national ART guidelines to actual practices. We suggest that at least the first 8-12 weeks and every 3 months afterwards, liver function test should be performed. In resource-limited countries, NVP based regimens were reported as the most preferred regimens and also 75% recommended the use of fixed dose combinations.[20] Although more concerns on its adverse events, recent studies have underlined the long-term efficacy-safety profiles of NVP.[21,22] In 2006 Cochrane revision, NVP-based regimens was assessed as having favorable efficacy and durability, associated with a low potential for drug-drug interactions.[23]

In this study, we did not find any significant demographic or baseline laboratory parameters to predict the development of toxicity, including gender, body weight, median baseline CD4 T-cell count as in a previous study.[22,24-26] This finding was a consequence of the fact that most Thai AIDS cases requiring HAART have CD4 counts of < 200 cells/ul (90.8% in this study). The majority of cases was naïve to antiretroviral drug (92.2%) and also, prior ART status (naïve or experienced) was not associated with development of severe hepatic toxicity.[27] Also, baseline transaminasemia was not associated with NVP toxicity. The explanation to this finding is due to less patients presenting abnormal baseline liver function test. However, the reduction of NVP clearance among the patients with preexisting hepatic abnormalities supported by a population pharmacokinetic study[28] is unclearly clinical implicated. The statistically significant association between history of drug allergy and development of overall toxicity (p = 0.006), in particular, development of hepatic toxicity (p = 0.016) we detected was presumed to address previous history of drug allergy especially sulfamethoxazole allergy (p = 0.015) as another risk factor. Adult AIDS patients with a history of sulfamethoxazole drug allergy were 3 times more likely to develop toxicity from the NVP-based regimen. However, we could not demonstrate a significant association between skin toxicity and history of sulfamethoxazole allergy as previously reported.[29,30] HIV infection has been reported to be a predisposing factor for development of drug allergy, especially multiple drug allergy.[31,32] It seems worthwhile asking about any history of drug allergy before prescribing HAART for HIV/AIDS patients.

Concomitant anti-TB treatment was significantly associated with the development of NVP associated liver toxicity ($p = 0.001$), and AIDS patients concurrently treated with anti-TB drugs were 18 times more likely to develop hepatic toxicity than those without anti-TB treatment. However, the liver toxicity was not significantly higher prevalent regarding baseline abnormal liver function. It should be emphasized that history of anti-TB treatment was a predictive factor for development of hepatitis among AIDS patients taking NVP. Also, AIDS patients with the opportunistic infections TB and PCP were 12 times and 5 times, respectively, more likely to develop hepatic toxicity from treatment with the NVP-based regimen. TB and concomitant anti TB was reported as no association with NVP liver toxicity,[26] in which the prevalence of TB and treatment exposure was much less than our study and the role of ethnicity remains controversial. Liver enzyme abnormalities emerge during antiretroviral therapy as a potential consequence of a broad spectrum of variables, most of them associated with factors other than NNRTI use (direct drug damage, mitochondrial toxicity, multiple metabolic abnormalities, concurrent viral hepatitis, substance and alcohol abuse, and opportunistic infections).[33,34]

In conclusion, NVP-related toxicity from antiretroviral treatment is not uncommon, mostly presenting with adverse cutaneous and hepatic events within 12 weeks of treatment. Significantly, history of drug allergy, especially sulfamethoxazole allergy was associated with overall NVP toxicity, and concommitant anti-TB drug predicted NVP-related liver toxicity. Avoidance of NVP should be emphasized among the patients. However, if NVP is inevitably used among HIV patients with history of drug allergy, especially to sulfamethoxazole, or concomitant anti-TB drugs, advice and follow-up and close monitoring of liver function tests must be provided, especially during the first few months after initiation of NVP therapy, to assure prompt management in case of the development of toxicity.

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