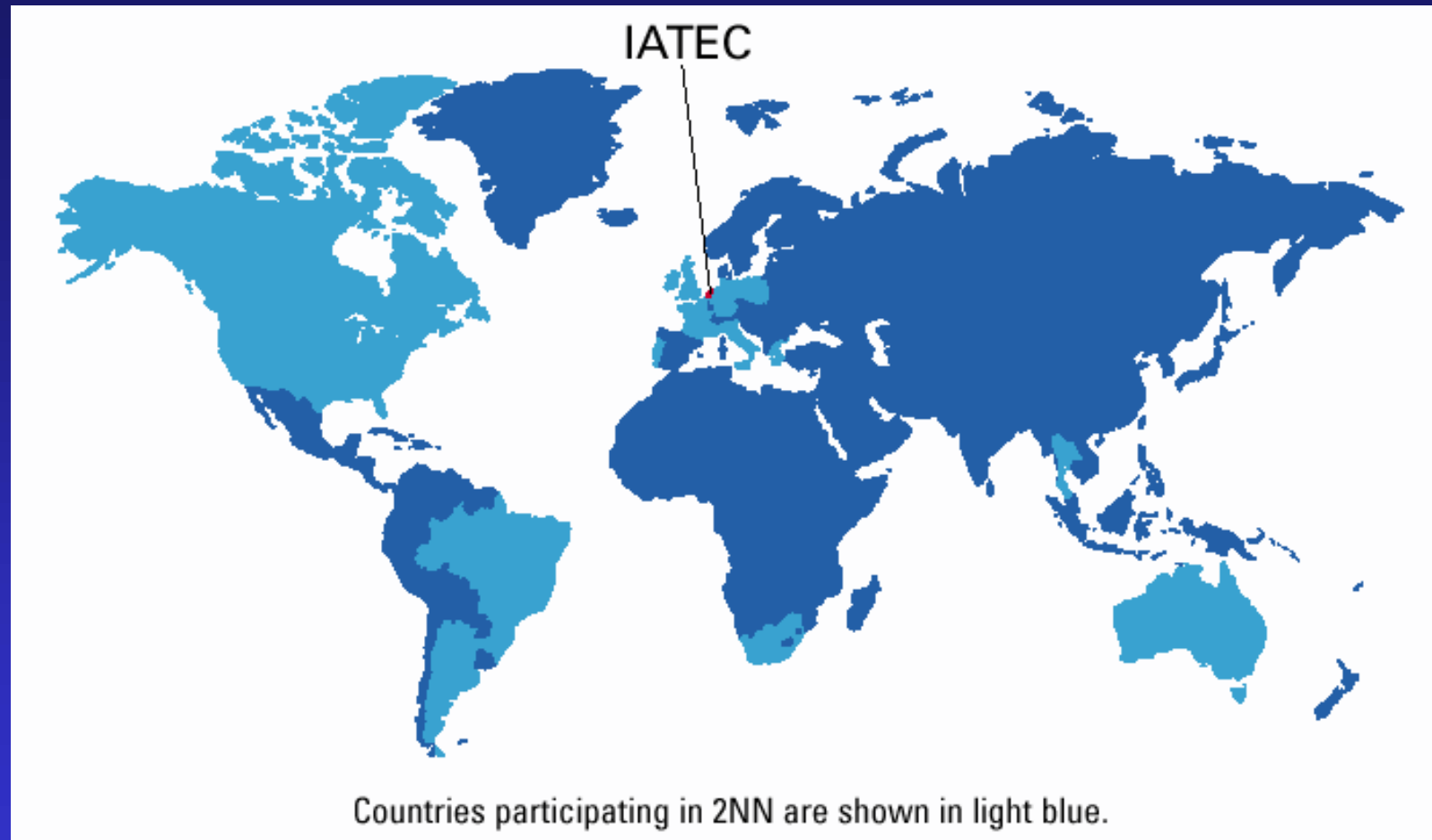


## The 2NN study

A randomised comparative open label trial of first-line antiretroviral therapy with regimens containing either nevirapine, efavirenz, or both drugs combined in addition to stavudine and lamivudine

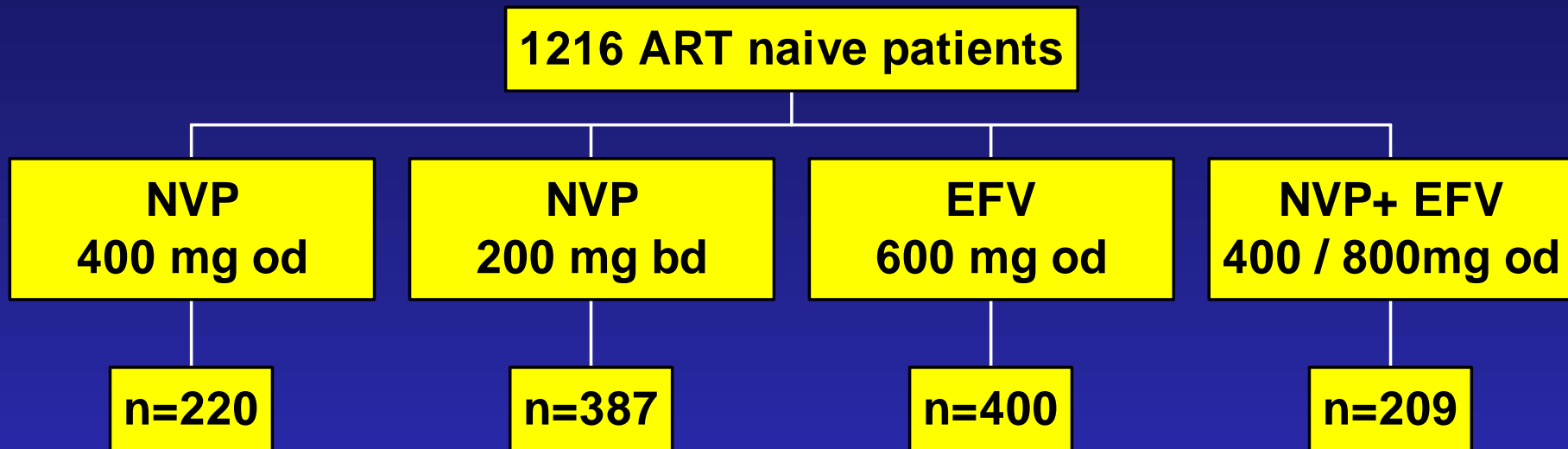
F. van Leth, E. Hassink, P. Phanuphak, S. Miller, B. Gazzard, P. Cahn, R. Wood, K. Squires, F. Raffi, C. Katlama, B. Santos, P. Robinson, R. van Leeuwen, F. Wit and J. Lange  
for the 2NN study team

# Participating countries



17 countries      65 centers

# Trial design



Nucleoside backbone: d4T and 3TC

Inclusion criteria: pVL > 5000 copies/mL  
any CD4 cell count  
any stage of CDC-classification

% of patients with treatment failure at week 48:

- less than 1log<sub>10</sub> decline in pVL in first 12 weeks
- 2 consecutive pVL > 50 copies/mL from week 24 onwards
- new CDC-C event or death
- change of allocated treatment

Secondary outcomes:

- % of patients with pVL < 50 copies/mL at each study week
- change in CD4+ cells
- incidence of adverse events
- change in lipid concentrations (poster 752)

- All analyses Intention-to-Treat (unless stated otherwise)
  - all randomised patients
- pVL data: missing=failure
- Four pre-defined pairwise comparisons
  - NVP-bd vs EFV
  - NVP-od vs NVP-bd
  - NVP-od vs NVP+EFV
  - EFV vs NVP+EFV

# Trial Flow

	NVP-od	NVP-bd	EFV	NVP+EFV
Randomised	220	387	400	209
Started treatment	208	378	381	199
Completed study	182	322	337	175
	83%	83%	84%	84%

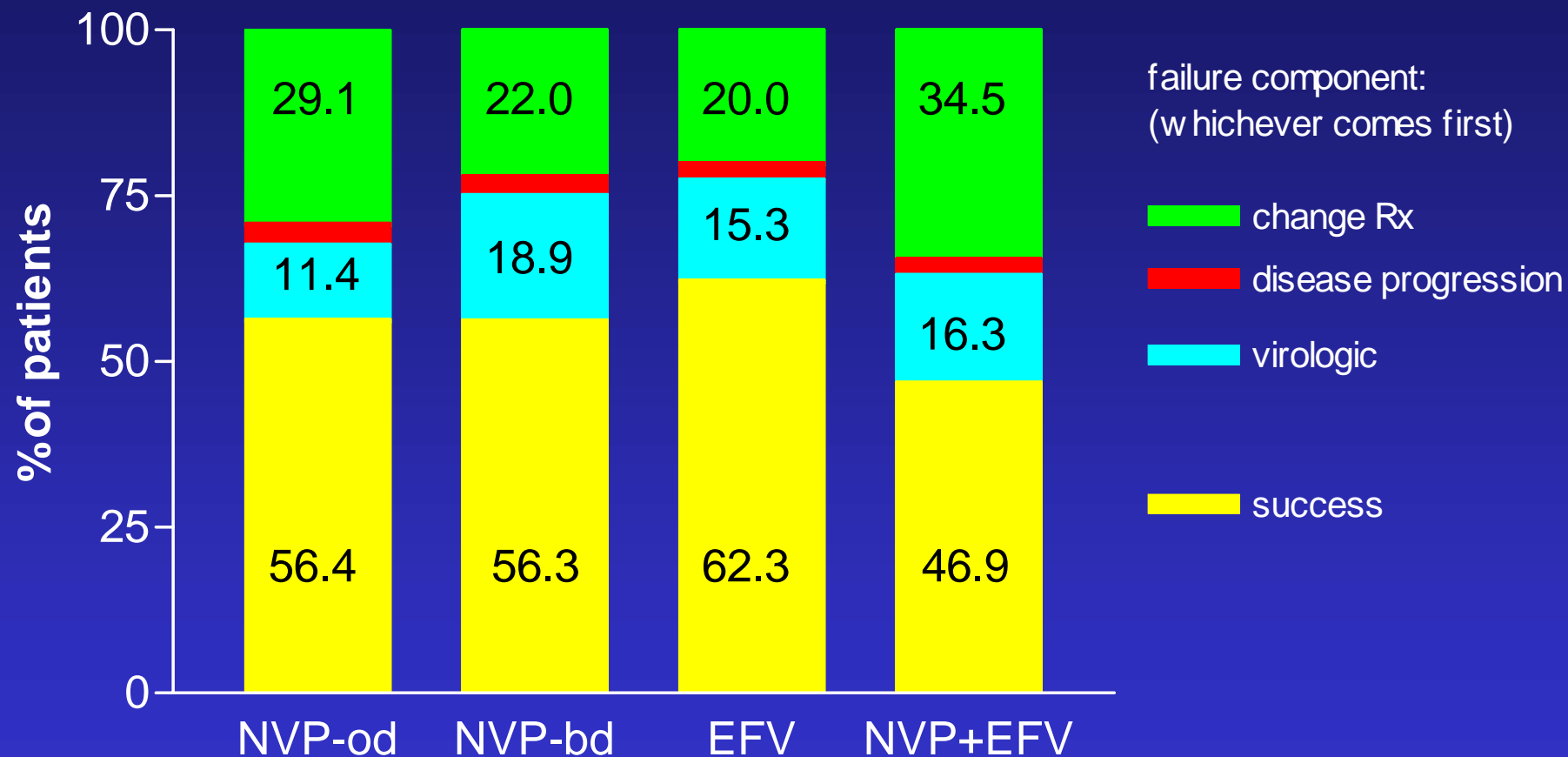
## Reason for discontinuation between randomisation and week 48

Death	7	9	7	2
before start Rx	1	0	1	0
Patients request	10	15	17	15
Lost to follow-up	16	24	26	11
Other	5	17	13	6

# Baseline characteristics

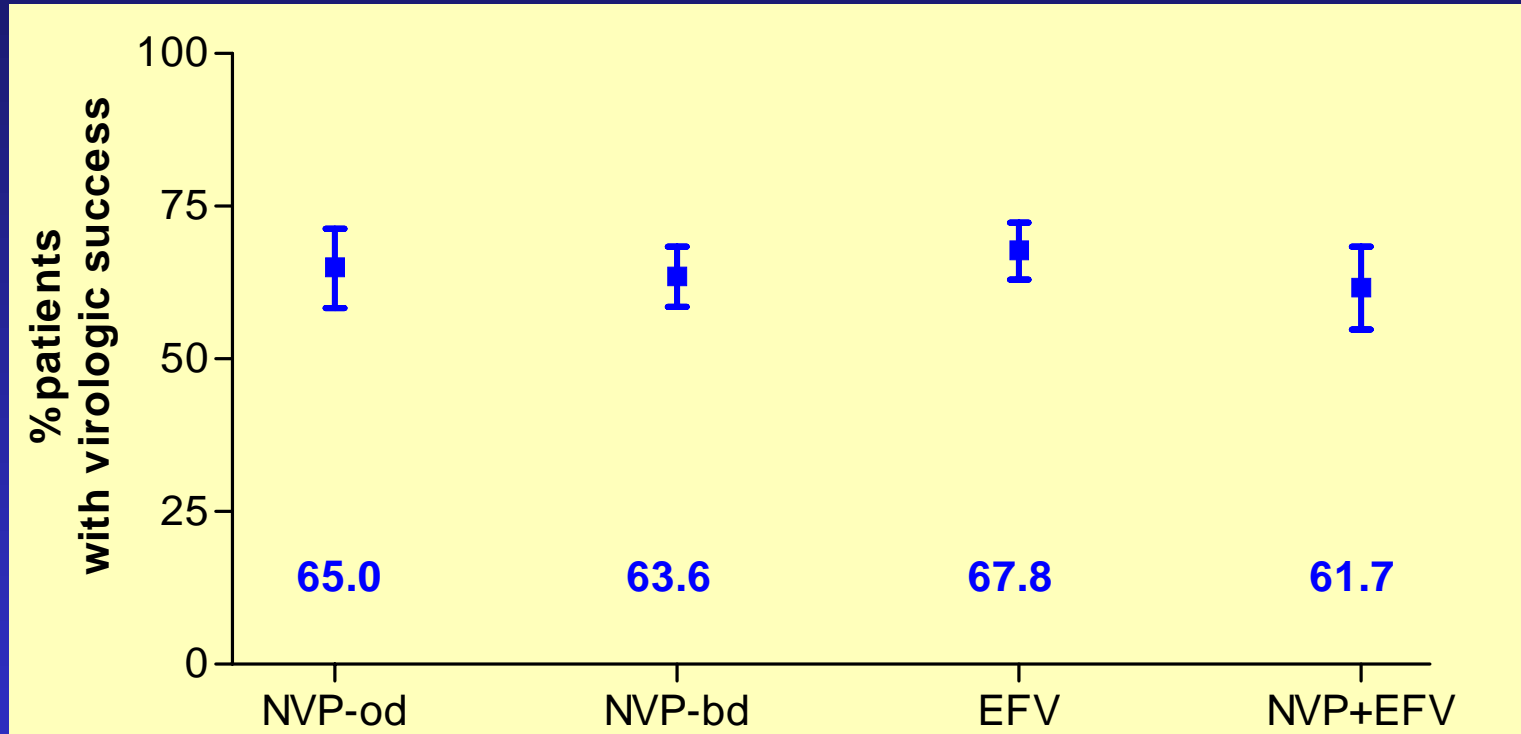
	<b>NVP-od</b> n=220	<b>NVP-bd</b> n=387	<b>EFV</b> n=400	<b>NVP+EFV</b> n=209	<b>TOTAL</b> n=1216
sex, % male	63	61	64	68	<b>63</b>
age, median (iqr)	34 (28-40)	34 (30-41)	35 (30-40)	33 (29-39)	<b>34</b> (29-40)
CD4 cells, cells/mm <sup>3</sup> median (iqr)	200 (55-340)	170 (60-310)	190 (80-350)	190 (80-330)	<b>190</b> (70-330)
HIV-1 RNA, log <sub>10</sub> median (iqr)	4.7 (4.4-5.4)	4.7 (4.4-5.5)	4.7 (4.4-5.5)	4.7 (4.4-5.4)	<b>4.7</b> (4.4-5.5)
CDC-class C, %	20	22	21	18	<b>21</b>
Risk behaviour, %					
heterosexual	56	61	56	53	<b>57</b>
homosexual	26	26	29	35	<b>29</b>
IVD	5	3	5	5	<b>5</b>
other, unknown	13	10	10	7	<b>9</b>
Hepatitis B, %	6.8	4.4	4.0	7.7	<b>5.3</b>
Hepatitis C, %	10.0	9.0	10.0	9.1	<b>9.5</b>

# Treatment success and failure



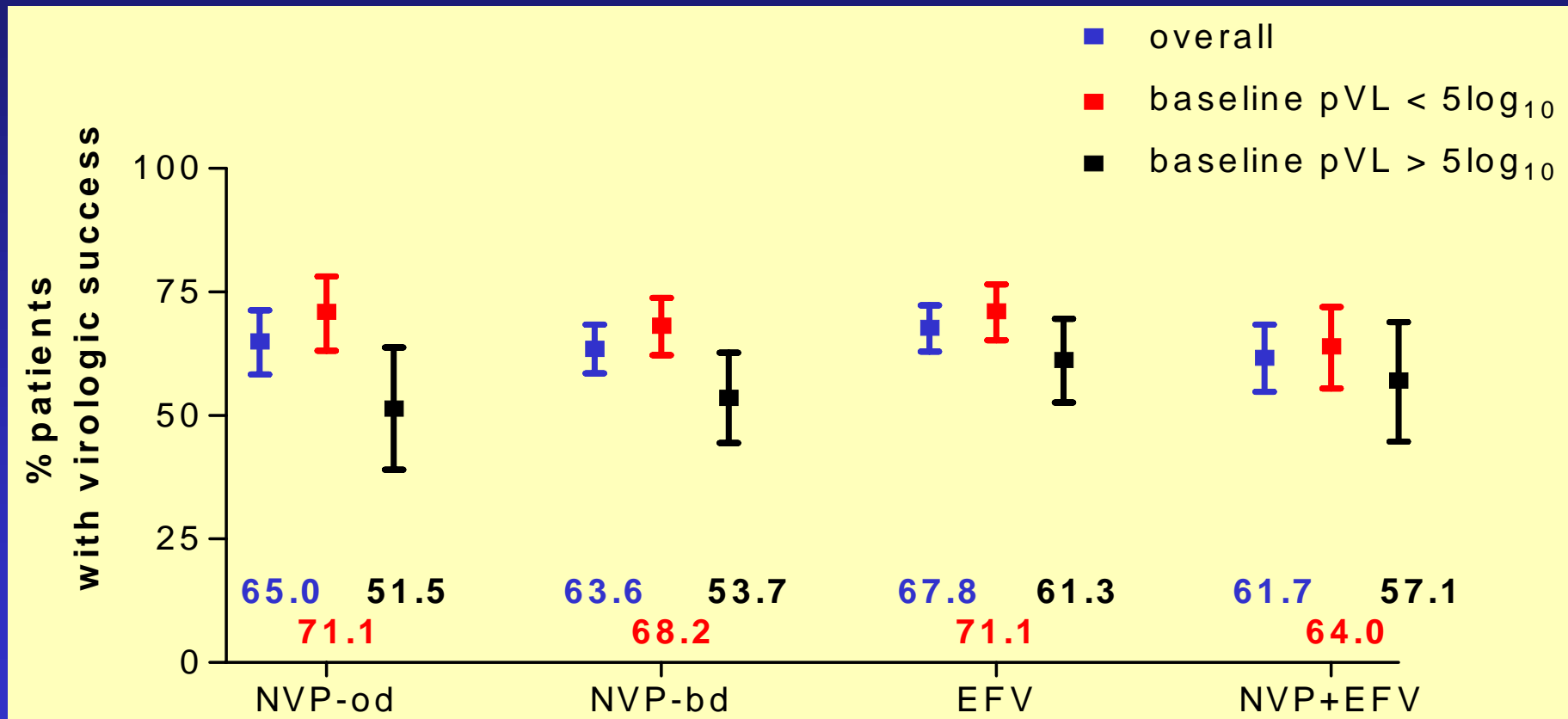
Success: only significant difference: EFV vs NVP+EFV,  $p < 0.001$

# Virologic success

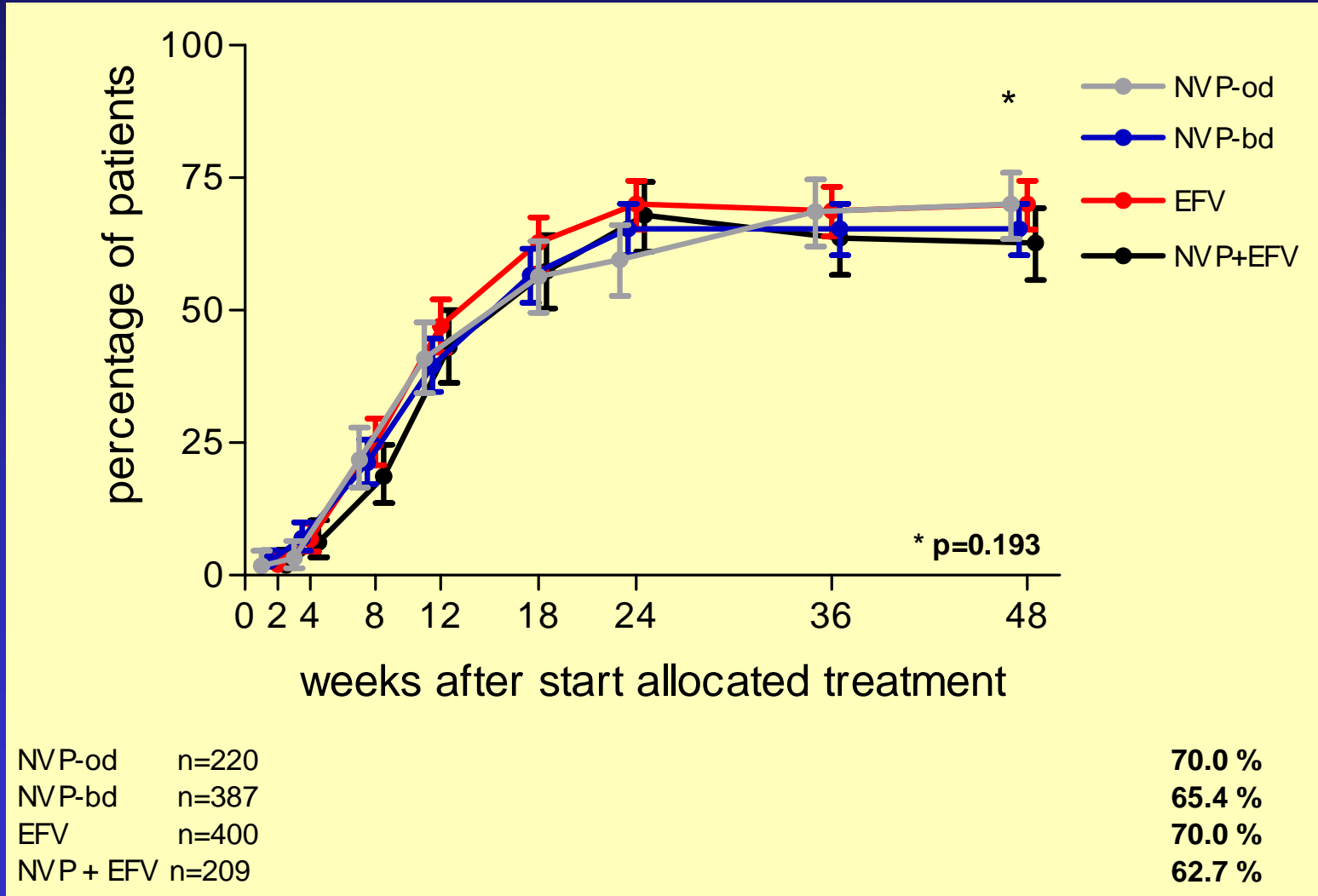


No significant differences in any of the pairwise comparisons

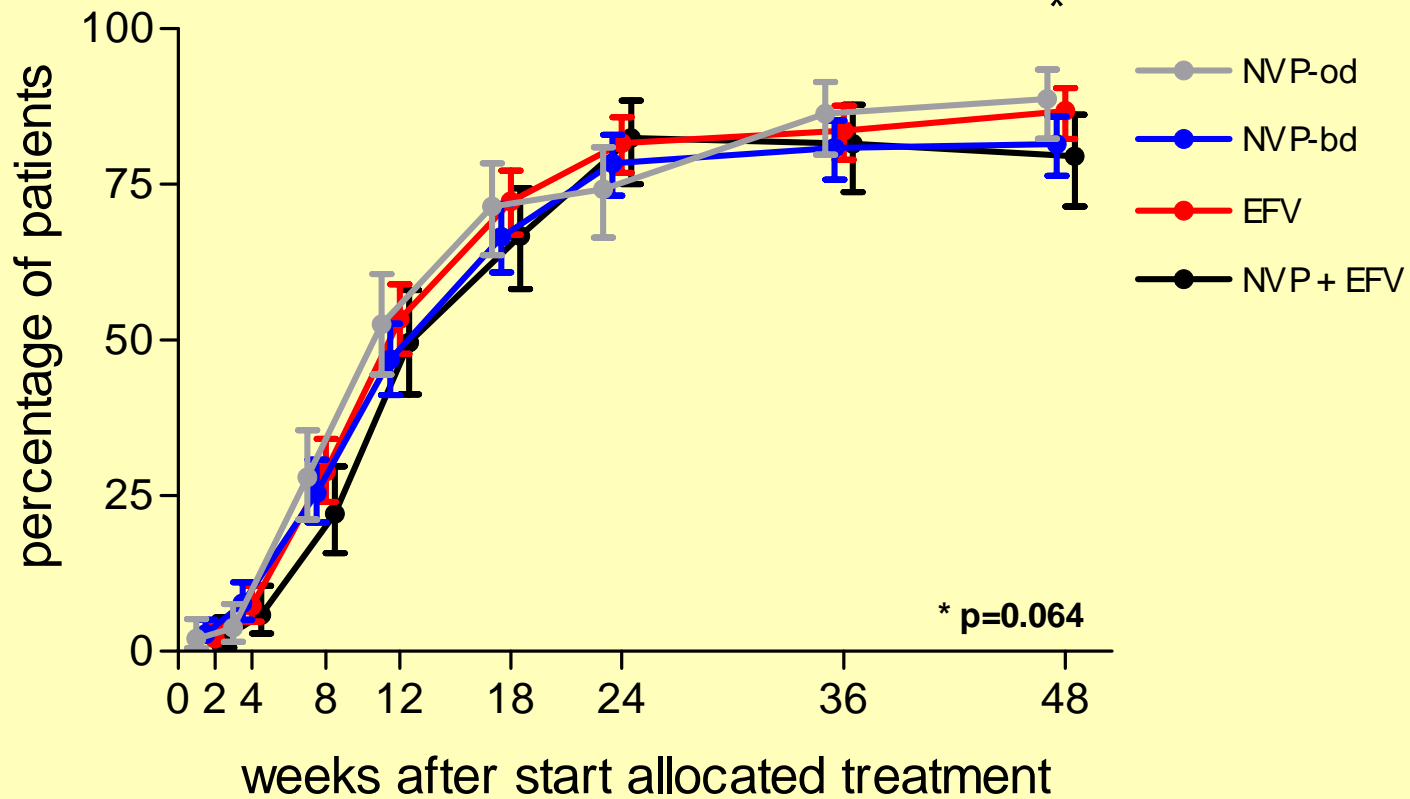
# Virologic success by baseline pVL



# pVL < 50 copies/mL ITT

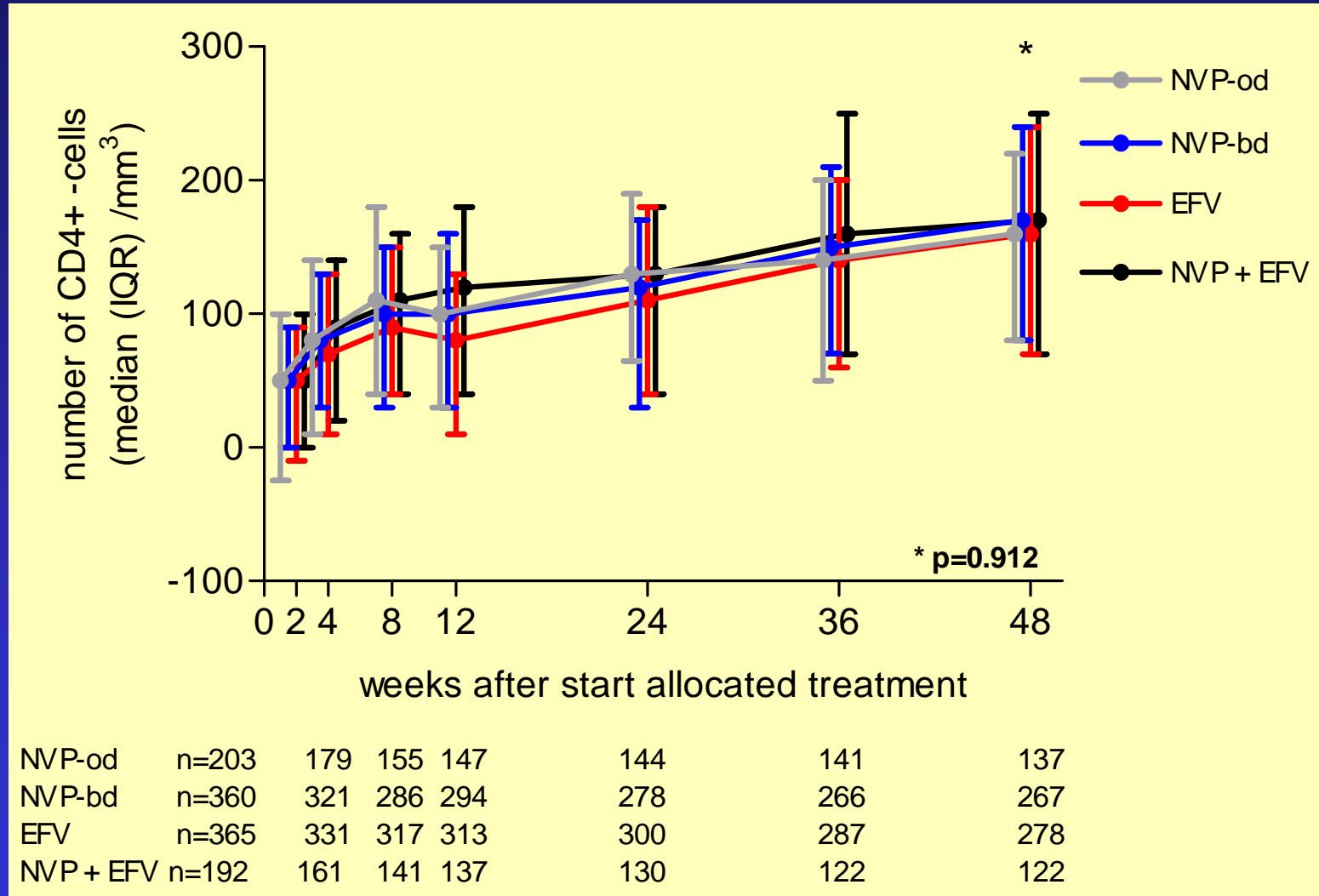


# pVL < 50 copies/mL OT



NVP-od	n=208	194	161	156	151	147	142	<b>88.7 %</b>
NVP-bd	n=378	336	306	305	291	282	275	<b>81.5 %</b>
EFV	n=381	342	329	322	310	299	289	<b>86.8 %</b>
NVP + EFV	n=199	170	149	145	137	130	127	<b>79.5 %</b>

# Increase in CD4 cells OT





# Grade 3 or 4 clinical adverse events

(all isolated laboratory events excluded)



	<b>NVP-od</b> n=220	<b>NVP-bd</b> n=387	<b>EFV</b> n=400	<b>NVP+EFV</b> n=209	p-value
<b>%</b>					
<b>Hepato-biliary</b>	<b>1.8</b>	<b>2.6</b>	<b>0.5</b>	<b>1.0</b>	0.082
hepatotoxicity	1.4	2.1	0.3	1.0	
<b>Cutaneous</b>	<b>4.1</b>	<b>3.6</b>	<b>3.8</b>	<b>5.7</b>	0.619
rash	4.1	3.1	1.8	3.8	
<b>CNS / Psychiatric</b>	<b>1.4</b>	<b>3.6</b>	<b>5.5</b>	<b>7.7</b>	0.001
insomnia / abn. dreams	-	-	1.5	2.4	
anxiety	-	-	1.0	1.4	
depression	-	0.3	1.5	0.5	
<b>Miscellaneous</b>					
diarrhoea	0.5	0.8	1.0	1.9	
vomiting	0.9	1.0	1.0	1.4	
pyrexia	0.9	2.1	0.8	1.0	
<b>Total % of patients *</b>	<b>15.0</b>	<b>20.4</b>	<b>18.0</b>	<b>24.4</b>	0.077
<b>Total % of patients discontin.†</b>	<b>24.1</b>	<b>21.2</b>	<b>15.5</b>	<b>29.7</b>	<0.001

\* patients with at least one grade 3/4 event.

† patients temporarily or permanently discontinuing Rx because of AE (any grade)

# Grade 3 or 4 laboratory toxicities

	<b>NVP-od</b> n=220	<b>NVP-bd</b> n=387	<b>EFV</b> n=400	<b>NVP+EFV</b> n=209	p-value
<b>%</b>					
<b>Hepatobiliary lab. toxicity *</b>	<b>13.2</b>	<b>7.8</b>	<b>4.5</b>	<b>8.6</b>	<b>0.002</b>
<b>Non-hepatobiliary lab. toxicity</b>	<b>8.2</b>	<b>12.9</b>	<b>8.8</b>	<b>9.6</b>	<b>0.161</b>
neutropenia	2.3	3.9	1.8	5.3	
amylase	1.8	3.1	3.5	1.4	
triglycerides	1.4	1.3	1.3	0.5	
alkaline phosphatase	0.5	1.3	0.8	1.9	

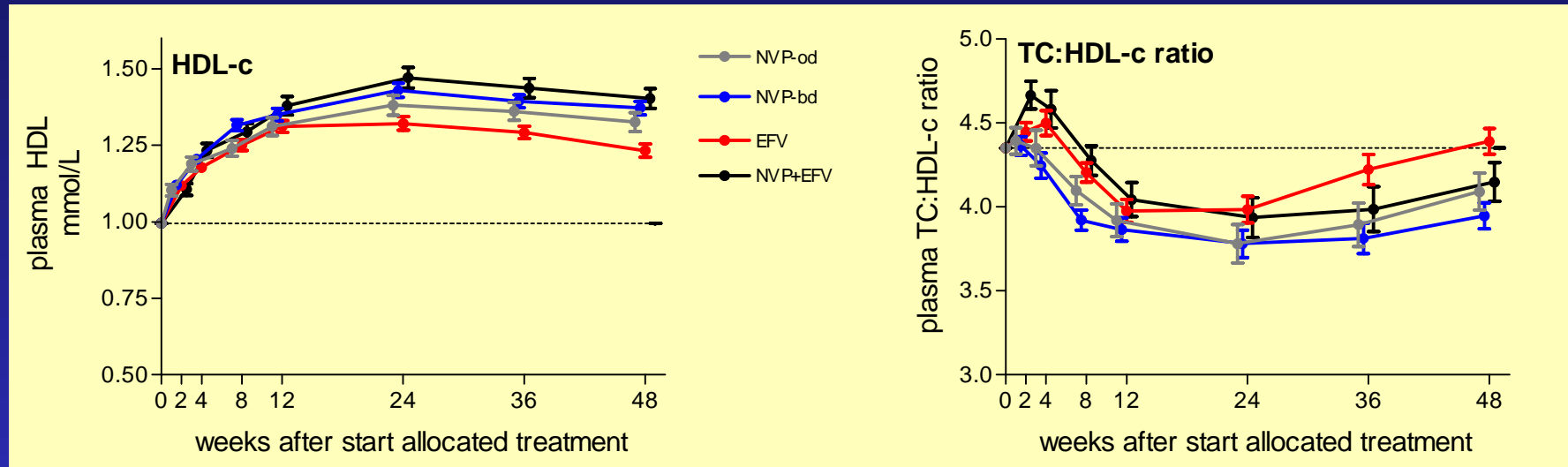
\* elevated ASAT and/or ALAT

hepatobiliary: only significant difference: NVP-od vs EFV,  $p < 0.001$

25 patients died during the study:

- 2 deaths attributed to NVP use
  - female from Argentina with toxic hepatitis without evidence of hepatic co-infection
  - Steven's Johnson syndrome from S. Africa. Died of MRSA septicaemia while recovering in hospital
- 1 death attributed to d4T use
  - lactic acidosis
- 11 deaths related to HIV-disease
- 11 deaths non-Rx and non-HIV related
  - none of suicides attributed to use of study medication

# Changes in lipid concentrations



Both NVP-only arms, compared to EFV:

- larger increase in HDL-c
- larger decrease in TC:HDL-c ratio

# Summary

	<b>NVP-od</b> A n=220	<b>NVP-bd</b> B n=387	<b>EFV</b> C n=400	<b>NVP+EFV</b> D n=209	significant difference
Rx-success, %	56.4	56.3	<b>62.3</b>	<b>46.9</b>	C vs D
pVL<50 c/mL, %	70.0	65.4	70.0	62.7	ns
CD4 increase, cells/mm <sup>3</sup>	170	160	160	150	ns
grade 3/4 clinical AE, %	<b>15.0</b>	20.4	18.0	<b>24.4</b>	A vs D
grade 3/4 liver associated lab AE, %	<b>13.2</b>	7.8	<b>4.5</b>	8.6	A vs C
grade 3/4 other lab AE, %	8.2	12.9	8.8	9.6	ns

# Conclusions

- NVP and EFV have comparable potency in suppressing HIV-1 replication
- NVP-od and NVP-bd show comparable efficacy
- Co-administration of NVP and EFV results in higher treatment failure due to increased toxicity



# Acknowledgements (1)



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