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

	ART naive n=263 (75 %)	ART experienced n=88 (25%)
• Male/female	151 (57,4%) / 112 (42.6%)	51 (58%) / 37 (42%)
• Median age: years (range)	36 (19-65)	39 (24-62)
• Previous ART		
- NRTI	0	88 (100)
- EFV	0	73 (83%)
- PI	0	15 (17%)
• Median duration of prior ARV drugs (months)	0	8
• Median CD4/mm3 (range)	104 (1-469)	250 (41-1372)
• History of adverse cutaneous reactions:		
- CTX	4 (1,7)	0
- Chloroquine	1 (0.42)	0
- Not available	25	1
• CTX prophylaxis	259 (98.5)	86 (97.7)

Early intolerance to nevirapine

Patients	Total n=351	Naive n=263	ART experienced n=88
Type of AE:	**30 (8.5%)**	**24 (9.5%)**	**6 (8.81%)**
- Cutaneous reactions	7 (2)	6 (2.3)	1(1.1)
- Hepatotoxicity	22 (6.2)	17 (6.5)	(6.7)
- Hypersensitivity syndrome	1 (0.3)	1 (0.4)	0
Severity grade 3-4	**8/30 (26%)**	**8/24 (33%)**	**0**
Leading to NVP discontinuation	**11/30 (36%)**	**10/24 (42%)**	**1 (1.1%)**

Cutaneous intolerance to Nevirapine

	Naïve ART n=7	ART experienced n=1
❑ **Clinical presentation**		
• Cutaneous reaction	7	1
• Pruritus	7	1
• Presence of rash	3	1
• Hypersensitivity syndrome	1	0
❑ **Severity Grade**: 1-2	5	1
3-4	2	0
• SSJ, Lyell	0	0
❑ **Time to onset of rash** (range)	19 days (8-35)	18 days
❑ **AE leading to NVP discontinuation**	2	1

Hepatotoxicity concomitant to nevirapine therapy

Type		ART naïve n=18/263	ART experienced n=5/88	Total n=23/351
• Jaundice		0	0	0
• Hepatic cytolysis		18 (100%)	5	23
• Severity grade:	1-2	12 (66%)	5 (100%)	17
	3	6 (33%)	0	6
	4	0	0	0
•Hypersensitivity syndrome		1 (5%)	0	1
• NVP discontinued		8 (44%)	0	8

Nevirapine induced hepatic toxicity was observed in :

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

Evolution

ART	Cutaneous intolerance n = 8	Hepatotoxicity n=23
• Spontaneous resolution	5	15
• Switch to EFV	3	6
• Switch to PI	0	1
• Reintroduction of NVP	0	1

Risk factors associated with intolerance to Nevirapine: 351 patients

	Intolerance (+) (n=30)	Intolerance (-) (n=321)	OR	p
• 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>250	9	59	1,81	0,15
• CD4<100	13	127	1,17	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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