Poster 709

# Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy.

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on behalf of the Nevirapine Toxicity Multicohort Collaboration.

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## Background

This collaboration of 7 observational clinical cohorts investigated risk factors for treatment-limiting toxicities in both antiretroviral naïve and experienced patients starting nevirapine-based combination antiretroviral therapy (NVPc).

## Methods

- Patients starting NVPc after 1/1/1998 were included.
- CD4 at starting NVPc was classified as high (≥400/mm$^3$/≥250/mm$^3$ for males/females respectively) or low.
- Cox models were used to investigate risk factors for (1) discontinuation of NVPc due to toxicities or patient/physician choice at any time (TOXPC, n=10,186), (2) TOXPC occurring within 18 weeks and (3) discontinuations due to hypersensitivity reactions (HSR) in cohorts with detailed information on reasons for discontinuation (n=6,547).
- Patients were classified according to prior antiretroviral treatment experience and CD4 / viral load at start NVPc.
- Models were stratified by cohort and adjusted for age, gender, ethnicity, nadir CD4 count, calendar year of start NVPc and mode of transmission.

## Results -1-

- Median time from starting NVPc to TOXPC and HSR were 162 days(IQR 31-737) and 30 days (IQR 17-60) respectively.
- Overall, 6,227 (61%) of the 10,186 patients who started NVPc were Caucasian, 274 (3%) were of Asian ethnicity and 2,791 (27%) were female. The NRTI backbone most often used in combination with nevirapine was zidovudine/lamivudine (4,620, 45%). (Table 1).
- The cohorts that collect the specific reasons for discontinuation of antiretroviral therapy contributed 6,547 patients to this study. Of these patients, 1,535 patients discontinued NVPc due to all-cause toxicity.
- 458 (30%) of these 1,535 patients discontinued NVPc due to hypersensitivity reactions: 334 (22%) due to skin rash and 124 (8%) due to hepatotoxicity without concomitant skin rash.
- 80 (6%) treatment-naïve patients who started NVPc with low CD4 counts (the reference group) discontinued NVP due to HSR. (Table 2).
- Of the treatment-experienced patients who initiated NVPc with high CD4 counts and undetectable viral load, 142 (8%) discontinued NVPc due to HSR and 75 (11%) of treatment experienced patients with high CD4 counts and detectable viral load (Table 2).
- Of all patients who started nevirapine, 87 (1%) died within 24 weeks of starting. Although none of the deaths were explicitely reported to be nevirapine-related, complete information on cause of deaths, such as by using the CoDe system (www.cphiv.dk ), were not routinely available and we cannot be certain that the deaths were unrelated to nevirapine use.

**Table 1. Baseline characteristics of 10369 patients starting nevirapine-based cART after 1 January 1998.**

| | Treatment naive patients | | Treatment experienced patients | | | |
|---|---|---|---|---|---|---|
| | Low CD4 | High CD4 | Low CD4, det VL | Low CD4, Undet VL | High CD4, det VL | High CD4, undet VL |
| Total | 3051 | 796 | 1865 | 1349 | 853 | 2272 |
| Female N (%) | 841 (28) | 456 (57) | 360 (13) | 161 (6) | 361 (13) | 612 (22) |
| Prior AIDS diagnosis | 617 (20) | 127 (16) | 720 (39) | 580 (43) | 243 (29) | 653 (29) |
| Country of origin N (%) | | | | | | |
| Europe/USA/Australia | 1543 (51) | 354 (45) | 1208 (65) | 935 (69) | 565 (66) | 1622 (71) |
| Africa | 1021 (34) | 304 (38) | 337 (18) | 235 (17) | 142 (17) | 344 (15) |
| Asia | 91 (3) | 13 (2) | 52 (3) | 31 (2) | 25 (3) | 62 (3) |
| Other | 396 (13) | 125 (16) | 268 (14) | 148 (11) | 121 (14) | 244 (11) |
| IDU | 222 (7) | 59 (7) | 325 (17) | 128 (10) | 108 (13) | 169 (7) |
| Hepatitis B | 81 (3) | 17 (2) | 103 (6) | 52 (4) | 34 (4) | 104 (5) |
| Hepatitis C | 129 (4) | 33 (4) | 234 (13) | 105 (8) | 87 (10) | 144 (6) |
| Start NVP after 2002 | 1209 (40) | 251 (32) | 398 (21) | 566 (42) | 131 (15) | 853 (38) |
| Age (yrs) | 37 (32-43) | 33 (29-39) | 39 (34-45) | 41 (36-49) | 37 (32-44) | 40 (35-47) |
| Plasma HIV RNA start NVP ($log_{10}$ c/ml) | 4.9 (4.3-5.2) | 4.3 (3.5-4.9) | 4.5 (3.8-5.0) | 1.7 (1.7-1.9) | 3.7 (2.9-4.3) | 1.7 (1.7-1.8) |

**Figure 1. Hazard ratios for toxicity and hypersensitivity reactions for treatment naïve and experienced patients stratified according to CD4 count and viral load.**

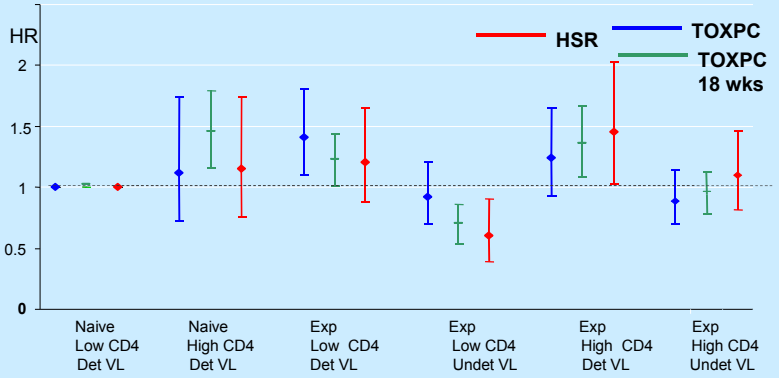


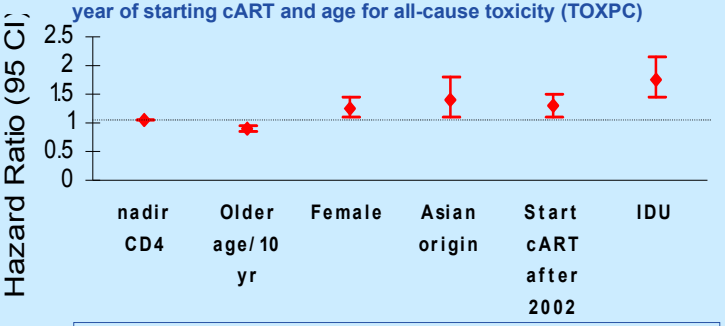

**Table 2. Percentages of patients that discontinue due to treatment-limiting toxicities at any time, within 18 weeks and due to hypersensitivity reactions.**

| | Treatment naive patients | | Treatment experienced patients | | | |
|---|---|---|---|---|---|---|
| | Low CD4 | High CD4 | Low CD4, Det VL | Low CD4, Undet VL | High CD4, Det VL | High CD4, Undet VL |
| Discontinuation due to TOXPC, n=2610/10186 | 690/3051 (23) | 284/796 (36) | 563/1865 (30) | 280/1349 (21) | 269/853 (32) | 524/2272 (23) |
| Discontinuation due to TOXPC within 18 weeks, n=1088/10186 | 289/3051 (10) | 139/796 (18) | 222/1865 (12) | 77/1349 (6) | 135/853 (16) | 226/2272 (10) |
| Discontinuation due to HSR, n=458/6547 | 80/1348 (6) | 37/378 (10) | 90/1265 (7) | 34/1011 (3) | 75/699 (11) | 142/1846 (8) |

## Results -2-

- In adjusted Cox analyses, compared to naïve patients with a low CD4 count, treatment-experienced patients with high CD4 and viral load≥400 had a significantly increased risk for TOXPC (HR 1.27, CI 1.09-1.49), TOXPC within 18 weeks (HR 1.34, CI 1.08-1.67) and HSR (HR 1.45, CI 1.03-2.03).
- In contrast, treatment-experienced patients with high CD4 and viral load<400 had no increased risk for TOXPC (HR 0.89, CI 0.70-1.14), TOXPC within 18 weeks (HR 0.94, CI 0.78-1.13) or HSR 1.10 (0.82-1.46).
- Female gender, Asian ethnicity and more recent calendar year of starting nevirapine were significantly associated with an increased risk for all three endpoints.
- Higher nadir CD4 count was associated with a slightly increased risk for all endpoints, for TOXPC the hazard ratio was 1.05, 95% CI (1.03-1.07).
- Intravenous drug use was significantly associated with TOXPC and TOXPC within 18 weeks, but not with HSR.
- Age was only significantly associated with TOXPC, not TOXPC within 18 weeks or HSR.

**Figure 2. Risk factors gender, race, intravenous drug use, nadir CD4, year of starting cART and age for all-cause toxicity (TOXPC)**




## Conclusions

We found that having a detectable viral load, higher current and nadir CD4 count, female gender, and Asian origin were each independently associated with an increased risk for treatment-limiting toxicities and hypersensitivity reactions associated with nevirapine. Our results suggest that it may be relatively safe to initiate nevirapine-based cART in antiretroviral-experienced patients with high CD4 counts provided there is no detectable viremia.