# The results of the ARTEN study

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ARTEN
The Viramune® ARTEN Study

# Nevirapine: a well-defined efficacy and tolerability profile

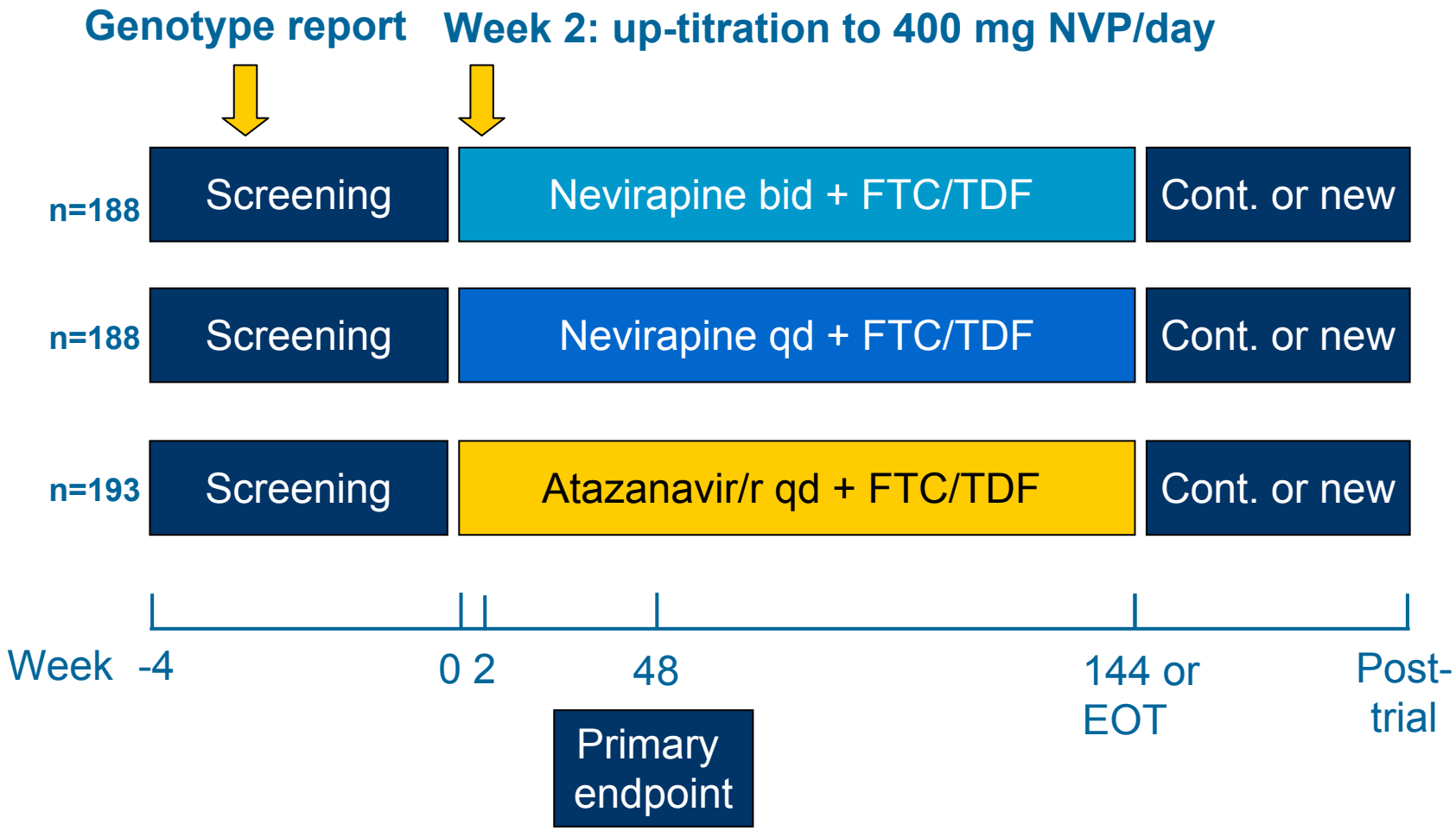
- High efficacy levels[1–3]
- Well-defined safety profile[4]
- Favourable lipid profile[5]
- Can be used in women of child-bearing age[6]

1. van Leth F et al. Lancet 2004;636:1250–1253; 2. Wit F et al. 4th IAS 2007, Sydney, Australia. Abstract WEPEB032;
3. Martinez E et al. AIDS 2007;21(3):367–369; 4. Storfer S et al. 10th EACS 2005, Dublin, Ireland. Abstract PE9.6/2;
5. Lundgren J et al. HIV Med 2008;9:72–81 (EACS guidelines); 6. Nevirapine US Prescribing Information

# 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$^3$
  - Women: <250 cells/mm$^3$
- 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 :<br>• Evaluation for adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues, …<br>• Perform resistance testing (usually reliable with plasma VL levels > 500-1000 c/ml)<br>• Consider TDM |
| Management of first line therapy failure | **If VL < 1000 c/ml**<br>• Check and improve compliance<br>• Check and improve PK<br>• Switch NNRTI's to boosted PI (s)<br>**If VL > 1000 c/ml :** Decision to change will depend on the resistance testing results :<br>• No R+ mutations found : re-check for adherence, perform TDM<br>• R+ mutations found : switch to a suppressive regimen ; multidisciplinary experts discussion advised |

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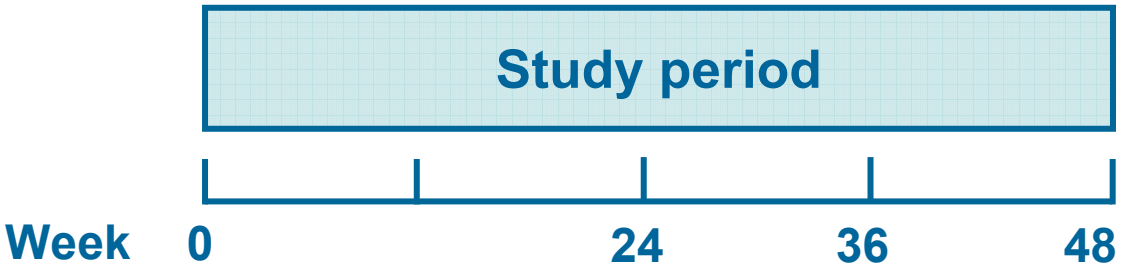
# ARTEN included a more stringent primary endpoint




**Primary endpoint:** HIV RNA <50: ✓ ✓ ✓

**TLOVR algorithm:** HIV RNA <50: - ✓ ✓
(sensitivity analysis)

**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 >$10^5$ 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 |

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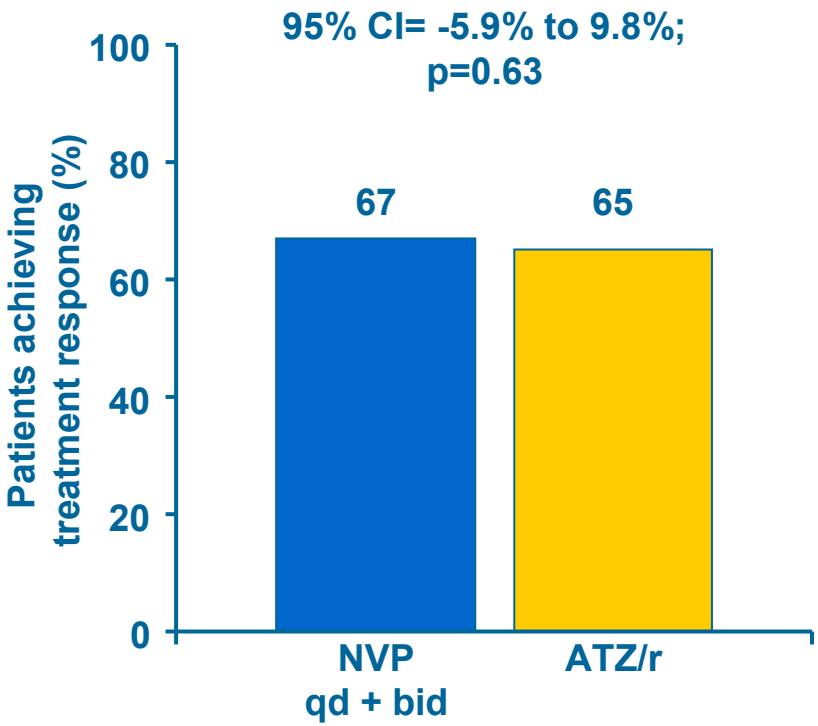
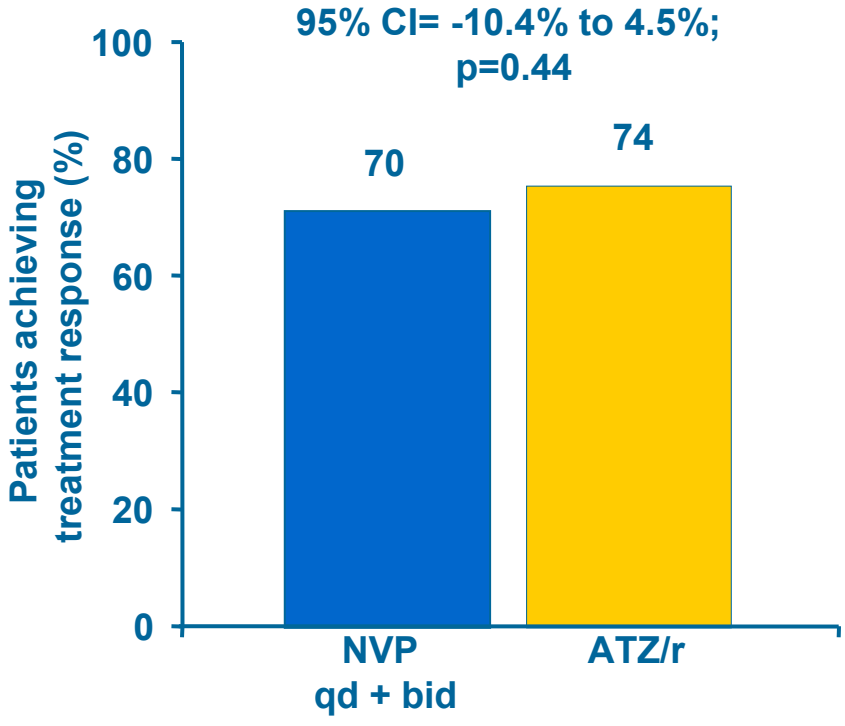
# ARTEN confirms the potency of nevirapine: ITT analyses (Week 48)

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




Treatment response by sensitivity analysis: TLOVR algorithm (ITT)

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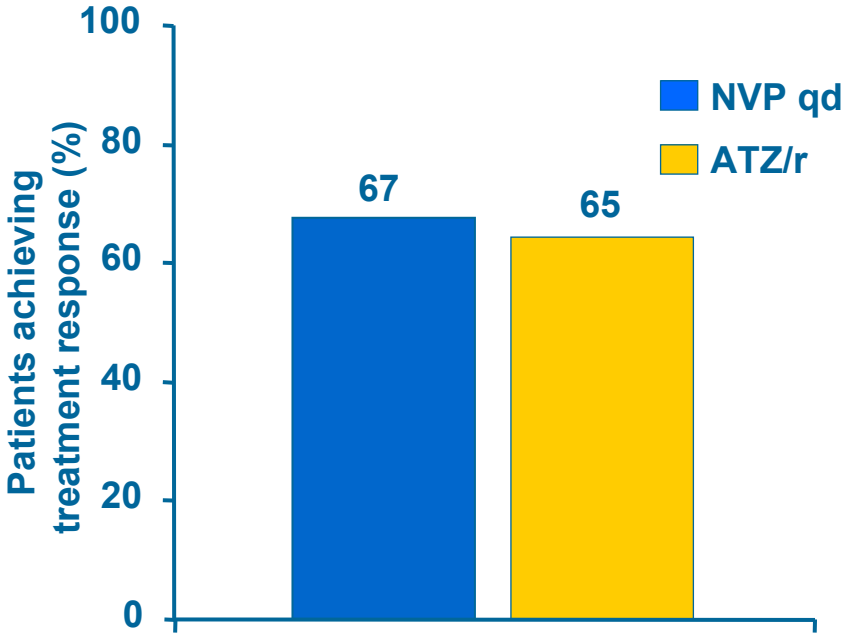
# Nevirapine qd and bid were similarly effective

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

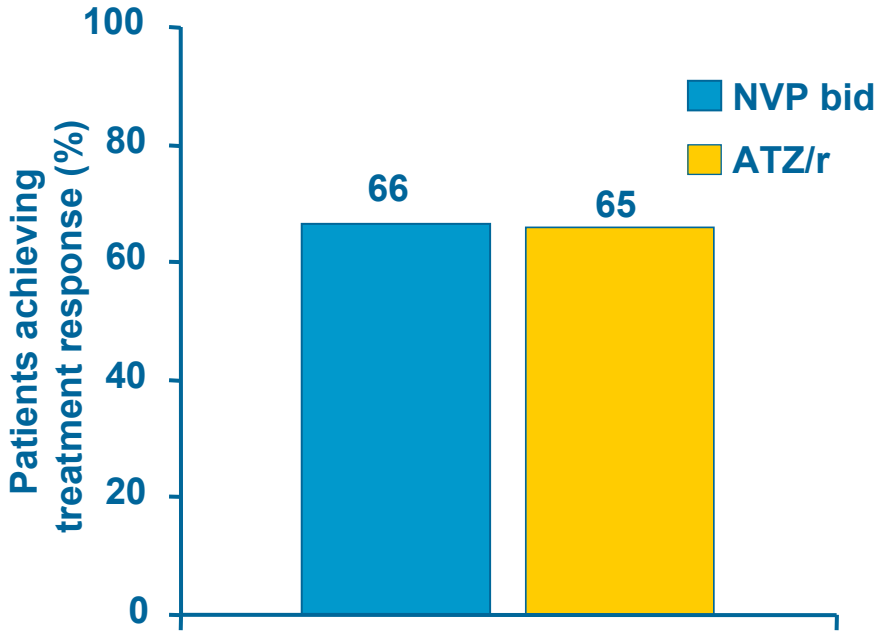
Nevirapine qd vs ATZ/r

**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**

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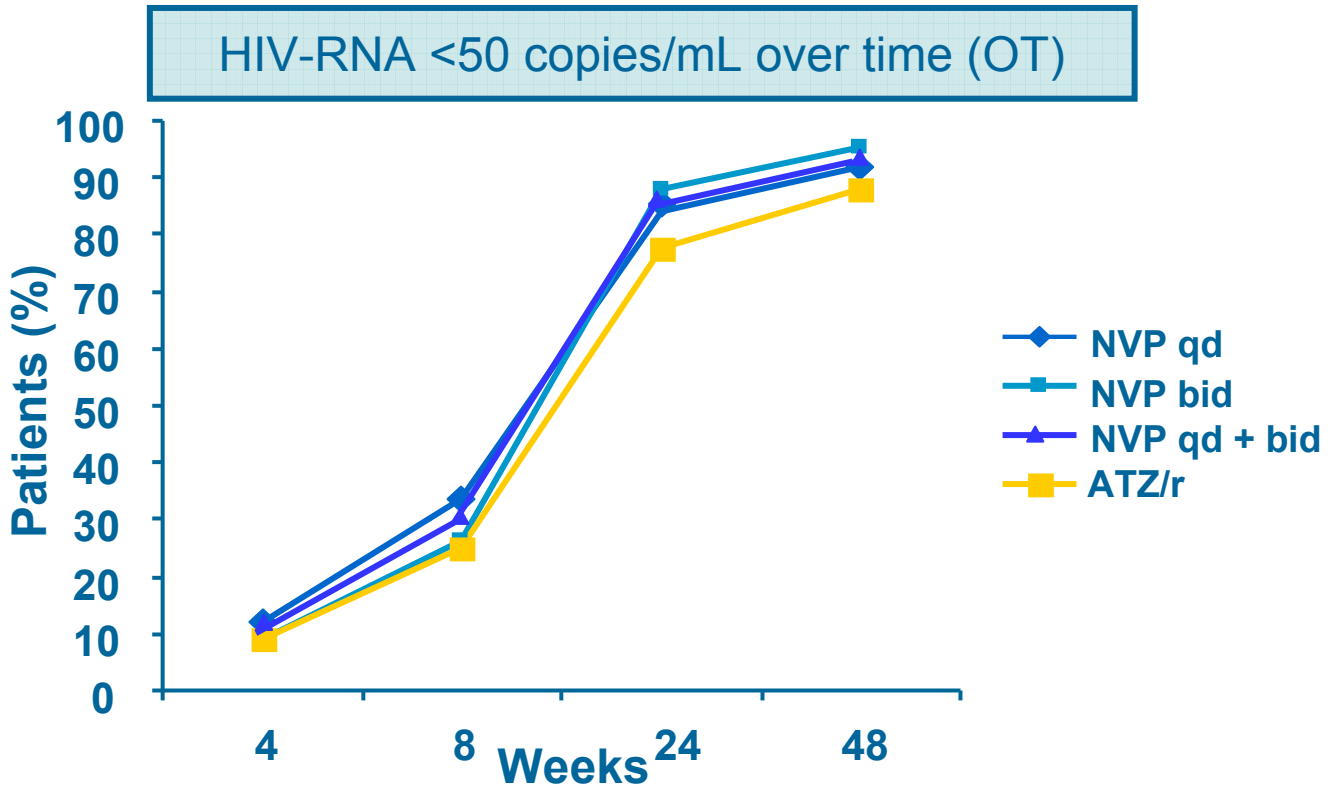
# ARTEN confirms the antiviral efficacy of nevirapine: OT analysis over time (single measurement)




| | 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.

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# 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 | |

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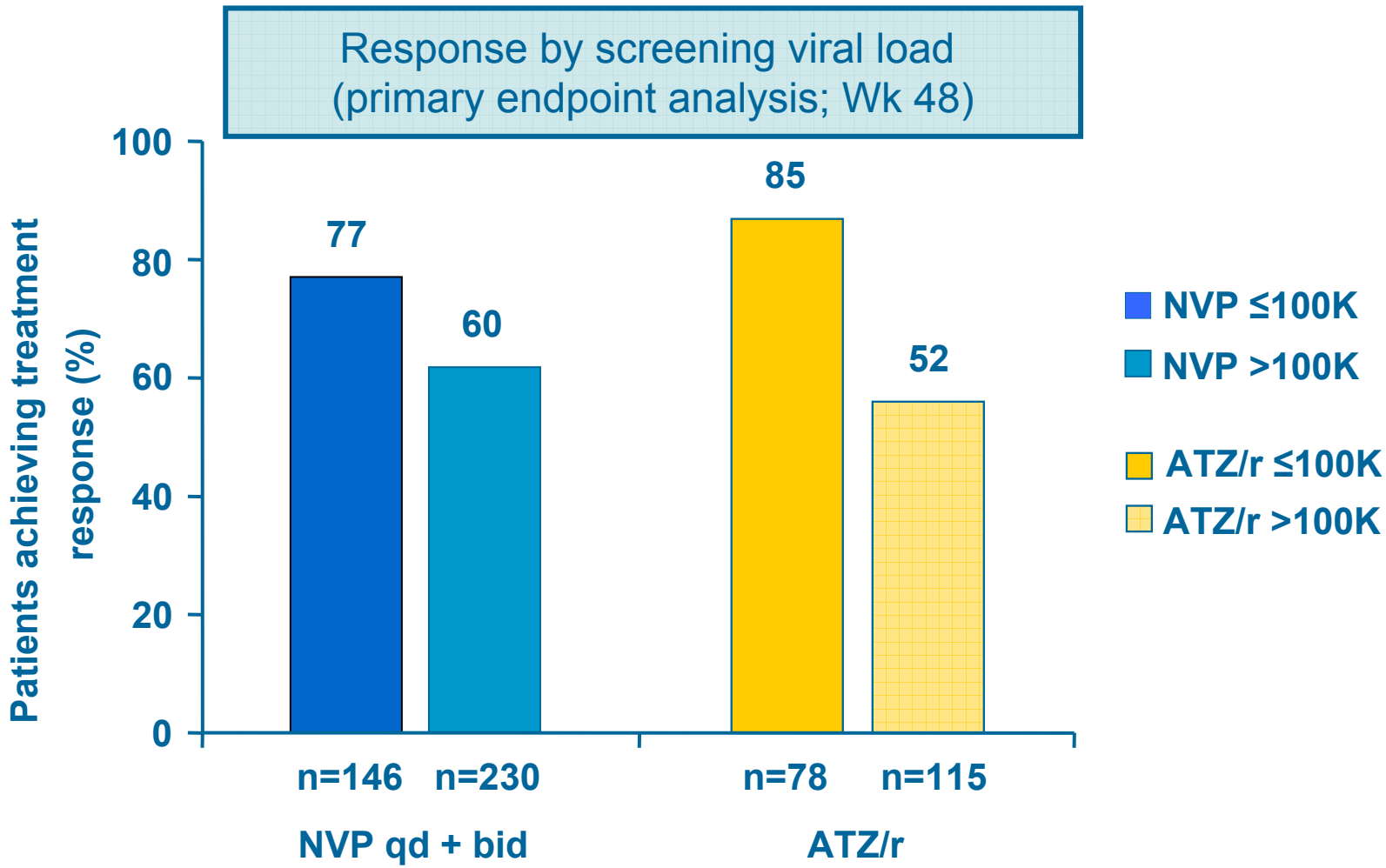
# Nevirapine is an effective choice in patients with high viral load

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

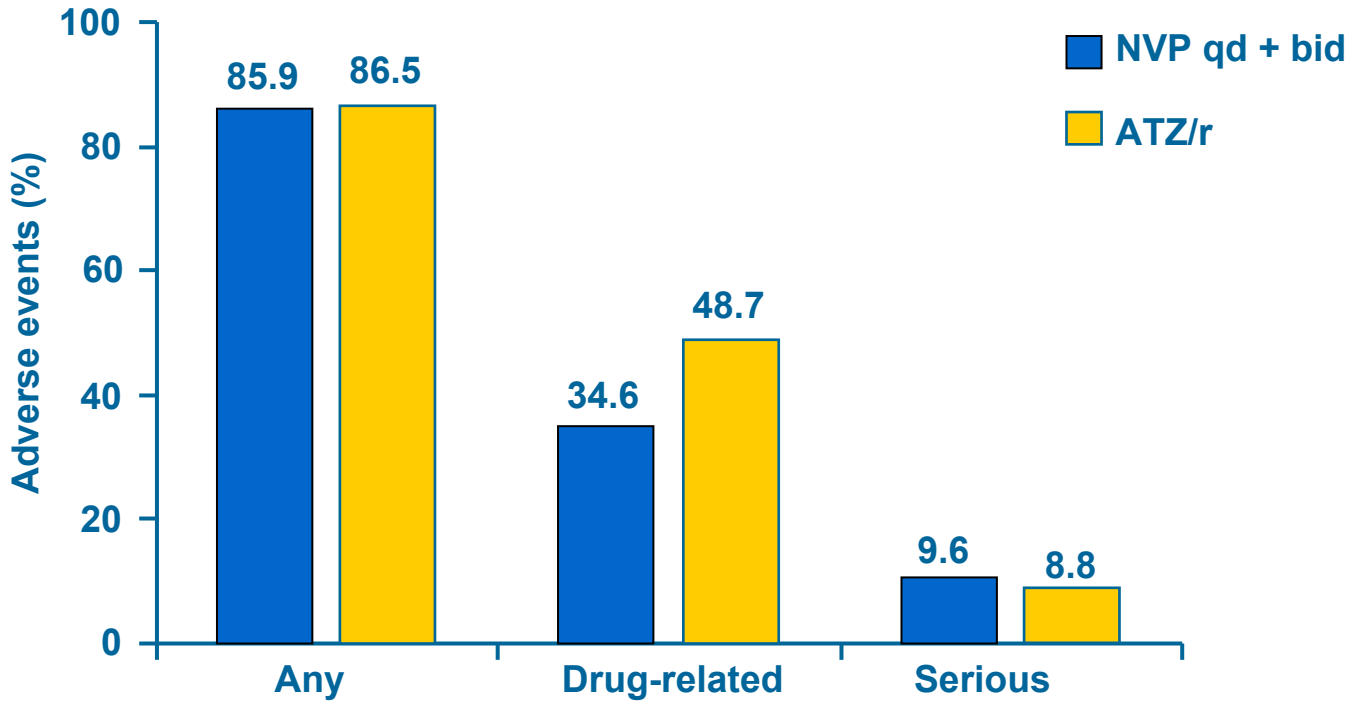
| | NVP qd (n=188) | NVP bid (n=188) | ATZ/r (n=193) |
|---|---|---|---|
| **Any premature discontinuation, up to Week 48, n (%)** | 41 (21.8) | 53 (28.2) | 18 (9.3) |
| **Discontinuations due to AEs, n (%)** | 20 (10.6) | 27 (14.4) | 5 (2.6) |
| **Lost to follow-up, n (%)** | 6 (3.1) | 2 (1.1) | 4 (2.1) |
| **"Lack of efficacy"*, n (%)** | 11 (5.9) | 21 (11.2) | 3 (1.6) |
| **Other, n (%)** | 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) |
|---|---|---|---|
| **Virologic failure, n (%)** | 21 (11.2) | 24 (12.8) | 27 (14.0) |
| **"Lack of efficacy" (investigator defined VF)** | 11 (5.9) | 21 (11.2) | 3 (1.6) |
| **No confirmed response at Wk 48=VF** | 10 (5.3) | 3 (1.6) | 24 (12.4) |

# Overall incidence of adverse events was similar between groups

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# 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 |
| **Rash** (including during lead-in phase) | 14.9 | 17.0 | 12.4 | 1.6 | 1.6 | 0.0 | 3.7 | 6.4 | 0.0 |
| **Hepatitis (excl.viral)** | 1.6 | 2.1 | 0.0 | 1.0 | 1.6 | 0.0 | 1.6 | 2.1 | 0.0 |
| **LEE** (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

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

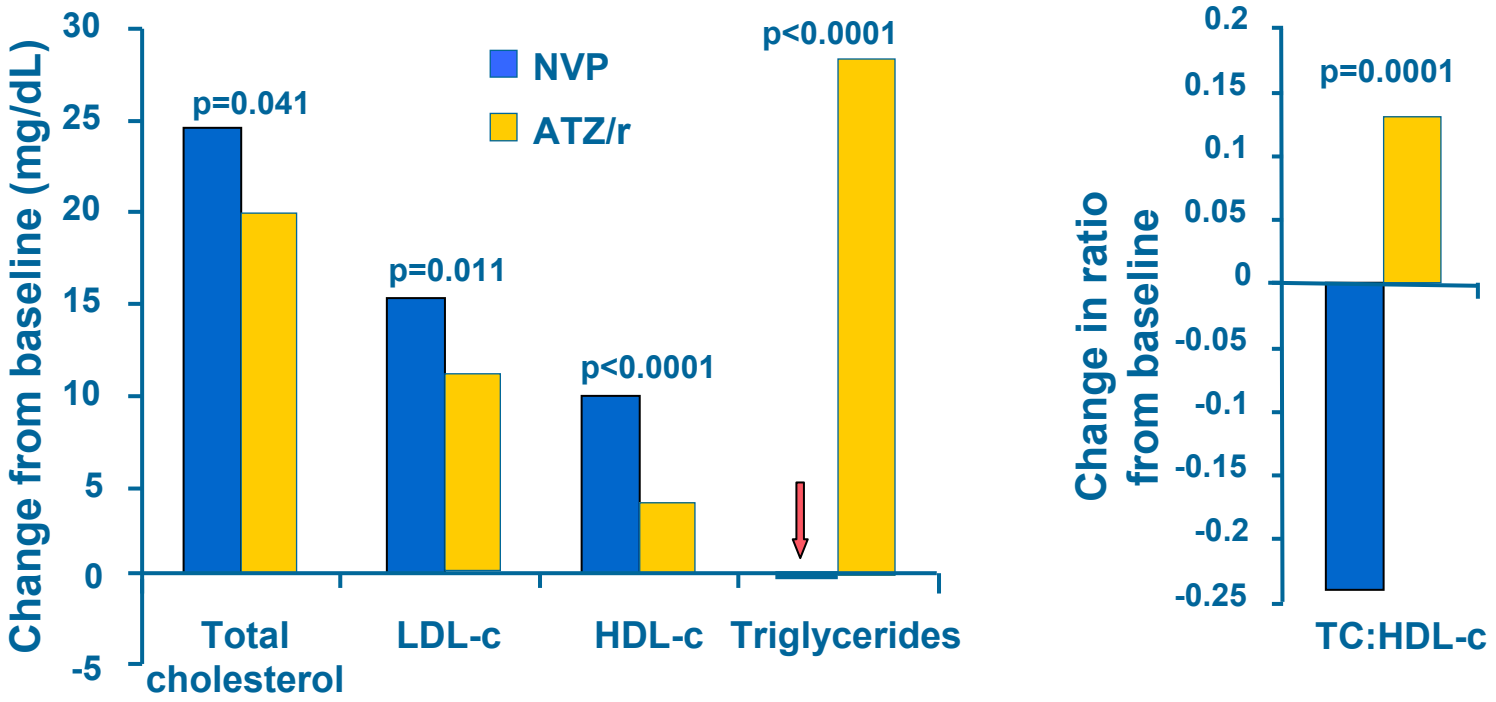
## Laboratory values of interest

| | NVP qd | | NVP bid | | ATZ/r | |
|---|---|---|---|---|---|---|
| DAIDS Grade (% patients) | G3 | G4 | G3 | G4 | G3 | G4 |
| 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)