

Solidarité thérapeutique et initiatives contre le Sida

Evaluation of safety and toxicity of nevirapine-containing regimen (D4T-3TC-NVP) in ARV nevirapine naive patients

in Niamey (Niger)

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Background

• High incidence of cutaneous reactions associated with Nevirapine:

5-20% Data from *Boehringer Ingelheim*

14.5% Antinori et al. AIDS 2001, 15: 1579-1581

11% Launay et al. CID 2004:38

Nevirapine-induced hepatitis

28% Havlir et al. J Infect Dis 1995. 171: 537-545

8% Carr and Cooper. Antiviral Chemotherapy 1996, 4

7% grade 3-4 *Anekthananon*. J *Med Assoc Thai, 2004 Jul; 87(7): 760-7*

Risk factors associated to NVP hypersensitivity

Female sex, CD4>250/mm3 Bersoff-Matcha and al. CID 2001; 32:124-129



Access to ARV drugs in Niger

- INAARV (Initiative nigérienne d'accès aux antirétroviraux):
 - Started in October 2004, first in Niamey (5 centres) then Galmi, Zinder and Tahoua.
 - Computerized data base (FUCHIA software)

• SOLTHIS:

- Medical NGO
- Technical, medical and scientific support for access to ARV

Protocol follow-up:

- Prior to ARV initiation: clinical examination and biological tests (NFS, creat, glycemy, ALAT, CD4). Starting of CTX prophylaxis
- Viral hepatitis serology not available
- First-line ARV therapy: [D4T 30 mg-3TC-NVP], Triomune®* 30 ou 40 mg? (CIPLA)
- NVP initiated at 200 mg q.d for 14 days, then increased to 200 mg bid
- Clinical and SGPT biological follow-up



Study objectives

- To evaluate the tolerance of a nevirapine-containing regimen [D4T-3TC-NVP] (Triomune®) during the first six weeks of therapy in HIV-1-infected nevirapine naive patients, with regards to:
 - cutaneous reactions,
 - hepatic toxicity.
- To evaluate the rate of nevirapine discontinuation and the evolution of adverse reactions.
- To assess the potential risk factors associated with nevirapine toxicity.



Study design

- A prospective cohort of patients starting ARV through INAARV included from 15/10/04 to 15/09/05
- Inclusion criteria:
 - HIV-1 confirmed infection (Determine HIV1/2*, ImmunoComb*)
 - adults > 18 years
 - Nevirapine-naive patient
 - first initiation of ARV therapy according to WHO criteria, or switch to nevirapine containing regimen
 - CD4 and biological tests including ALT available
- Exclusion criteria:
 - known intolerance to NNRTI
 - concomitant treatment with rifampin
 - serum alanine aminotransferase (ALT) levels > 5 N
 - pregnancy



Diagnosis of nevirapine cutaneous toxicity

- Cutaneous reactions: clinical evaluation at each time point: D15, M1, M2 and monthly
 Time to onset of rash, severity of AE graded (1/2 or 3/4)
- Hepatoxicity:
 - Clinical examination
 - Evaluation of ALT between D15 and D30

Graded as: 1-2: 1,25 N < ALT < or = 5 N

3: ALT between 5 and 10 N

4: ALT > 10 N

 Discontinuation of NVP (recommended in toxicity 3-4) and evolution were notified



Patients disposition

- 508 patients received ARV through INAARV between October 2004 and September 2005
- 133 not evaluable for the study:
 - 14 children, 12 pregnant women
 - 12 VIH2 (VIH2: n=6, VIH1+2 n=6)
 - 12 NVP experienced, 4 NNRTI failure
 - 3 pre-existent hepatic cytolysis, 61 rifampin concomitant treatment
 - 15 serum alanine transferase not available



Patients disposition

- 375 patients evaluable
- 24 patients (6,4%) discontinued NVP before M2
 - 9 deaths (between D10 and D30):
 - . malaria,
 - . life threatening AIDS conditions,
 - . 5/9 had normal AST,
 - . 4/9 non evaluable,
 - . all had normal skin
 - 14 lost to follow-up (7 after D15, 5 after M1, 1 after D0)
 - 1 stop NVP because concomitant tuberculosis
- 351 patients with follow-up >2 months:

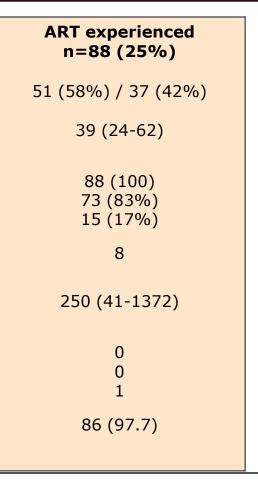
Median follow-up (months): 8 min-max [2-11]



Patients Baseline Characteristics n=351

- Male/female
- Median age: years (range)
- Previous ART
 - NRTI
 - EFV
 - PI
- Median duration of prior ARV drugs (months)
- Median CD4/mm3 (range)
- History of adverse cutaneous reactions:
 - CTX
 - Chloroquine
 - Not available
- CTX prophylaxis

ART naive n=263 (75 %) 151 (57,4%) / 112 (42.6%) 36 (19-65) 0 104 (1-469) 4 (1,7) 1(0.42)25 259 (98.5)





Early intolerance to nevirapine

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Type of AE:

- Cutaneous reactions
- Hepatotoxicity
- Hypersensitivity syndrome

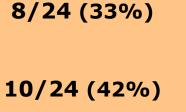
Severity grade 3-4

Leading to NVP discontinuation

Total n=351
30 (8.5%)
7 (2)
22 (6.2)
1 (0.3)

1 (0.3)
8/30 (26%)
11/30 (36%)

Naive n=263
24 (9.5%)
6 (2.3)
17 (6.5)
1 (0.4)



ART experienced n=88
6 (8.81%)
1(1.1)
(6.7)
0
0
1 (1.1%)



Cutaneous intolerance to Nevirapine

□ Clinical presentation

- Cutaneous reaction
- Pruritus
- Presence of rash
- Hypersensitivity syndrome
- Severity Grade: 1-2
- SSJ, Lyell
- ☐ Time to onset of rash (range)
- **□** AE leading to NVP discontinuation

Naïve ART n=7
7
7
3
1
5
2
0
19 days
(8-35)
2

ART experienced n=1
1
1
1
0
1
0
0
18 days
1



Hepatotoxicity concomitant to nevirapine therapy

Туре	ART naïve n=18/263
• Jaundice	0
• Hepatic cytolysis	18 (100%)
• Severity grade: 1-2 3 4	12 (66%) 6 (33%) 0
•Hypersensitivity syndrome	1 (5%)
NVP discontinued	8 (44%)

ART experienced n=5/88
0
5
5 (100%) 0 0
0
0

Total n=23/351
0
23
17 6 0
1
8

Nevirapine induced hepatic toxicity was observed in :

- mostly grade ½
- leading to NVP discontinuation in 44%



Evolution

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- Spontaneous resolution
- Switch to EFV
- Switch to PI
- Reintroduction of NVP

Cutaneous intolerance n = 8

Hepatotoxicity n=23
15
6
1
1



Risk factors associated with intolerance to Nevirapine: 351 patients

	Intolerance (+) (n=30)	Intolerance (-) (n=321)	OR	р
• Female sex	19	130	2,53	< 0,02
 History of adv cut reaction 	1	4	2,73	< 0,5
 Previous EFV ART 	6	82	0,72	0,5
• Age>40 years	10	118	0,86	ns
Baseline ALT>1,25N	5	23	2,59	0,06
CD4>250CD4<100	9 13	59 127	1,81 1,17	0,15 0,8

Note: Intol, intolerance; CR, cutaneous reactions, HPTX, hepatotoxicity; adv cut reaction, adverse cutaneous reaction; CD4/mm3



Study limitations and perspectives

Limitations:

- missing data particularly on early deaths
- no HBV, HCV investigations

Perspectives:

- longer follow-up needed
- evaluation of other adverse events (neuropathy, lipodystrophy)
- evaluation of immunological and virological efficacy: in progress



Conclusion

- A fixed dose combined regimen with D4T-3TC-NVP (Triomune^{®)} is safe and possible in a context of poor resource country, with no prior experience of ARV prescription.
- Intolerance potentially related to nevirapine was observed in 8.5% of cases, but only 2.3% is graded as 3-4, and only 3.1% with NVP discontinuation, mainly on patients with known risk factors as the female sex and particularly cutaneous intolerance.
- Mostly hepatic transaminase elevation (6%) and less frequently cutaneous reactions
 (2%) were observed.
- 5% of these cases were graded 3-4.
- Only 30% led to NVP discontinuation.
- Females were more at risk as well as patients with transaminase elevation at baseline.
- Online data of major importance to evaluate safety and efficacy of access to antiretroviral therapy programme.



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