Comparison of resistance profiles between patients starting nevirapine and efavirenz in EuroSIDA

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BACKGROUND

Virological outcomes of regimens containing a non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP) or efavirenz (EFV), were compared in mainly drug-experienced patients in a EuroSIDA study (Phillips *et al*, 2001). In common with other observational studies, a lower failure rate was observed for EFV. However, a randomised clinical trial making the same comparison in mainly antiretroviral (ARV)-naïve patients suggested little difference between NVP and EFV (Van Leth *et al*, 2004).

The subsequent development of the EuroSIDA genotypic resistance database has allowed a re-investigation of this question. Using stored plasma samples, genotypic resistance at the start of the NNRTI regimen (baseline) was determined to assess whether variations in resistance between those starting either of the two NNRTIs could explain the virological outcome.

OBJECTIVES

In HIV-1 infected patients starting NVP- vs EFV-containing regimens:

- To compare the rate of virological failure after adjusting for ARV resistance found to be present at baseline.
- To compare resistance profiles at baseline and failure time.

PATIENTS

Analysis was carried out on patients who met the following inclusion criteria:

- Initiated a regimen containing either NVP or EFV (not both) after July 1997.
- No previous exposure to NNRTIs.
- Had a known pre-therapy viral load measurement and CD_4 cell count.
- Had at least two viral load measurements after start of the NNRTI regimen.
- Had genotypic resistance test results available within one year before starting the regimen.

METHODS

- For patients with unsuppressed baseline viral load (› 500 copies/mL), virological failure was defined as two consecutive viral loads › 500 copies/mL at least 6 months after starting NNRTI regimen (any time after start of regimen for those with viral load ≤500 cps/mL at baseline).
- Time to virological failure (the first of these two values) was analysed using Cox proportional hazards models with follow-up to penultimate viral load measurement.
- The Rega algorithm v6.3 was used to interpret ARV resistance. Resistance to nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and NNRTIs was defined as at least one drug in the class showing full or intermediate resistance.

RESULTS

- **Table 1:** The baseline characteristics of the 537 patients who started an NNRTI-containing regimen (323 NVP and 214 EFV) are displayed. 13% were antiretroviral-naïve (10% NVP and 17% EFV, p=0.025).
- There were similar low levels of baseline NNRTI resistance in the two groups (4% NVP and 5% EFV, p=0.584). NRTI resistance was also similar (65% NVP and 61% EFV, p=0.352) however PI resistance was slightly higher in the EFV group (77% NVP and 85% EFV, p=0.022).
- **Figure 1:** The percentage of patients with virological failure over time is shown. In total, 227 (70%) NVP patients, 95% confidence interval (CI): (65%-75%) and 101 (47%) EFV patients, 95% CI: (41%-54%) had experienced virological failure by one year, p<0.001.
- **Figure 2:** The relative hazards (RH) of experiencing virological failure were adjusted for variables considered to be potential confounders in the previous EuroSIDA analysis (number of previous NRTIS/PIs, previous AIDS, year started cART, baseline CD_4 count, CD_4 nadir, viral load, max ever viral load) with the addition of number of active non-NNRTI drugs in the regimen defined by the Rega score (median 1.5 for NVP, 1.5 for EFV, p=0.552), and whether or not the NNRTI in the regimen was active.
- The adjusted RH on EFV compared to NVP was 0.51, 95% CI: (0.40-0.66), p<0.001, displayed in Figure 2. Adjustment for type of NRTI backbone and duration of previous therapy did not change results.
- **Table 2:** Among patients who experienced virological failure, 35% NVP and 24% EFV patients had resistance test results available at time of failure. NNRTI resistance was found to be fairly similar and was high in both groups (86% NVP and 71% EFV, p=0.091), as was NRTI and PI resistance.
- Restricting to patients who were still on an NNRTI regimen at time of failure as well as having a resistance test left 24% of the 248 NVP patients and 19% of the 116 EFV. NNRTI resistance was even higher in these groups as expected but still not significantly different (92% NVP and 86% EFV, p=0.676).
- **Figure 3:** The percentages of new mutations associated with NNRTI resistance that emerged in the two groups highlighted that resistance profiles at failure were quite different. The most prevalent mutations in those starting NVP were rt181C and rt190A and in those starting EFV, rt100I and rt103N.

CONCLUSIONS

- Baseline resistance profiles in patients starting NVP- and EFV-containing regimens cannot explain the difference in virological outcome found in this analysis.
- Similar proportions of those failing NVP and EFV regimens carried NNRTI resistance mutations but different resistance profiles emerged.

COMMENTS

- **Could the difference in virological outcome be explained by further unmeasured confounding factors? For example, patients suffering from depression may be less adherent to the drugs and also may be more likely to receive NVP due to the side effects of EFV.**
- **Could EFV be more effective than NVP in NRTI/PI-experienced patients? Randomised trials have only investigated virological efficacy in ARV-naïve patients.**

REFERENCES

Philips AN, Pradier C, Lazzarin A, *et al*. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens of 2203 mainly antiretroviral-experienced patients. *AIDS* 2001, **15**:2385-2395.

Van Leth F, Phanuphak P, Ruxrungtham K, *et al*. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *The Lancet* 2004, **363**:1253-1263.

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Table 1

Characteristics at start of NNRTI regimen

	NVP		EFV		p
All	323	(60%)	214	(40%)	-
n (%)					
Antiretroviral-naïve	33	(10%)	36	(17%)	0.025
Resistance*					
NNRTI	12	(3.7%)	10	(4.7%)	0.584
NRTI	209	(65%)	130	(61%)	0.352
PI	247	(77%)	181	(85%)	0.022
Median (IQR)					
Date started NNRTI regimen	Jul 98	(Jan 98-Mar 99)	May 99	(Sep 98-Feb 00)	<.001
CD_4 nadir (cells/mm^3)	96	(30-198)	90	(24-184)	0.297
CD_4 count (cells/mm^3)	220	(125-328)	223	(142-330)	0.466
Viral load (log_{10}cps/mL)	4.4	(3.8-5.0)	4.5	(3.7-5.0)	0.979

*Full or intermediate resistance according to Rega algorithm v6.3

Figure 1

Kaplan-Meier plot of % of patients with virological failure over time

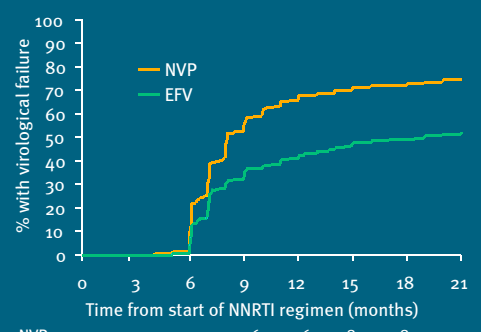

Figure 2

Adjusted relative hazards of virological failure

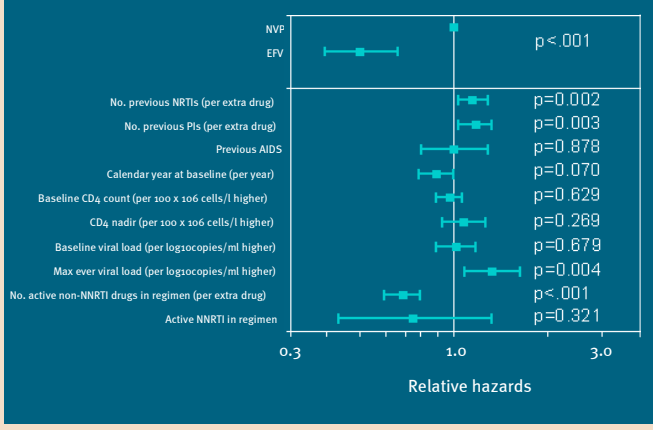

Table 2

At time of virological failure

	NVP		EFV		p
All	248	(77%)	116	(54%)	-
n (%)					
Resistance test at failure	86	(35%)	28	(24%)	0.043
Resistance*					
NNRTI	74	(86%)	20	(71%)	0.091
NRTI	62	(72%)	20	(71%)	0.946
PI	78	(91%)	25	(89%)	0.999
Still on NNRTI and resistance test at failure	59	(24%)	22	(19%)	0.313
Resistance*					
NNRTI	54	(92%)	19	(86%)	0.676
NRTI	42	(71%)	17	(77%)	0.584
PI	55	(93%)	21	(95%)	0.999

*Full or intermediate resistance according to Rega algorithm v6.3

Figure 3

New NNRTI resistance mutations