

**Comparisons of efavirenz and
nevirapine:
Have the cohorts mislead us?**

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Background

- A number of cohort studies have published findings showing that individuals starting regimens including efavirenz (EFV) generally experience a better outcome than those starting regimens including nevirapine (NVP)
- However, results from 2NN suggest no major difference in treatment failure rates between those receiving EFV or NVP in combination with d4T and 3TC
- These results have cast doubt on the conclusions drawn from the cohort studies, and on the value of using such data when making treatment comparisons

Question

Have the cohort studies mislead us, or can the differences in findings be explained by differences in facets of the design or analysis of the trial?

Issues to be considered

- Populations studied and treatments received
- Frequency of virological monitoring
- Drop-outs and loss-to-follow-up
- Treatment changes
- Definition of endpoints/analytical approach

The UK Collaborative HIV Cohort (UK CHIC) study

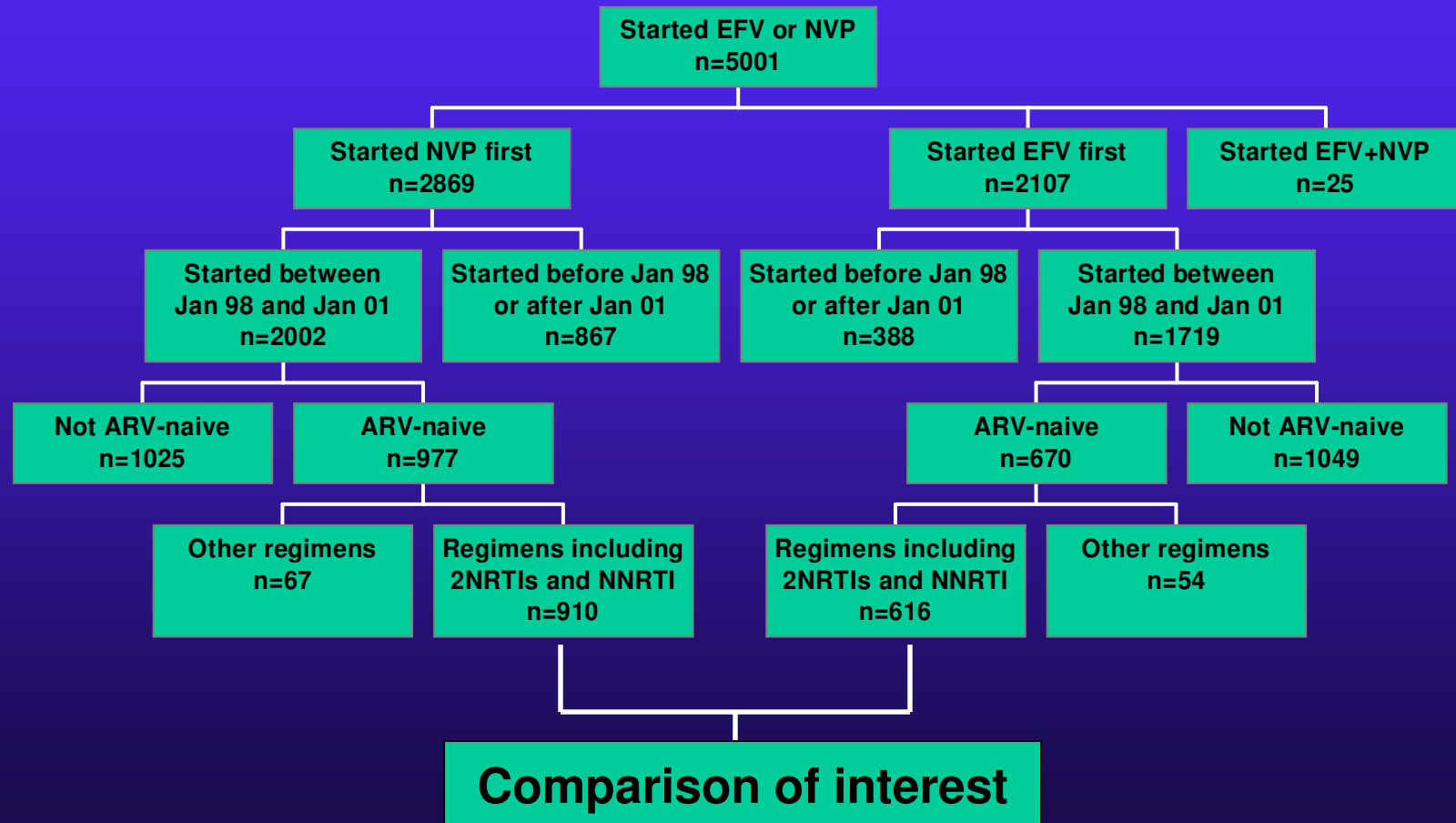
- Collaboration of 7 of the largest HIV centres in the UK
- Cohort formed by merging existing clinical databases from each of the centres in the collaboration
- Criteria for inclusion: HIV+ve, aged >16 years and seen at one of the centres at any time since 1/1/96
- Data on demographics, clinical events and deaths, ARV treatment and laboratory tests provided in standardised format, agreed by all centres at the outset of the study
- To date, cohort contains information on 13,833 individuals seen at 6 of the 7 centres

Populations studied

Broad inclusion criteria

- Started treatment with EFV or NVP between 1/1/98 and 1/1/01 (to ensure availability of ultrasensitive assays, comparable time periods, and to allow for potential for 48 weeks of follow-up)
- ARV-naïve (in 2NN, up to 2 weeks prior NRTI exposure allowed if stopped >3 months prior to start)
- Aged \geq 16 years
- Started treatment combinations including 2 NRTIs only

Populations studied (cont)



Demographics of study population

		Total	NVP	EFV	P-value
No. of patients		1526	910	616	
Gender (%)	Female	21.1	25.9	14.0	0.001
Risk group (%)	Homo/bisexual	59.0	54.3	66.1	0.001
	IDU	3.7	3.6	3.7	
	Heterosexual	30.7	35.3	23.9	
	Other/not known	6.6	6.8	6.3	
Ethnicity (%)	White	51.9	45.7	61.0	0.001
	Black African	22.3	26.9	15.4	
	Other	13.4	15.5	10.4	
	Not known	12.4	11.9	13.2	
Year of start		99 (98-00)	99 (98-00)	00 (98-00)	0.0001
Age at start		35 (17-83)	34 (17-83)	36 (17-72)	0.0001
CD4 at start		206 (0-1410)	216 (0-1410)	189 (0-1000)	0.0001

Populations studied

Other drugs received

	NVP	EFV	P-value
Number of patients	910	616	
Stavudine + lamivudine	142 (15.6)	162 (26.3)	0.001
Zidovudine + lamivudine	452 (49.7)	287 (46.6)	
Didanosine + stavudine	235 (25.8)	111 (18.0)	
Zidovudine + didanosine	60 (6.6)	24 (3.9)	
Didanosine + lamivudine	10 (1.1)	9 (1.5)	
Lamivudine + Abacavir	5 (0.6)	10 (1.6)	
Other	6 (0.7)	13 (2.1)	

Frequency of virological monitoring

Week	Window (weeks)	% with value in window*		
		Total	NVP	EFV
2	1-3	19.3	16.8	23.1
4	2-6	39.6	36.3	44.5
12	8-16	47.7	47.5	48.1
18	14-22	40.2	44.1	34.6
24	20-28	37.2	39.6	33.6
36	32-40	32.4	36.3	26.6
48	44-52	29.8	33.6	24.0

* Comparisons of proportion with available value are significant ($p < 0.05$) at all time points except week 12

Drop-outs and loss-to-follow-up

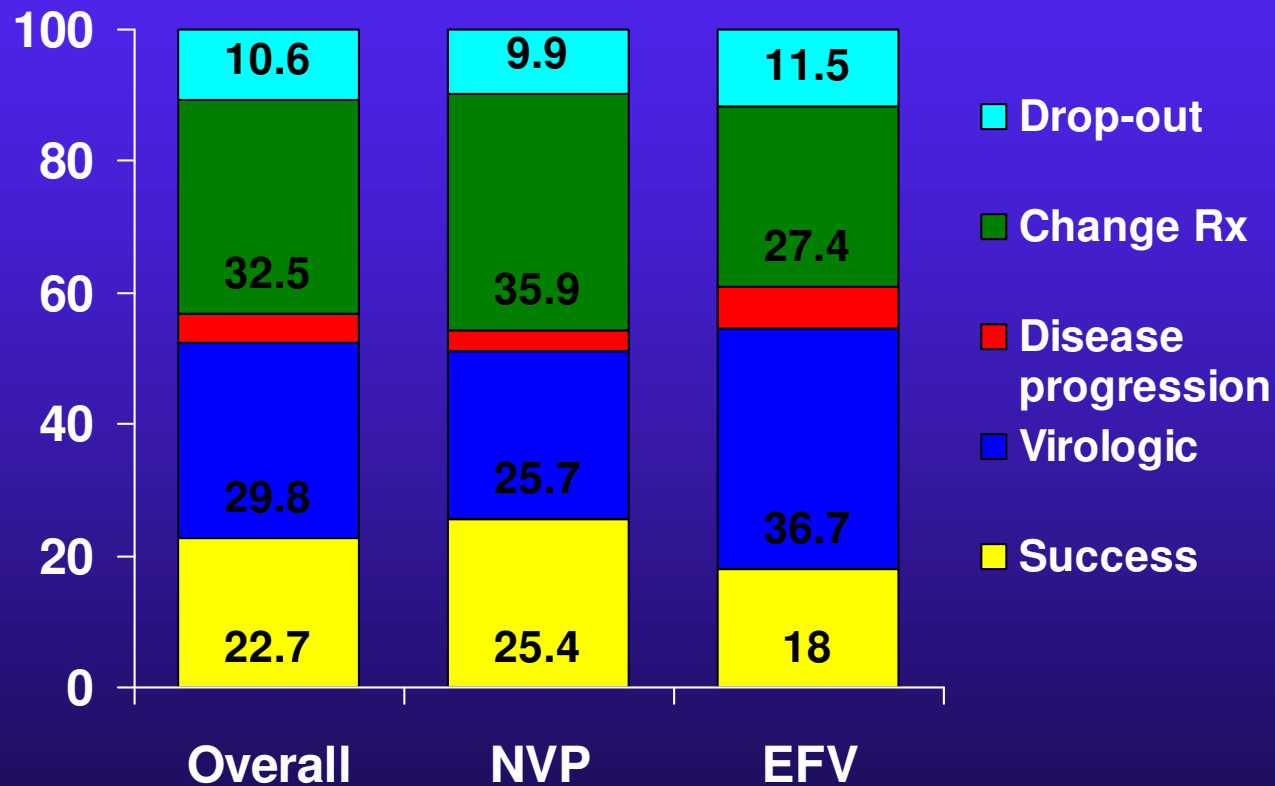
- Difficult to assess using cohort as patients move in and out of cohort over time
- Only available information from cohort is 'last visit date'
- Overall, 344 (22.5%) patients had a last visit date at one of the centres in first 52 weeks after start of therapy
- NVP: 20.2%, EFV: 26.0%, $p=0.008$

First treatment change in 48 weeks

	Total	NVP	EFV
	%	%	%
No change to regimen	60.8	58.8	63.8
Started a new drug not in initial regimen (either NRTI, PI or NNRTI)	0.4	0.3	0.5
Stopped at least one drug in regimen	26.3	29.8	21.3
Switched (ie. stopped and started on same day) at least one drug in regimen	12.5	11.1	14.5

Majority of changes were likely to be due to toxicity (56%) or in those who failed to go < 50 copies/ml (35%)

2NN endpoints in UK CHIC Study – stratified by treatment group



Endpoints:

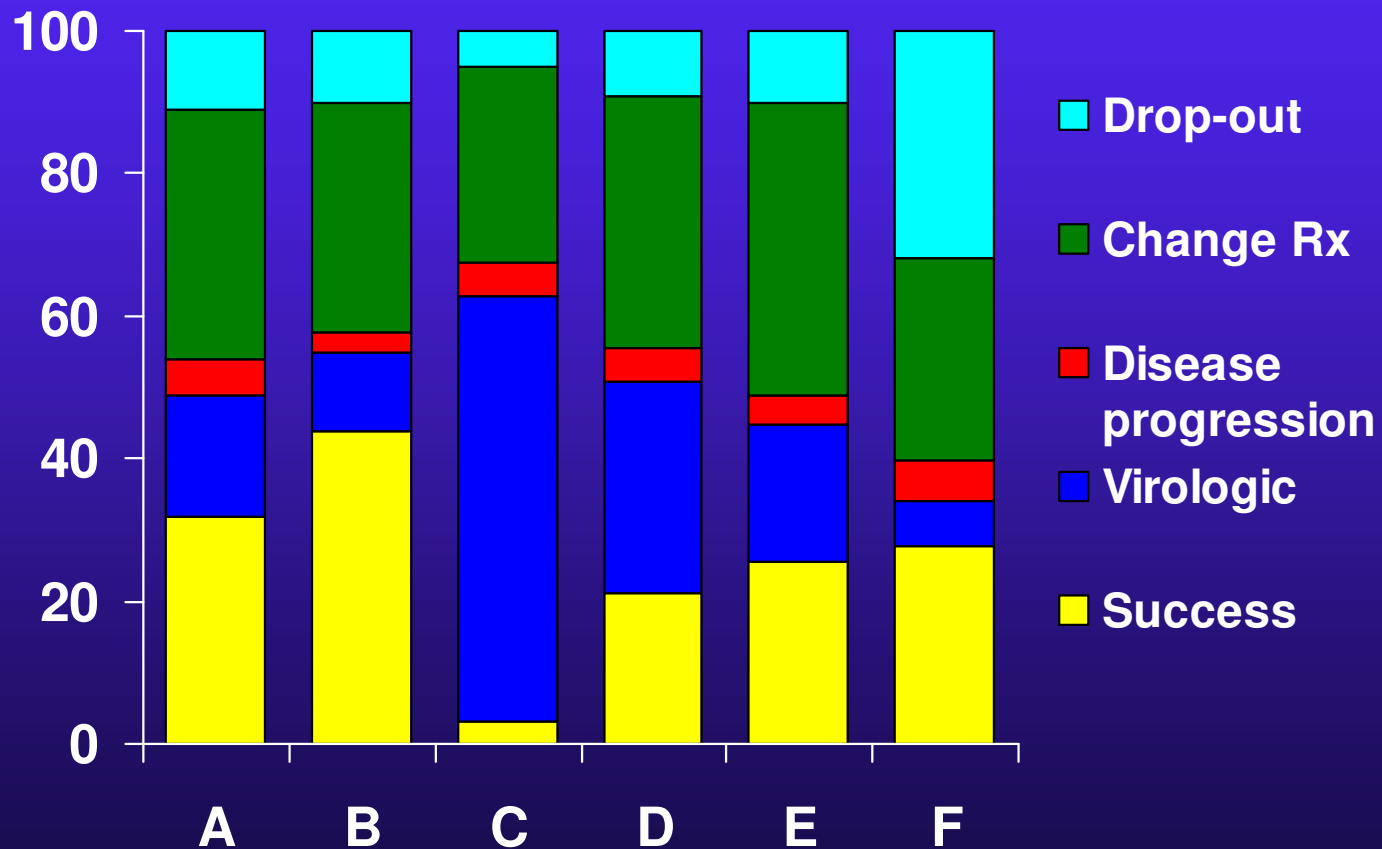
1184
(77.6%)

679
(74.6%)

505
(82.0%)

P=0.001,
Chi-square test

Endpoints in UK CHIC Study – stratified by centre



Centre-specific results

Centre	% of patients in each cohort treated with		Crude OR for failure (EFV vs NVP)
	NVP	EFV	
A	49.0	51.0	0.41 (0.17-0.99)
B	92.4	7.6	1.31 (0.52-3.26)
C	46.2	53.8	1.58 (0.54-4.61)
D	38.8	61.2	1.02 (0.54-1.92)
E	77.6	22.4	0.48 (0.25-0.90)
F	52.2	47.8	1.47 (0.73-2.97)

Results of logistic regression analysis – 2NN definition

Effect of EFV vs NVP	Odds ratio for failure	95% CI	P-value
Unadjusted	1.55	1.20-2.00	0.0007

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As above, plus adjusting for centre	1.02	0.71-1.46	0.92

Results of logistic regression analysis – alternative definitions

Change to definition	OR (95% CI) of failure for EFV vs NVP, p-value*
2NN definition	1.02 (0.71-1.46) P=0.92
Ignoring treatment changes	0.87 (0.65-1.17) p=0.36
Excluding drop in VL in first 12 weeks	0.89 (0.63-1.26) p=0.51
Use of cut-off of 400 copies/ml	0.97 (0.74-1.28) p=0.85
Define endpoint at 6 months, use cut-off of 400 copies/ml and exclude drop in first 12 weeks	0.79 (0.61-1.03) p=0.08

* All values estimated from multivariable logistic regression models after adjusting for patient demographics, year of starting HAART, CD4 and HIV RNA at baseline, and centre

Use of 'usual' cohort time-to-event approaches (Cox regression)

Approach taken	RH for EFV vs NVP (95% CI)*
Time to undetectable VL (<400) ignoring treatment changes	1.15 (1.00-1.33)
Time to undetectable VL (<400) censoring at treatment changes	1.12 (0.97-1.29)
.....	
Time to rebound from baseline, treating patients as failure if not <400 by 52 weeks	1.08 (0.95-1.23)
Time to rebound from date of first VL<400 copies/ml	0.75 (0.49-1.14)

* All values estimated from multivariable logistic regression models after adjusting for patient demographics, year of starting HAART, CD4 and HIV RNA at baseline, and centre

Summary

- Patients receiving NVP and EFV in the cohort have different demographics to those in 2NN – less likely to be female and heterosexual and more likely to be homosexual
- In the cohort, those receiving EFV are less likely to be female or heterosexual, more likely to be white, older and had lower CD4 counts than those on NVP
- In addition, those on EFV were treated in later calendar periods, were receiving different NRTIs and had less regular follow-up VL monitoring than those receiving NVP

Summary (2)

- Drop-outs and treatment changes were more common in cohort – many occurred in first 12 weeks or in those with VL<50 and are likely to be due to toxicity
- Comparison of rates of treatment failure is difficult due to differences in assays and frequency of monitoring – ‘treatment failure’ appears to be more common in cohort, suggesting that definition used may be less appropriate for cohort studies than for trials
- Results of comparison are affected by centre differences, threshold chosen for virological success, components included in the definition of ‘failure’ and analytical approach taken

Discussion

So, have the cohort studies mislead us or have they simply given us an answer to a different question to that posed in 2NN?

Acknowledgements

Steering Committee

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