



Low Hepatotoxicity in Patients Randomized to Switching to Nevirapine QD vs. Continuing with Nevirapine BID

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BACKGROUND

Convenience is an important factor to improve adherence to HAART. Many antiretroviral drugs can be given in once-daily (QD) doses. Nevirapine (NVP) QD was associated with a higher risk of hepatotoxicity as compared with the standard BID regimen in ARV-naïve patients enrolled in the 2NN trial (Van Leth F. Lancet 2004; 363: 1253-63). A great proportion of patients with NVP-related hepatotoxicity present the event in the first 12-18 weeks as part of a hypersensitivity reaction.

OBJECTIVE

To compare hepatotoxicity, other safety parameters, and efficacy in stable patients tolerating a standard BID NVP-containing regimen who switched to QD NVP.

PATIENTS AND METHODS

Design: Randomised, open, multicenter trial
Setting: 24 Hospitals in Spain with extensive experience in HIV management

Patients: Adult HIV-infected pts receiving a standard BID NVP-containing HAART regimen, for at least 12 weeks (18 if women with CD4 >250 cells/uL), with undetectable plasma viral load and ALT <2.5 times the upper normal limit (UNL).

Intervention: After stratification by CD4 count (≥ or <200 cells/uL) and HCV (+ or -), patients were centrally randomised to 1) switch to NVP 400 mg QD or 2) continue with NVP 200 mg BID.

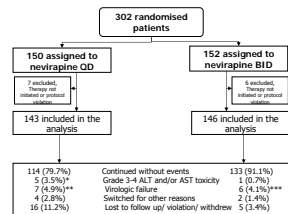
Follow-up: Clinical status (adverse effects, HIV-related symptoms, adherence) and laboratory parameters (blood cells, ALT, AST, alkaline phosphatase, GGT, creatinine, glucose, total cholesterol, triglycerides, HDLc, LDLc, CD4 count and viral load) were assessed at baseline, and months 1, 3, 6, 9 and 12.

Primary outcome: Time to ALT and/or AST Grade ≥ 3 (>5 times above normal values, or >3.5 times the baseline value if grade >0 at baseline).

Statistical analysis: The primary endpoint was analysed using intent-to-treat Switch=Toxicity (ITT S=T) and intent-to-treat observed (ITT observed) approaches:

- In the ITT S=T analysis, switch of treatment or loss to follow-up was considered as toxicity.
- In the ITT observed analysis, loss to follow-up was censored.
- Predictive factors of ALT and/or AST toxicity were assessed using a logistic regression model for dichotomous responses. A 2-sided p-value of 0.05 was considered statistically significant.

OUTCOME OF RANDOMIZED PATIENTS



* 2 patients presented acute A and C viral hepatitis, respectively
 ** 3 patients had VF and continued with nevirapine up to 48 weeks, 1 patient had VF and discontinued, 2 patients also switched for other reasons and 1 patient also had grade 3-4 ALT and/or AST toxicity.
 *** 4 patients had VF and continued with nevirapine up to 48 weeks, 1 patient had VF and discontinued and 1 patient had grade 3-4 ALT and/or AST toxicity.

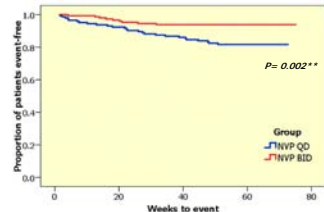
BASELINE CHARACTERISTICS OF 289 EVALUABLE PATIENTS

Variable	NVP QD (n=143)	NVP BID (n=146)	All subjects (n=289)	p-value
AGE, YEARS	Mean (SD) 42.3(10.1)	44.3(10.3)	43.3(10.2)	
MEDIAN (Range)	42.0(21.0-77.0)	42.0(14.0-74.0)	42.0(21.0-77.0)	0.093*
SEX (%)	Male 95(66.5)	109(74.7)	204(70.6)	0.125*
RACE (%)	Caucasian 137(95.8)	143(97.9)	280(96.9)	0.450*
	Heterosexual 52(36.4)	39(26.7)	91(31.5)	
RISK PRACTICE (%)	Homosexual 43(30.1)	52(35.6)	95(32.9)	0.226*
Drug users	40(28.0)	49(33.5)	89(30.8)	
Others	8(5.6)	6(4.1)	14(4.8)	
AIDS (%)	49(34.5)	37(25.5)	86(30.0)	0.240*
CD4	Mean (SD) 606.1(299.0)	634.2(299.4)	620.2(299.0)	0.196*
Median (Range)	551(11-1790)	621(36-2187)	585(2-2187)	
HCV (%)	45(31.5)	50(34.2)	95(32.9)	0.615*
HBS Ag (%)	6(4.2)	3(2.1)	9(3.1)	0.295*
ALT (%)	Grade 1 30(20.9)	31(21.2)	61(21.1)	0.990*
Grade 2 11(7.7)	5(47.3)	10(36.5)	15(5.2)	0.375*
Grade 3 1(0.7)	4(28.3)	5(17.7)	9(3.1)	
Grade 4 0	0	0	0	
MONTHS WITH PREVIOUS NEVIRAPINE**	Mean (SD) 42.4(13.9-91.9)	43.8(10.8-93.6)	43.1(13.9-91.9)	0.850*
Median (Range)	42.4(1.3-91.9)	43.8(1.0-93.6)	43.1(1.3-91.9)	

(1) Mann Whitney (Strat); (2) T-test for independent samples; (3) Chi-Square
 *AST level was not used as an exclusion criteria
 ** 73.0% of patients in both arms had received standard BID nevirapine for more than 24 months, 10.7% for 12-24 months, and 11.0% for 3-12 months.

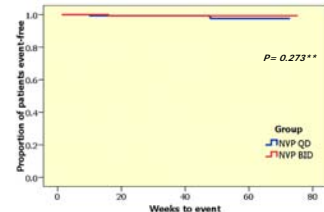
RESULTS

TIME TO GRADE 3-4 LIVER TOXICITY, LOSS TO FOLLOW-UP OR NEVIRAPINE SWITCH ACCORDING TO ARM*



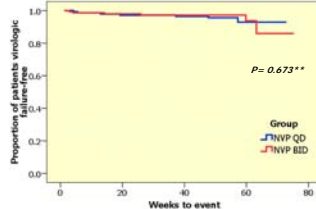
* Intent-to-treat: missing/switch=toxicity.
 ** Log-Rank test

TIME TO GRADE 3-4 LIVER TOXICITY ACCORDING TO ARM*



* Intent-to-treat observed analysis. Two patients with acute A and C viral hepatitis respectively, were not considered to have toxicity due to NVP
 ** Log-Rank test

VIROLOGIC FAILURE ACCORDING TO ARM*



* Intent-to-treat observed analysis
 ** Log-Rank test

PATIENTS WITH GRADE 3-4 HEPATOTOXICITY DURING THE STUDY PERIOD

Patient No.	Arm	Age (years)/Sex/Race	CD4 Cells/uL (AL)	HCV Ab/HCV Ag	Previous months with NVP (NRTI/ART)	ALT/AST at baseline	ALT/AST increase and date (maximum value)	No final outcome and observations
0222	QD	26/M/Caucasian	767	Positive/Negative	38 (AZT/3TC)	Grade 0/Grade 1	Grade 3*/Grade 3* Week 48	No clinical symptoms. NVP stopped. Reason: B.
0312	QD	36/M/Caucasian	975	Positive/Negative	31 (AZT/3TC)	Grade 0/Grade 1	NV Grade 3* Week 8	Acute symptomatic hepatitis A (IgM+). NVP stopped. Alcohol consumption < 100g alcohol intake (1000g).
0911	QD	41/M/Caucasian	646	Positive/Positive	65 (AZT/3TC)	Grade 1/Grade 1	Grade 4*** Week 10	Acute symptomatic hepatitis. NVP stopped and reinitiated 3 months later after resolution, without new increase of AST/ALT. Alcohol consumption < 100g alcohol intake (1000g).
2112	BID	41/M/Caucasian	1425	Negative/Negative	4 (ABC/3TC)	Grade 0/Grade 0	Grade 3*/Grade 2* (Week 12)	No clinical symptoms. NVP stopped. Alcohol: B.
2203	QD	43/F/Caucasian	486	Positive/Negative	64 (AZT/3TC)	Grade 0/Grade 1	Grade 3*/Grade 3* (Week 48)	No clinical symptoms. Received despite continuing with NVP. After by physician to concentrate increase of INR (max alcohol: B).
2403	QD	39/M/Caucasian	987	Negative/Negative	23 (AZT/3TC)	Grade 0/Grade 2	Grade 4*** Week 24	Acute symptomatic hepatitis C (seroconversion after sharing syringe with HCV+). NVP stopped. Alcohol consumption < 100g alcohol intake (1000g).

NR=Not Reported. M=Male. F=Female. *≥5 times the baseline value. **≥10 times the UNL.
 † Plasma alcohol intake >28 units of alcohol/week in male (NR=0).
 ‡ Two pts had confirmed acute A and C viral hepatitis. If these 2 pts were considered to have NVP hepatotoxicity, the proportion of patients with grade 3-4 hepatotoxicity was 3.5% (QD) vs. 0.7% (BID), p=0.084 (chi-square). If the 2 pts with viral hepatitis are excluded, the proportions are 2.1% (QD) vs. 0.7% (BID), p=0.044 (chi-square). **Note:** were there significant differences between arms in the proportion of patients with grade 2 hepatotoxicity (QD 11.2% vs. BID 18.3%, p=0.002 (chi-square)).

VARIABLES ASSOCIATED WITH ALT AND/OR AST TOXICITY GRADE ≥ 2*

Variables	p-value	Exp(B) (OR)	95% C.I. for Exp(B)
Age (reference = "> 40 years")	0.519	1.305	0.582 - 2.926
Gender (reference = "Male")	0.524	1.341	0.544 - 3.303
HCV Ab (reference = "Negative")	<0.001	5.853	2.355 - 14.550
HBS Ag (reference = "Negative")	0.509	1.714	0.347 - 8.467
AST at baseline (reference = "Basal grade <1")	0.518	1.441	0.476 - 4.300
ALT at baseline (reference = "Basal grade <1")	<0.001	3.519	1.289 - 9.607
Group (reference = "NVP BID")	0.199	1.682	0.760 - 3.720
Constant	<0.001	0.036	

* Logistic regression model

CONCLUSIONS

- In patients under standard NVP-containing regimens for at least 12-18 weeks, switching to a QD NVP regimen is associated with a low frequency of hepatotoxicity while viral suppression is maintained.
- HCV+ and increased ALT levels at baseline were independently associated with hepatotoxicity in this cohort.

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