a multicentre study

EuroSIDA

Risk of discontinuation of nevirapine due to toxicities in antiretroviral naive and experienced patients with high and low CD_4 counts

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on behalf of the EuroSIDA study group

Background

- Severe and potentially fatal toxicities reported in ARV-naive patients starting nevirapine based cART (NVPc) with high CD_4 counts
- NVPc not recommended for patients with high CD_4 counts due to symptomatic liver toxicity
  - $>400/mm^3$ for men
  - $>250/mm^3$ for women
- Not known if NVPc 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 : ≤250/mm^3 females, ≤400/mm^3 males
High CD4 : >250/mm^3 females, >400/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

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

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

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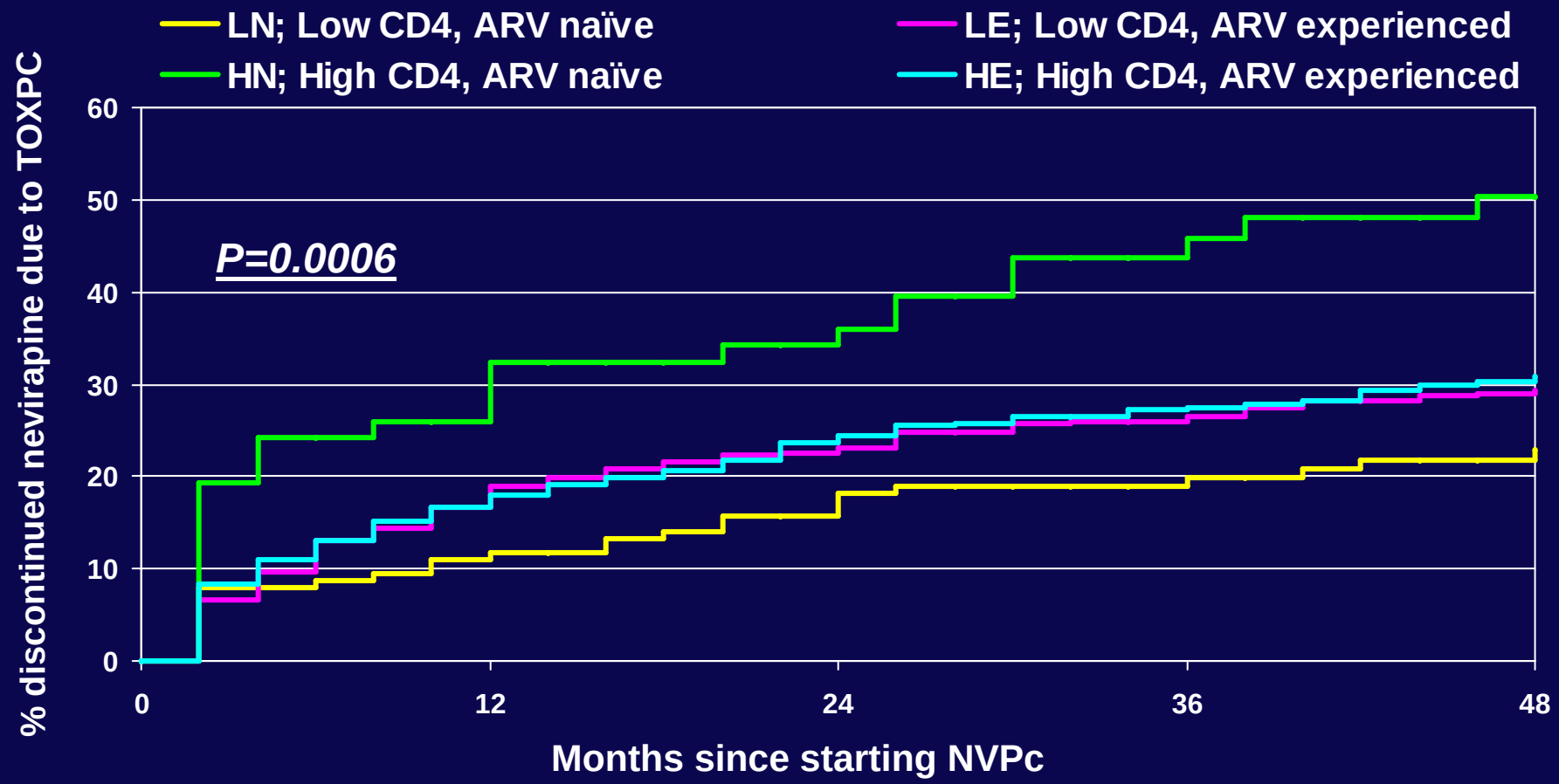
Kaplan-Meier time to discontinuation of nevirapine due to TOXPC



N under follow-up

LN	140	115	100	89	65
LE	588	440	378	315	257
H N	62	41	35	25	20
HE	781	596	482	399	294

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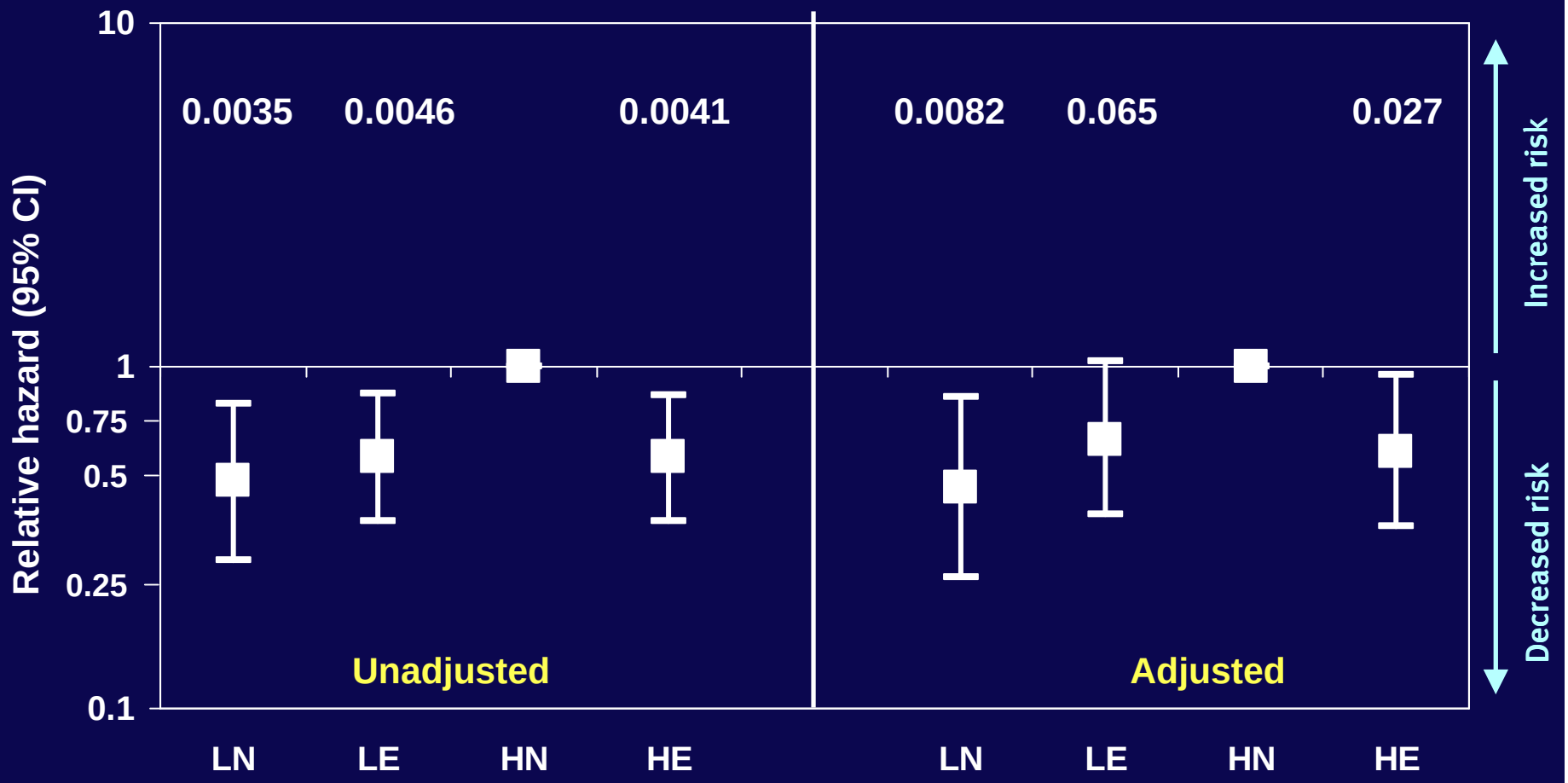
RH discontinuation of nevirapine due to TOXPC

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

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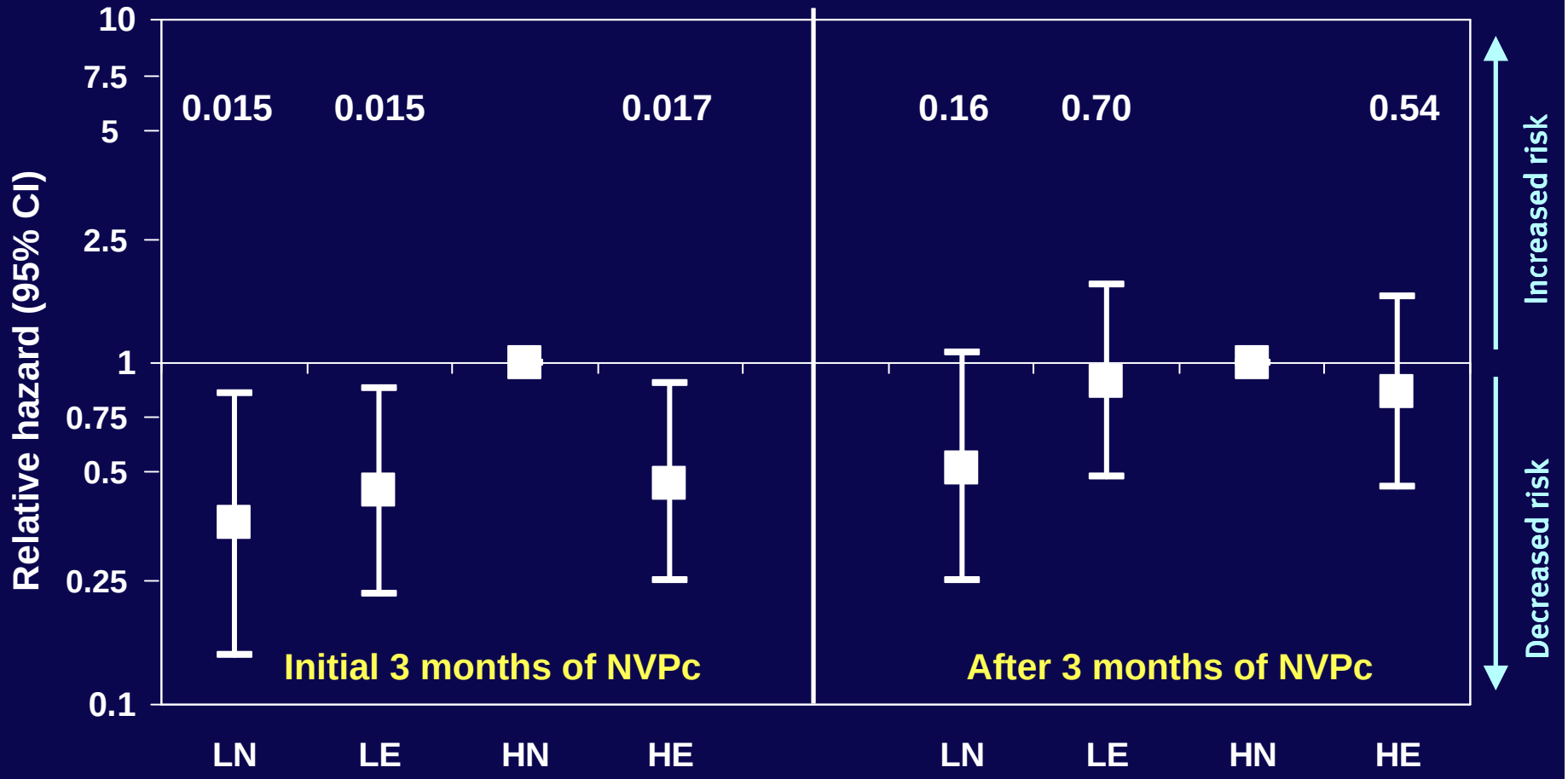
Adjusted RH discontinuation of nevirapine due to TOXPC

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

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Discontinuation due to TOXPC in patients starting other cART regimens

	Efavirenz-based cART		PI-based cART	
	HN	HE	HN	HE
N	88	970	121	369
MV RH disc*	1	0.91	1	1.13
95% CI	-	0.60 – 1.38	-	0.77 – 1.66
p-value	-	0.66	-	0.52

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

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Patients who died with ≤ 3 months exposure to NVPc and died within 6 months of stopping NVPc

	1	2	3*	4*
Group	LN	LE	HE	HE
Started NVPc	3/99	3/99	9/99	4/00
Exposure (weeks)	2	12	2	4
Weeks to death	18	12	26	4
Gender	F	F	F	F
CD4 at NVPc	137	8	346	1200
VL at NVPc	2560	17504	<50	462000
Cause of death	NHL	Cervical cancer	Cirrhosis/HCV Upper GI bleed	Cirrhosis/HCV Upper GI bleed
Nucs	d4T/3TC	d4T/3TC	d4T/3TC	3TC/ABC

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)

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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

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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