Risk of discontinuation of nevirapine due to toxicities in antiretroviral naive and experienced patients with high and low CD4 counts

A Mocroft, S Staszewski, R Weber, J Gatell, J Rockstroh, J Gasiorowski, G Panos, A d’Arminio Monforte, A Rakhmanova, AN Phillips, JD Lundgren on behalf of the EuroSIDA study group
Background

- Severe and potentially fatal toxicities reported in ARV-naive patients starting nevirapine based cART (NVPr) with high CD4 counts
- NVPr not recommended for patients with high CD4 counts due to symptomatic liver toxicity
  - >400/mm³ for men
  - >250/mm³ for women
- Not known if NVPr is safer to start in ARV-experienced patients
Objectives

- compare the risk of discontinuation of nevirapine due to toxicities or patient/physician choice (TOXPC)* in 4 groups starting NVPc
  - LN – ARV naive, low CD4 count
  - LE – ARV experienced, low CD4 count
  - HN – ARV naive, high CD4 count
  - HE – ARV experienced, high CD4 count

Low CD4 : ≤250/mm³ females, ≤400/mm³ males
High CD4 : >250/mm³ females, >400/mm³ males

*discontinuation due to any toxicity, patient or physician choice, as per EuroSIDA
follow-up form at www.cphiv.dk
Patients

- All patients starting NVPC
  - nevirapine plus 2 nucleosides/nucleotides
  - after 1 January 1999
  - CD4/VL measured in 6 months prior to NVPC
  - stratified into 4 groups
    - LN – ARV naive, low CD4 count
    - LE – ARV experienced, low CD4 count
    - HN – ARV naive, high CD4 count
    - HE – ARV experienced, high CD4 count

Low CD4 : \( \leq 250/\text{mm}^3 \) females, \( \leq 400/\text{mm}^3 \) males
High CD4 : \( >250/\text{mm}^3 \) females, \( >400/\text{mm}^3 \) males
Methods

- Kaplan-Meier/Cox proportional hazards models used to compare
  - time to discontinuation of nevirapine
  - risk of discontinuation of nevirapine
due to toxicities or patient/physician choice (TOXPC)
## Patient Characteristics

**N=1571**

<table>
<thead>
<tr>
<th></th>
<th>LN</th>
<th>LE</th>
<th>HN</th>
<th>HE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>140</td>
<td>588</td>
<td>62</td>
<td>781</td>
</tr>
<tr>
<td>Male (%)</td>
<td>74.3</td>
<td>83.5</td>
<td>51.6</td>
<td>60.8</td>
</tr>
<tr>
<td>IDU (%)</td>
<td>23.6</td>
<td>25.8</td>
<td>19.3</td>
<td>19.6</td>
</tr>
<tr>
<td>HCV+ (%)</td>
<td>19.3</td>
<td>23.1</td>
<td>24.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Median CD4</td>
<td>194</td>
<td>230</td>
<td>479</td>
<td>561</td>
</tr>
<tr>
<td>Median VL</td>
<td>4.75</td>
<td>3.50</td>
<td>4.43</td>
<td>1.90</td>
</tr>
</tbody>
</table>

- **LN; Low CD4, ARV naïve.**
- **LE; Low CD4, ARV experienced.**
- **HN; High CD4, ARV naïve.**
- **HE; high CD4, ARV experienced.**
Kaplan-Meier time to discontinuation of nevirapine due to TOXPC

Comparison between low (LN) and high (HN) CD4 counts and ARV experience (naïve vs. experienced) shows a significant difference in time to discontinuation (P=0.0006).

- LN: Low CD4, ARV naïve
- LE: Low CD4, ARV experienced
- HN: High CD4, ARV naïve
- HE: High CD4, ARV experienced

N under follow-up:
- LN: 140
- LE: 588
- HN: 62
- HE: 781

Percentage discontinued due to TOXPC by months since starting NVPC:
- 0 months: LN 140, LE 588, HN 62, HE 781
- 12 months: LN 115, LE 440, HN 41, HE 596
- 24 months: LN 100, LE 378, HN 35, HE 482
- 36 months: LN 89, LE 315, HN 25, HE 399
- 48 months: LN 65, LE 257, HN 20, HE 294

Source: EuroSIDA
RH discontinuation of nevirapine due to TOXPC

LN; Low CD4, ARV naïve. LE; Low CD4, ARV experienced.
HN; High CD4, ARV naïve. HE; High CD4, ARV experienced.

Models stratified by centre. Multivariate; adjusted for gender, exposure group, HCV status, prior AIDS diagnosis, age, CD4 nadir, VL at starting NVPc and date started NVPc.
Adjusted RH discontinuation of nevirapine due to TOXPC

Initial 3 months of treatment and after this time

LN; Low CD4, ARV naïve. LE; Low CD4, ARV experienced.
HN; High CD4, ARV naïve. HE; high CD4, ARV experienced.

Models stratified by centre. Multivariate; adjusted for gender, exposure group, HCV status, prior AIDS diagnosis, age, CD4 nadir, VL at starting NVPc and date started NVPc
Discontinuation due to TOXPC in patients starting other cART regimens

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz-based cART</th>
<th>PI-based cART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HN</td>
<td>HE</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>88</td>
<td>970</td>
</tr>
<tr>
<td><strong>MV RH disc</strong></td>
<td>1</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>-</td>
<td>0.60 – 1.38</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>-</td>
<td>0.66</td>
</tr>
</tbody>
</table>

LN; Low CD4, ARV naïve. LE; Low CD4, ARV experienced. HN; High CD4, ARV naïve. HE; high CD4, ARV experienced.

*MV RH disc.; multivariate relative hazard of discontinuation of efavirenz or PI due to TOXPC in patients starting efavirenz or PI-based cART. Model stratified by centre and adjusted for gender, exposure group, HCV status, prior AIDS diagnosis, age, CD4 nadir, VL at starting cART and date started cART.*
Patients who died with ≤ 3 months exposure to NVPC and died within 6 months of stopping NVPC

<table>
<thead>
<tr>
<th>Group</th>
<th>1 LN</th>
<th>2 LE</th>
<th>3* HE</th>
<th>4* HE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks to death</td>
<td>2</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gender</td>
<td>18</td>
<td>12</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>CD4 at NVPC</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>VL at NVPC</td>
<td>137</td>
<td>8</td>
<td>346</td>
<td>1200</td>
</tr>
<tr>
<td>Cause of death</td>
<td>2560</td>
<td>17504</td>
<td>&lt;50</td>
<td>462000</td>
</tr>
<tr>
<td>Nucs</td>
<td>d4T/3TC</td>
<td>d4T/3TC</td>
<td>d4T/3TC</td>
<td>3TC/ABC</td>
</tr>
</tbody>
</table>

LN; Low CD4, ARV naïve. LE; Low CD4, ARV experienced. HN; High CD4, ARV naïve. HE; high CD4, ARV experienced.

*CoDe form completed (details at www.cphiv.dk)
Limitations of analyses

- Based on observational data
- Patients not randomised to treatment regimens
- Used TOXPC as an indication of general toxicities associated with regimen
- Limited power – small number of patients in HN group
Conclusions (1)

- HE group starting NVPc had significantly lower risk of discontinuation of nevirapine due to TOXPC compared to HN group

- Most pronounced difference in initial 3 months of NVPc

- Significant differences between HN and HE groups was not found in patients starting either efavirenz or PI-based regimens
Conclusions (2)

- In patients with high CD4 counts, NVPC may be a safer option for ARV-experienced patients compared to ARV-naïve patients.

- Potentially relevant in developed countries and treatment programs in developing countries where NVPC is one of the cheapest and most commonly prescribed regimens.
The EuroSIDA Study Group (national coordinators in parenthesis).

**Argentina:** (M Losso), A Duran. **Austria:** (N Vetter). **Belarus:** (I Karpov), A Vassilenko, **Belgium:** (N Clumeck) S De Wit, B Poll, R Colebunders, **Czech Republic:** (L Machala), D Sedlacek. **Denmark:** (J Nielsen) J Lundgren, T Benfield, O Kirk, J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, C Pedersen. **Estonia:** (K Zilmer). **France:** (C Katlama), J-P Viard, P-M Girard, T Saint-Marc, P Vanhems, C Pradier, F Dabis. **Germany:** M Dietrich, C Manegold, J van Lunzen, H-J Stellbrink, S Staszewski, M Bickel, F-D Goebel, G Fätkenheuer, J Rockstroh, R Schmidt. **Greece:** (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, G Panos, A Filandras, E Karabatsaki. **Ireland:** (F Mulcahy). **Israel:** (I Yust) D Turner, M Burke, S Pollack, G Hassoun, Z Sthoeger, S Mallan. **Italy:** (A Chiesi) R Esposito, I Mazeu, C Arici, R Pristera, F. Mazzotta, A Gabbuti, M Lichtner, A Chirianni, E Montesarchio, AD Cotugno, Antonucci, F Iacomi, Narciso, Zaccarelli, A Lazzarin, R Finazzi, A D’Arminio Monforte. **Latvia:** (L Viksna). **Lithuania:** (S Chaplinskas). **Luxembourg:** (R Hemmer), T Staub. **Netherlands:** (P Reiss) **Norway:** (J Bruun) A Maeland, V Ormaesan. **Poland:** (B Knysz) J Gasiorowski, A Horban, D Prokopowicz, A Wiercinska-Drapalo, A Boron-Kaczmarska, M Pynka, M Beniowski, E Mularska, H Trocha. **Portugal:** (F Antunes) E Valadas, K Mansinho, F Maltez. **Romania:** (D Duiculescu), A Streinu-Cercel. **Russia:** E Vinogradova, A Rakhmanova. **Serbia & Montenegro:** (D Jevtovic). **Slovakia:** (M Mokráš) D Staneková. **Spain:** (J González-Lahoz) M Sánchez-Conde, T García-Benayas, L Martín-Carbonero, V Soriano, B Clotet, A Jou, J Conejero, C Tural, JM Gatell, JM Miró, P Domingo, MGutierrez, G Mateo, MA Sambeat. **Sweden:** (A Blaxhult), A Karlsson, P Pehrson. **Switzerland:** (B Ledergerber) R Weber, P Francioli, A Telenti, B Hirschel, V Soravia-Dunand, H Furrer. **Ukraine:** (E Kravchenko) N Chentsova. **United Kingdom:** (S Barton), AM Johnson, D Mercey, A Phillips, MA Johnson, A Mocroft, M Murphy, J Weber, G Scullard, M Fisher, R Brettle.

**Virology group:** B Clotet (Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study. **Steering Committee:** F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, Karlsson, C Katlama, B Ledergerber (Chair), A D’Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh. **Coordinating Centre Staff:** J Lundgren (project leader), I Gjørgup, O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, C Holkmann Olsen, J Kjær.

EuroSIDA
Incidence of death from nevirapine associated toxicities in HE group

- No deaths directly related to nevirapine during 2404 PYFU

Incidence 0 (95% CI 0 – 1.5) per 1,000 PYFU

- up to 1.5 deaths from nevirapine-associated toxicities in 1,000 patients starting NVPc in HE group with 1 year FU
- Reduce upper limit of 95% CI:
  - <1 requires 3691 PYFU
  - <0.5 requires 7375 PYFU
  - <0.1 requires 36698 PYFU