Incidence of nevirapine-associated hypersensitivity reactions is different in patients with prior treatment experience compared to treatment-naïve patients The ATHENA cohort study

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BACKGROUND

Recommendations that nevirapine should be avoided in females with CD4>250/µL or in males with CD4>400/µL are based on findings in treatment-naïve patients (nevirapine package insert, Boehringer Ingelheim). It is unclear whether these guidelines also apply to treatment-experienced patients switching to nevirapine-based combination therapy (NVPc).

METHODS

Inclusion criteria

All HIV-1 infected patients in the Netherlands ATHENA observational cohort who started NVPc between 1 April, 1998 and 1 March, 2006 and for whom data were available on their last known CD4 count before their first use of any antiretroviral therapy (i.e. CD4 nadir) as well as at first time initiation of nevirapine.

Definition of hypersensitivity reactions (HSR)

We identified all patients who discontinued the use of nevirapine because of an adverse event compatible with a nevirapine-induced hypersensitivity reaction within 18 weeks after first starting nevirapine.

All rash- related events and/or hepatotoxicity that occurred in this time window and led to discontinuation of nevirapine are regarded as hypersensitivity reactions.

Reasons for discontinuation are systematically collected and validated in the ATHENA database and include discontinuation due to rash- and liver-related events.

Grouping of patients according to CD4 count

Patients were classified into those who started nevirapine while still being antiretroviral treatment-naïve, and those who were already treatment-experienced with other antiretrovirals when first initiating nevirapine-based treatment.

Both treatment-naïve and -experienced patients were grouped according to CD4 count at the start of NVPc as high (>250/µL/>400/µL female/male) or low. Treatment-experienced patients were subdivided according to last available CD4 count prior to first ever antiretroviral therapy (i.e. nadir CD4) using the same criteria.

Statistical Analysis

Rates of discontinuation due to skin rashes and liver-related events were calculated and compared between groups using the chi-square statistic.

Potential risk factors for nevirapine-induced HSR were investigated using multivariate logistic regression: gender, country of origin, plasma HIV-1 RNA levels, age, hepatitis B and hepatitis C coinfections, body mass index, prior treatment with any antiretroviral agent, and prior treatment with efavirenz.

RESULTS

Of 3752 patients that started nevirapine-based cART, HSR occurred in 231 patients (6.2%).

Of those 231 patients, 182 discontinued NVP due to skin rash (4.9%) and 57 due to hepatotoxicity (1.5%).

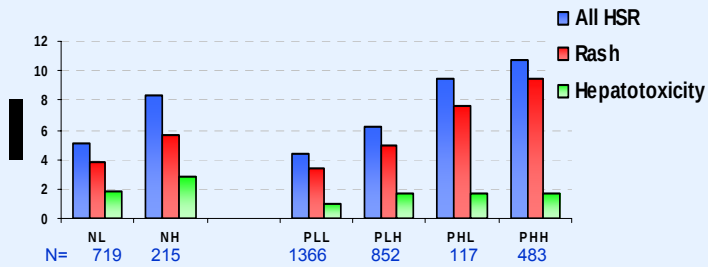
8 patients had to discontinue NVP due to the occurrence of both rash and hepatotoxicity.

Table 1. Characteristics of 3752 patients who started nevirapine-based cART between 1 April 1998 and 31 March 2006

	Treatment naive		Treatment experienced	
	No HSR	HSR	No HSR	HSR
No. of patients n=3752	879	55	2642	176
Age median (yrs)	37	36	40	38
West.origin (%)	59	64	72	68
Male (%)	73	60 *	80	66 *
AIDS diagnosis (%)	18	11	33	25 *
Plasma HIV RNA< 50 copies/mL at start nevirapine n (%)	-	-	1112 (42)	57 (32) *
CD4 count median (x10^6/L)				
at start ART	230	263	200	282 *
at start NVP	230	263	350	398 *

*Significant at p<0.05 level

Figure 1. Rates of discontinuation of nevirapine due to hypersensitivity reactions*



*NL Naive patients, low CD4 count; NH Naive patients, high CD4 count; PLL Pretreated patients low nadir CD4, low current CD4 counts; PLH Pretreated patients low nadir CD4, high current CD4 counts; PHL Pretreated patients high nadir CD4, low current CD4 counts; PHH Pretreated patients, high nadir CD4 and high current CD4 counts

*Low CD4 counts: Women with CD4 counts ≤250 cells/mm³ and men with CD4 counts ≤400 cells/mm³

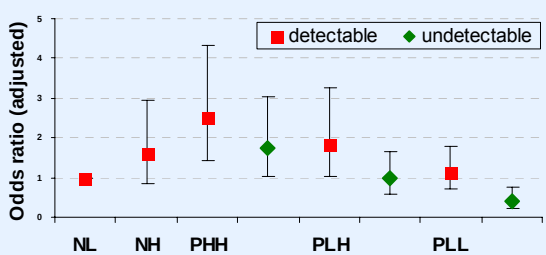
Table 2. Multivariate logistic regression of parameters associated with discontinuation of nevirapine due to hypersensitivity reactions

	Odds ratio	(95%CI)	p-value
Treatment naïve			
NL Low CD4 *	Ref	Ref	Ref
NH High CD4	1.53	(0.84-2.77)	0.16
Treatment experienced			
PLL Low nadir, low current CD4	1.02	(0.67-1.57)	0.92
PLH Low nadir, high current CD4	1.77	(1.10-2.85)	0.02
PHL High nadir, low current CD4	2.06	(1.01-4.18)	0.05
PHH High nadir, high current CD4	2.71	(1.69-4.35)	<0.0001
Gender & region of origin			
Female vs. male	1.39	(1.02-1.90)	0.04
Asian female vs. non-asian male **	6.14	(2.97-12.69)	<0.0001
Asian male vs. non-asian male	0.84	(0.25-2.63)	0.73
Undetectable at start nevirapine	0.53	(0.38-0.75)	0.0003

*Reference are treatment naive patients that start NVP with low CD4 counts

**11 out of 40 Asian females developed HSR, 10 of which were skin rashes and 1 case of liver-related toxicity

Figure 2. Odds ratios for risk of discontnuation of nevirapine due to hypersensitivity reactions adjusted for gender and region of origin. *



*This model is a good reflection of absolute rates of discontinuation due to HSR: 5.3% of patients in NL group developed HSR versus 9% of patients in the NH group, 13.5% in the detectable PHH group, 9.3% in the undetectable PHH group, 9.3% in the detectable PLH group, 5.2% in the undetectable PLH group, 5.7% in the detectable PLL group and 1.7% in the undetectable PLL group.

CONCLUSIONS

Treatment-experienced patients with low nadir and high current CD4 counts with plasma HIV RNA levels below detection limit have a similar risk for developing HSR when they switch to NVPc compared to treatment-naïve patients with low CD4 counts.

This suggests that NVPc may be safely initiated in these patients. However, in similar patients with a detectable plasma viral load levels, it is prudent to continue adhering to current CD4 thresholds.

Patients that start nevirape with detectable plasma HIV-1 RNA levels, females and especially Asian females are at increased risk for developing NVP-associated hypersensitivity .