

# The results of the ARTEN study

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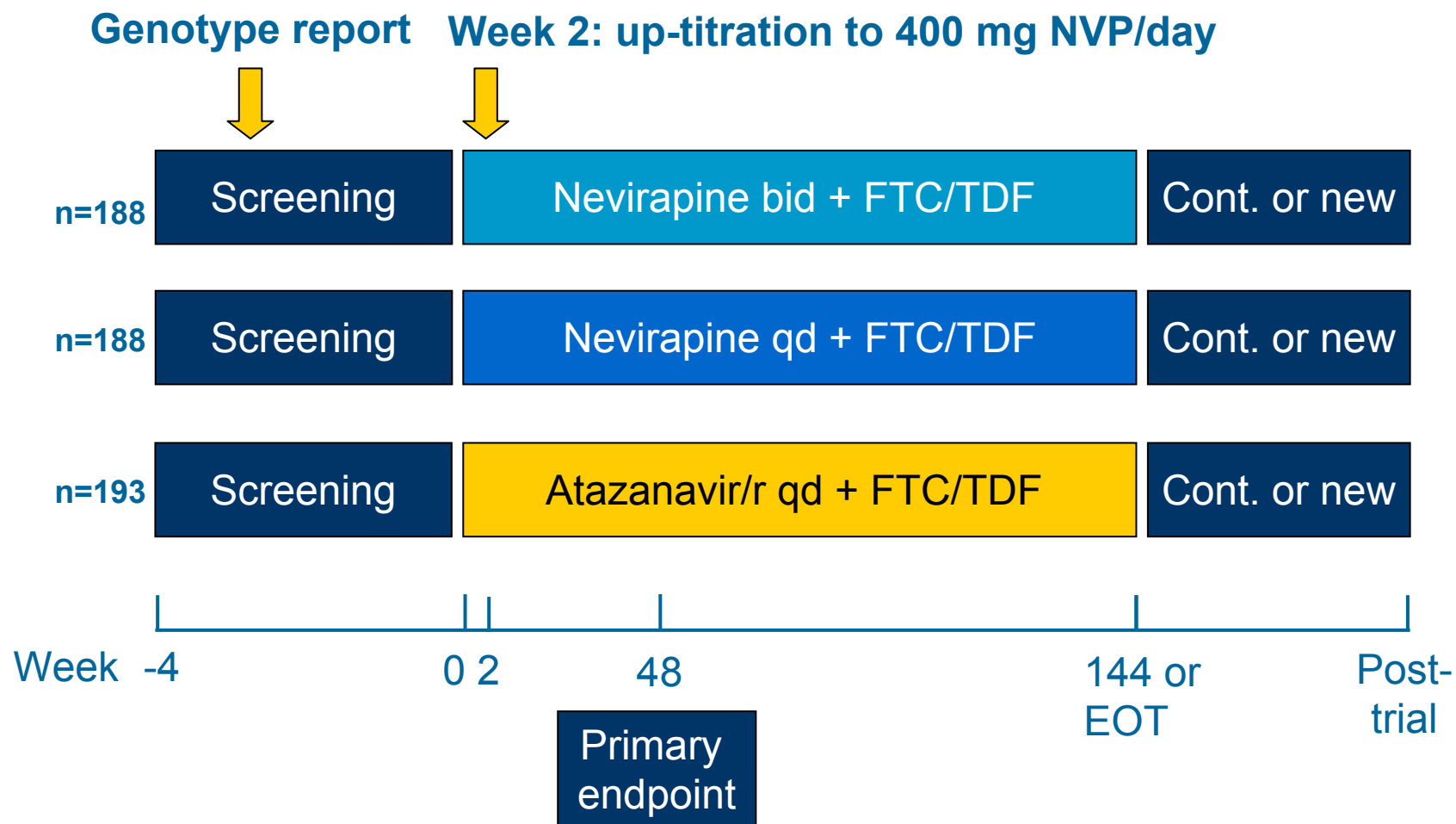
# Nevirapine: a well-defined efficacy and tolerability profile

- High efficacy levels<sup>1-3</sup>
- Well-defined safety profile<sup>4</sup>
- Favourable lipid profile<sup>5</sup>
- Can be used in women of child-bearing age<sup>6</sup>

# ARTEN aimed to provide new information about nevirapine

- Compare safety and efficacy of atazanavir/r (ATZ/r) and nevirapine (NVP; Viramune®)
- Provide well-controlled clinical data on the combination of NVP, emtricitabine and tenofovir DF (FTC/TDF; Truvada®)
- Prospectively examine NVP use within the CD4+ cell count thresholds
  - Men: <400 cells/mm<sup>3</sup>
  - Women: <250 cells/mm<sup>3</sup>
- Compare the metabolic profile of two lipid-‘friendly’ regimens

# The ARTEN study



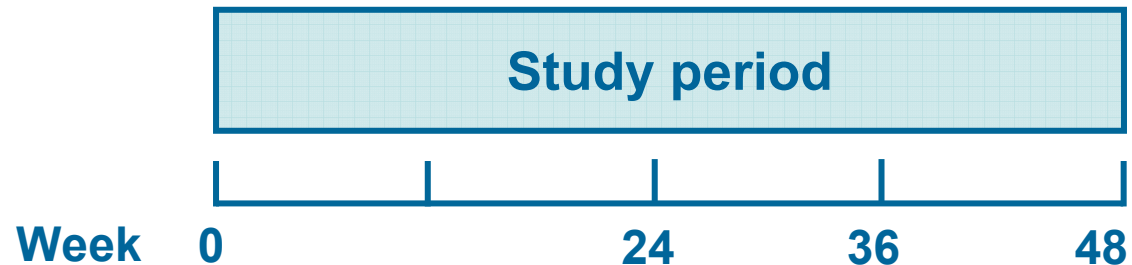
# Rationale for the choice of primary endpoint

EACS guidelines 2005:  
response at 24 weeks considered important

## MANAGEMENT OF VIROLOGIC TREATMENT FAILURE

Treatment objectives	VL decline > 2 log at W4 ; VL < 400 c/ml at W12 VL < 50 c/ml at W24
Definition of failure	VL repeatedly > 50 c/ml 6 months after initiating or changing therapy
Management	General measures : <ul style="list-style-type: none"><li>• Evaluation for adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues, ...</li><li>• Perform resistance testing (usually reliable with plasma VL levels &gt; 500-1000 c/ml)</li><li>• Consider TDM</li></ul>
Management of first line therapy failure	<b>If VL &lt; 1000 c/ml</b> <ul style="list-style-type: none"><li>• Check and improve compliance</li><li>• Check and improve PK</li><li>• Switch NNRTI's to boosted PI (s)</li></ul> <b>If VL &gt; 1000 c/ml</b> : Decision to change will depend on the resistance testing results : <ul style="list-style-type: none"><li>• No R+ mutations found : re-check for adherence, perform TDM</li><li>• R+ mutations found : switch to a suppressive regimen ; multidisciplinary experts discussion advised</li></ul>

# ARTEN included a more stringent primary endpoint



<b>Primary endpoint:</b>	HIV RNA <50:	✓	✓	✓
<b>TLOVR algorithm:</b> (sensitivity analysis)	HIV RNA <50:	-	✓	✓

**Primary analysis:** 95% CI for difference between the combined NVP groups and ATZ/r in proportion of responders (primary endpoint); non-inferiority margin -12%

## Secondary endpoints included efficacy, safety and impact on lipids

- Proportion of patients with HIV RNA <50 copies/mL at Week 48 among patients on treatment at Week 48 (OT analysis)
- Virological failure
- Change in CD4+ count from baseline to Week 48
- Rate of liver enzyme elevations (LEE)
- Changes in lipid parameters

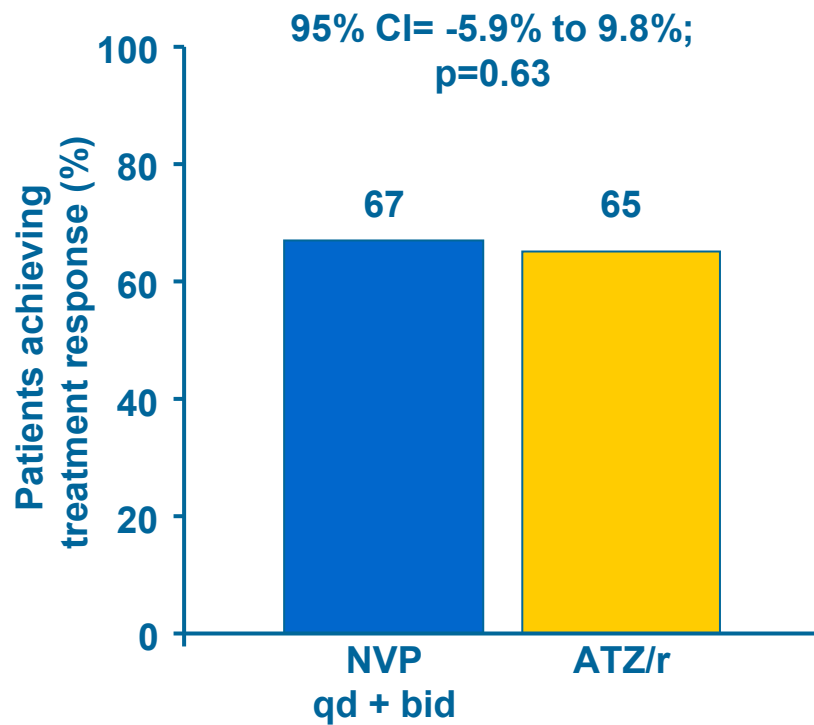
# ARTEN involved a relatively advanced ARV-naïve population

## Baseline demographics

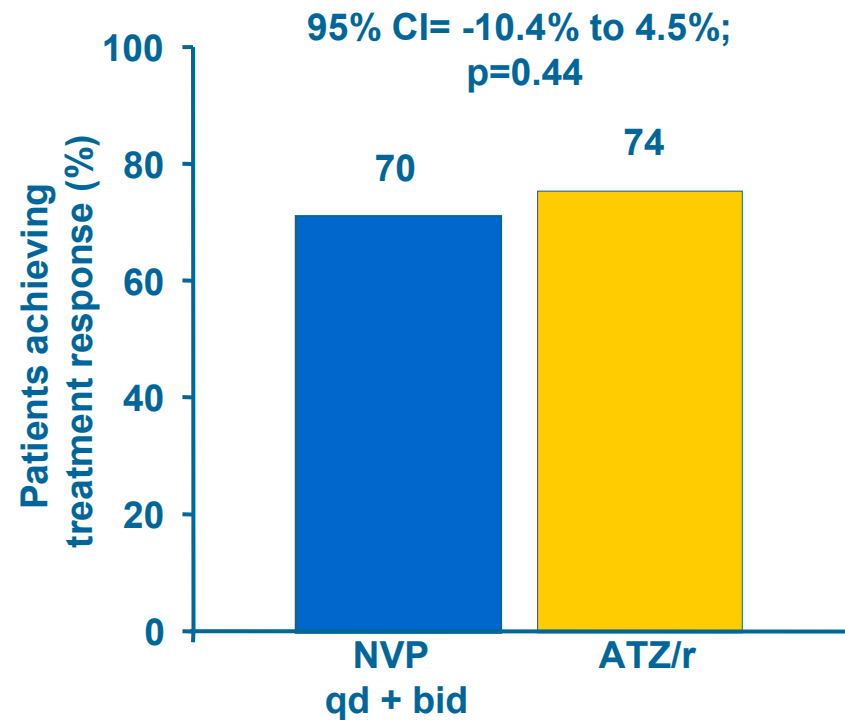
	NVP qd (n=188)	NVP bid (n=188)	ATZ/r (n=193)
Mean age (years)	38.4	40.0	37.6
Male gender (%)	80.9	86.7	83.9
Caucasian (%)	78.2	81.9	79.8
Western Europe (%)	72.3	71.8	68.4
Hepatitis at screening (%)	11.2	10.6	11.9
MSM / IDU (%)	50.5/5.9	54.8/5.9	52.8/6.7
pHIV-RNA >10 <sup>5</sup> log copies/mL (%)	62.8	62.8	65.8
Mean CD4+ count (cells/μL)	176.8	187.4	187.8
CD4+ count <50 cells/μL (%)	7.4	9.0	6.2

# ARTEN confirms the potency of nevirapine: ITT analyses (Week 48)

Treatment response by primary endpoint (ITT) (two visits prior Wk 48)



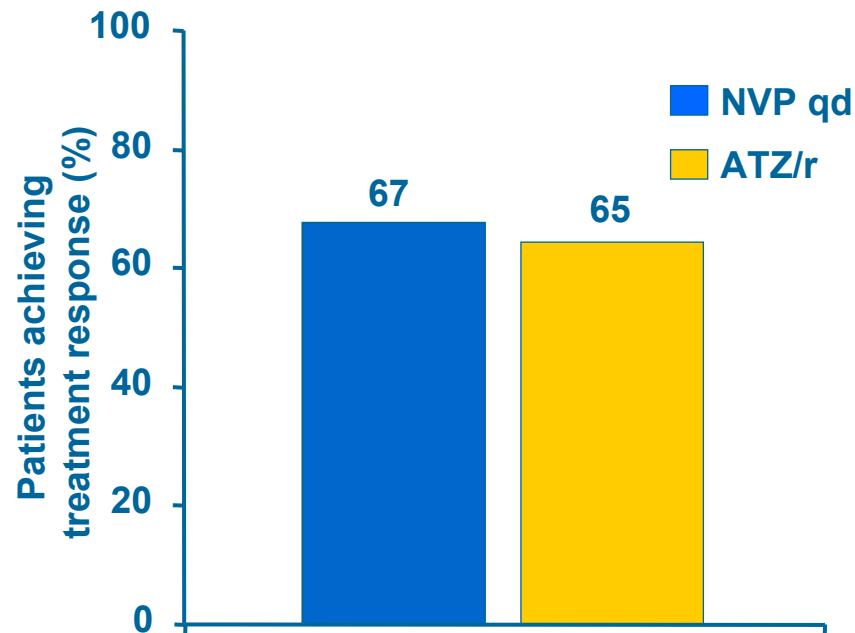
Treatment response by sensitivity analysis: TLOVR algorithm (ITT)



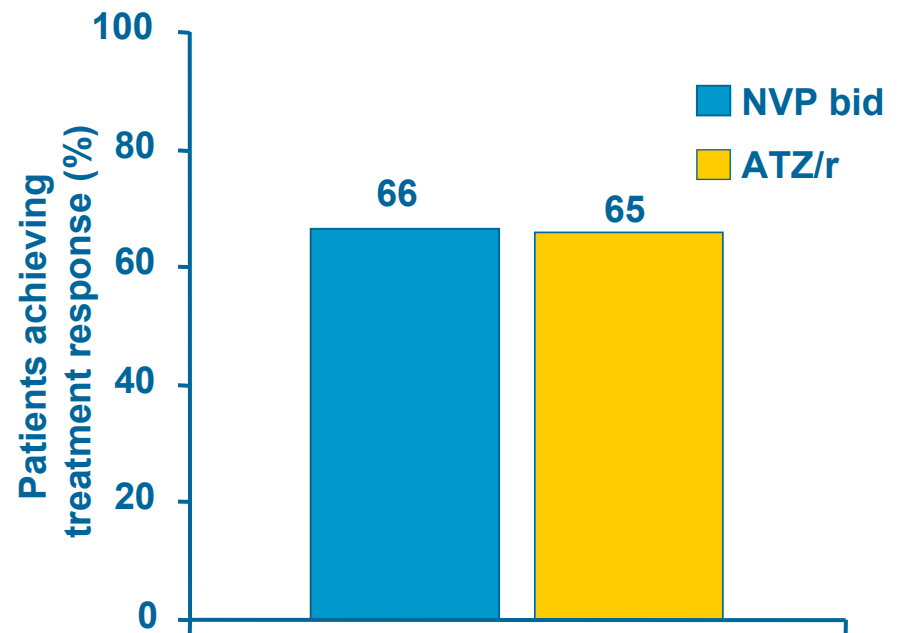
# Nevirapine qd and bid were similarly effective

Treatment response by primary endpoint (ITT):  
by nevirapine dose schedule

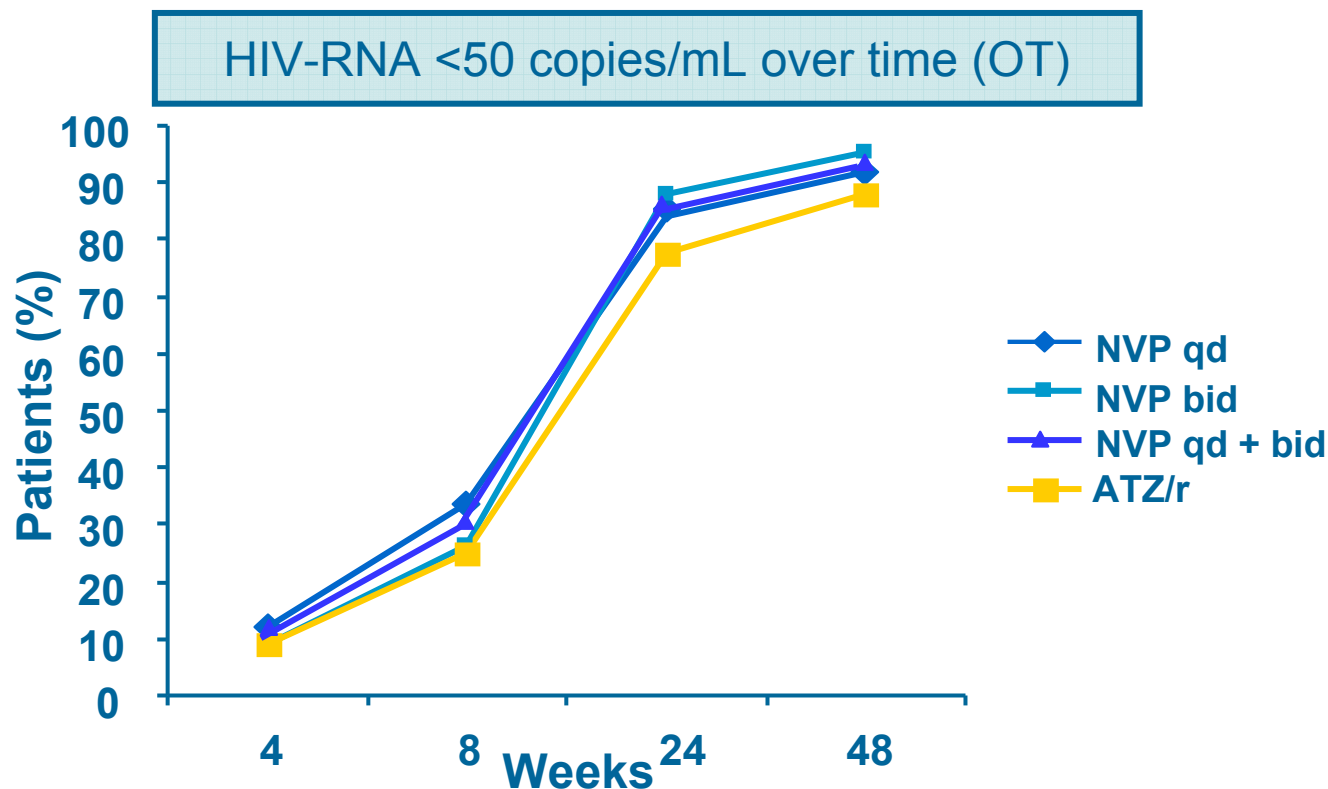
Nevirapine qd vs ATZ/r  
95% CI= -6.5% to 11.5%; p=0.58



Nevirapine bid vs ATZ/r  
95% CI= -7.7% to 10.7%; p=0.75



## ARTEN confirms the antiviral efficacy of nevirapine: OT analysis over time (single measurement)



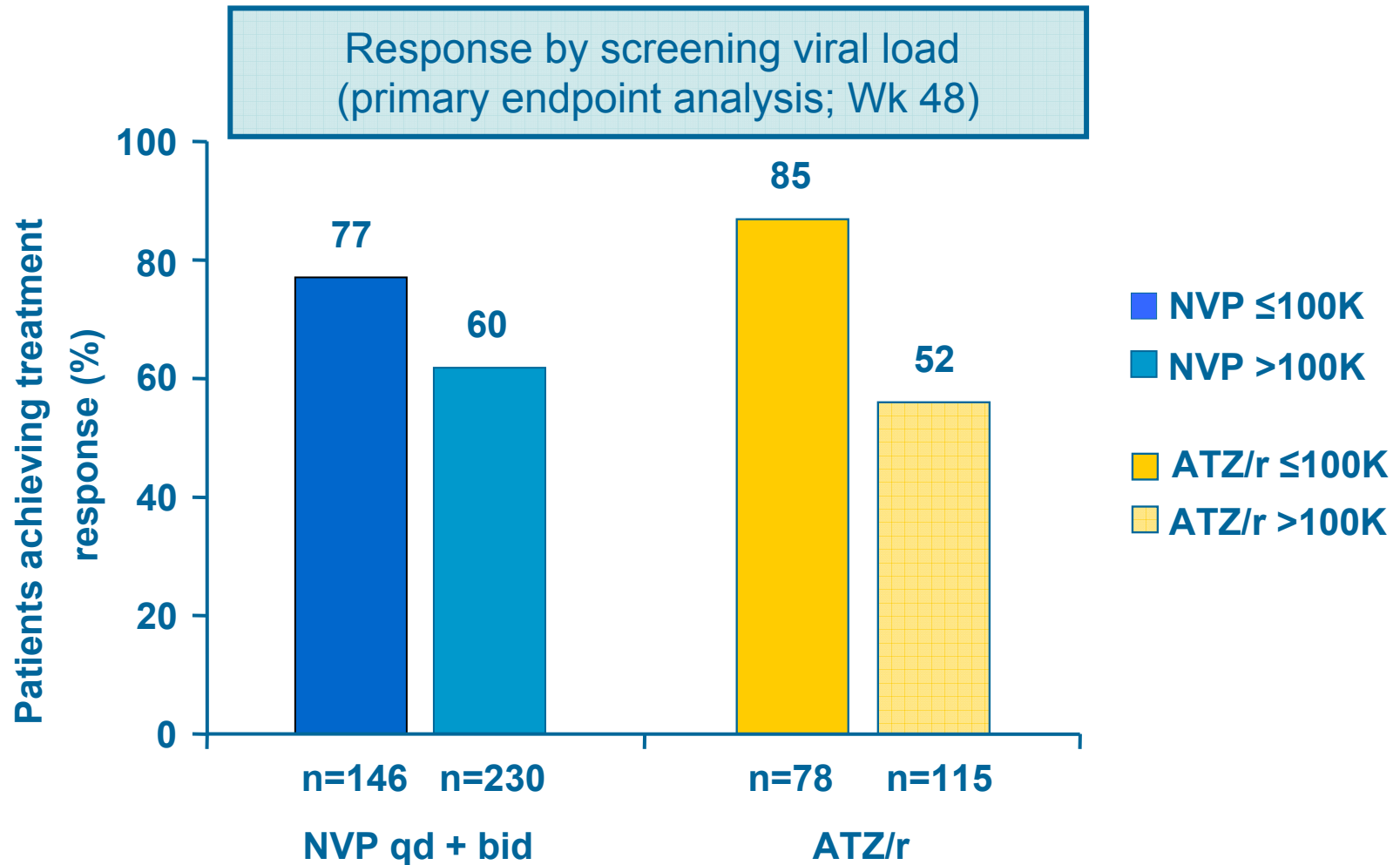
	NVP qd	NVP bid	NVP qd + bid	ATZ/r
HIV-RNA <50 copies/mL at 48 weeks, n (%)	132/144 (91.7)	124/130 (95.4)	256/274 (93.4)	154/175 (88.0)

Total excluding missing data, based on pre-defined time windows, numbers differ from TLOVR endpoint values.

## ARTEN confirms the efficacy of nevirapine: CD4 cell count improvement to Week 48

	NVP qd + bid (n=269)	ATZ/r (n=173)
CD4 count increase (mean)	170	185
95% CI	-39.3 to 7.4	
p value	0.18	

# Nevirapine is an effective choice in patients with high viral load



## Non-inferiority was reached despite a higher premature discontinuation rate in the NVP arm up to Week 48

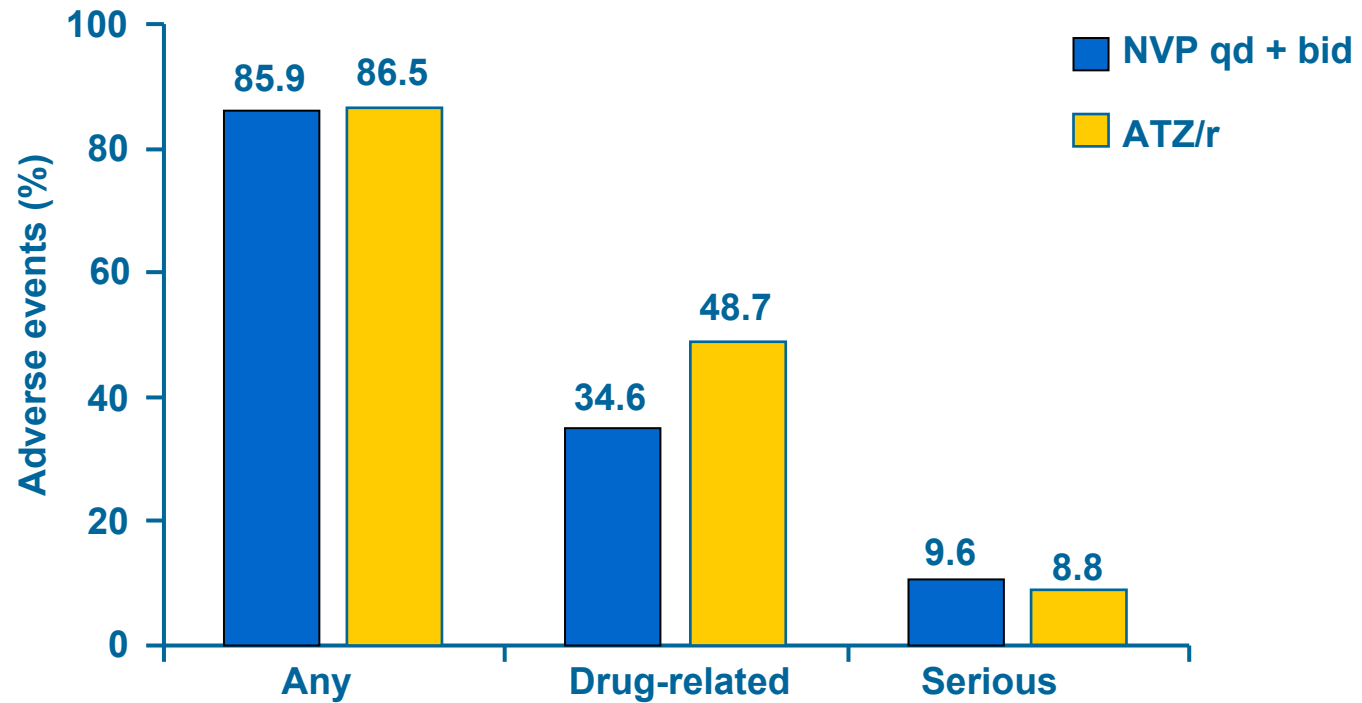
	NVP qd (n=188)	NVP bid (n=188)	ATZ/r (n=193)
<b>Any premature discontinuation, up to Week 48, n (%)</b>	41 (21.8)	53 (28.2)	18 (9.3)
<b>Discontinuations due to AEs, n (%)</b>	20 (10.6)	27 (14.4)	5 (2.6)
<b>Lost to follow-up, n (%)</b>	6 (3.1)	2 (1.1)	4 (2.1)
<b>“Lack of efficacy”*, n (%)</b>	11 (5.9)	21 (11.2)	3 (1.6)
<b>Other, n (%)</b>	4 (2.1)	3 (1.6)	6 (3.2)

\*As defined by the investigator

## Despite differences in ‘lack of efficacy’, rates of overall virologic failure were similar between groups

	NVP qd (n=188)	NVP bid (n=188)	ATZ/r (n=193)
<b>Virologic failure, n (%)</b>	21 (11.2)	24 (12.8)	27 (14.0)
<b>“Lack of efficacy” (investigator defined VF)</b>	11 (5.9)	21 (11.2)	3 (1.6)
<b>No confirmed response at Wk 48=VF</b>	10 (5.3)	3 (1.6)	24 (12.4)

## Overall incidence of adverse events was similar between groups



## Low rate of rash or hepatic events with NVP used as in label

%	Any degree			Grade 3-4			Leading to discontinuation		
	NVP qd	NVP bid	ATZ/r	NVP qd	NVP bid	ATZ/r	NVP qd	NVP bid	ATZ/r
<b>Rash</b> (including during lead-in phase)	14.9	17.0	12.4	1.6	1.6	0.0	3.7	6.4	0.0
<b>Hepatitis (excl.viral)</b>	1.6	2.1	0.0	1.0	1.6	0.0	1.6	2.1	0.0
<b>LEE</b> (coded as AE, excluding hyperbilirubinaemia)	5.9	7.4	1.6	3.2	4.8	1.5	2.1	3.2	1.0

- In 39 of these 60 NVP pts (65%) the rash occurred during the lead-in phase
- No Grade 4 rashes
- No cases of SJS, TEN, or deaths due to liver or skin toxicity

# Overall low rates of grade 3–4 liver enzyme elevations

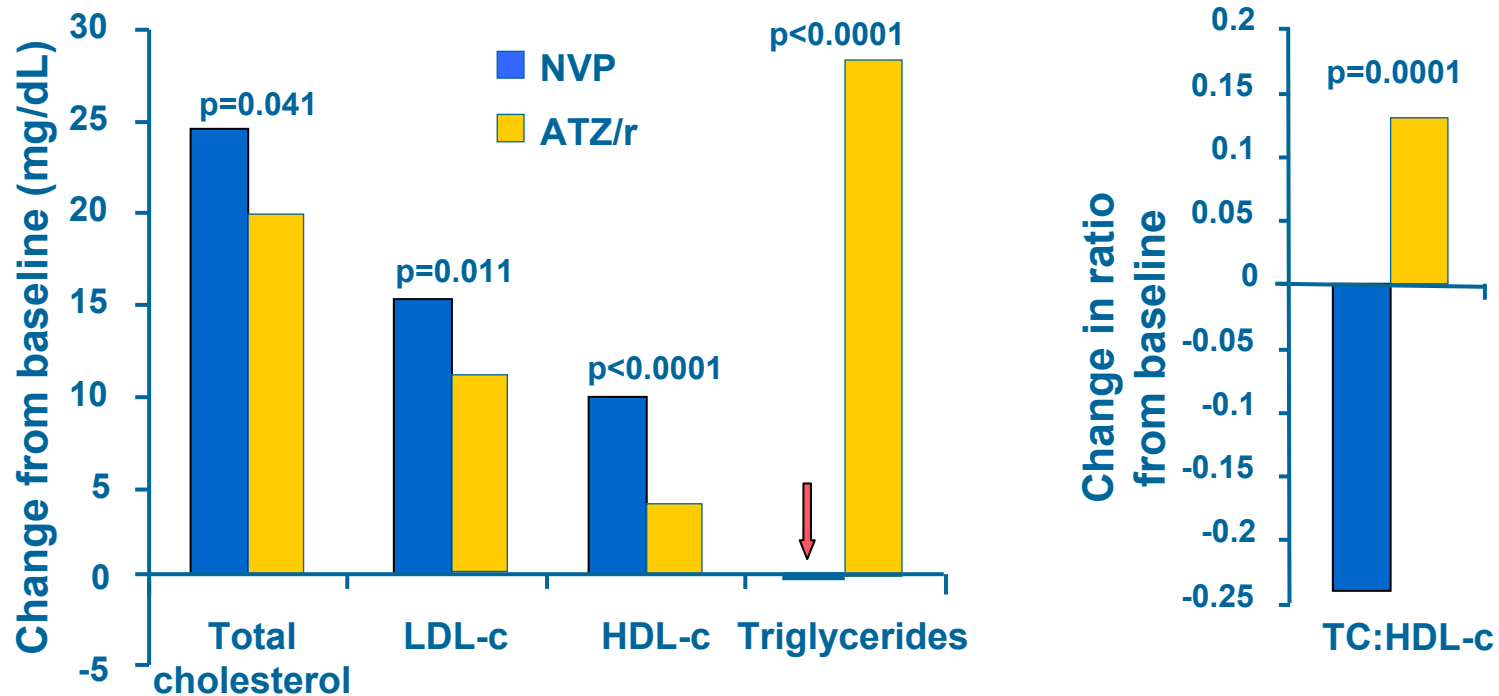
## Laboratory values of interest

	NVP qd		NVP bid		ATZ/r	
	G3	G4	G3	G4	G3	G4
DAIDS Grade (% patients)						
ALT	3.2	2.7	4.3	4.3	2.1	0
AST	4.3	1.6	4.3	2.7	2.6	0.5
Total bilirubin	1.1	1.6	2.1	1.6	45.6*	8.8

\*Leading to discontinuation in one patient

# ARTEN confirms the favourable lipid profile of nevirapine

Change in lipid and cardiovascular risk parameters from baseline to Week 48



# Summary

- Nevirapine is a potent first-line choice
  - Efficacy non-inferior to ATZ/r
  - Effective in combination with Truvada®
  - Effective in patients with high screening viral load (>100,000 c/mL)
    - Efficacy of qd and bid NVP/Truvada® regimens similar
- Nevirapine/Truvada® demonstrates a more favourable lipid profile than ATZ/r
- Low rate of hepatic adverse events in ARTEN in which the CD4 count guidance was applied
- Most rashes occurred in the early treatment phase when patients are being closely monitored (thus avoiding grade 4 events)

