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Early Virological and Immunological Response is Comparable between Nevirapine and RTV-boosted Atazanavir: An ARTEN Sub-analysis

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Abstract

Background: Early virological response has been proposed as a marker of early efficacy of HAART. In ARTEN, nevirapine (NVP) showed a similar efficacy to ritonavir-boosted atazanavir (ATZ/r), with a more favourable lipid profile after 48 weeks.[1] This subanalysis presents the early virological and immunological response data.

Methods: Analysis was of early viral decay (log_{10}), percentage of patients with HIV-RNA <50 copies/mL at each visit and mean CD4+ cell count increase within the first 12 weeks of treatment in the ARTEN study. Time to treatment response (TTR) was defined as time from start of treatment until the first measurement of the first confirmed virological response evaluated among the responders.

Results: 62.8% of 376 patients in the combined NVP arm and 65.8% of 193 patients in the ATZ/r arm had VL >100,000 copies/mL at baseline. Comparing all NVP vs. ATZ/r patients at weeks 4, 8 and 12, 9.6% vs. 8.3%, 26.6% vs. 23.8%, and 44.4% vs 39.4% achieved VL<50 copies/mL, respectively.

Table: Early virological and immunological response

Parameter	NVP combined	ATZ/r	ANCOVA
Mean HIV-1 RNA (log_{10}) (SD)			
Baseline	5.12 (0.64)	5.12 (0.66)	
Change from baseline at Week 4	-2.32 (0.58)	-2.16 (0.53)	p=0.004
Change from baseline at Week 12	-2.98 (0.83)	-2.94 (0.64)	n.s.
Mean CD4+ count (SD)			
Baseline	193 (95)	193 (96)	
Change from baseline at Week 4	+78 (94)	+86 (94)	n.s.
Change from baseline at Week 12	+121 (113)	+114 (117)	n.s.

Distributions of TTR were significantly better for combined NVP than for ATZ/r (Cox hazard ratio 0.74; Cox regression p=0.003).

Conclusions: NVP and ATZ/r, both combined with TDF/FTC, led to comparable virological and immunological responses. However, VL decay within the first 4 weeks and TTR were significantly better for NVP.

Reference: 1. Soriano V *et al.* 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, 19–22 Jul 2009 (Poster LBPEB07).

Introduction

- The ARTEN Phase IIIb trial compared the virologic efficacy and safety of nevirapine (NVP) (Figure 1) and ritonavir-boosted atazanavir (ATZ/r) (Figure 1) both in combination with tenofovir DF and emtricitabine (TDF/FTC).[1]
- In the ARTEN study, NVP showed a similar efficacy to ATZ/r (Figure 2) with a more favourable lipid profile after 48 weeks.[1]
- On-treatment, early predictors (e.g. assessment of viral load [VL] change 4 to 12 weeks after initiating therapy) have been investigated in the past to evaluate whether they serve as an indicator of longer-term virologic responses.[2–4]
- Early predictors for long-term treatment response can be used to prevent the accumulation of drug-resistance-associated mutations and the development of drug-related adverse events, by avoiding unnecessary exposure to ineffective regimens.[3]
- This subanalysis presents the early virological and immunological response data from the ARTEN study.

Figure 1. Chemical structures

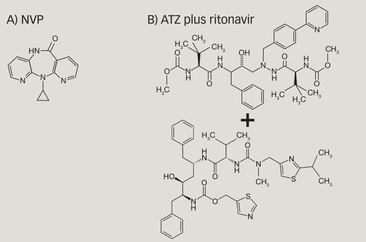
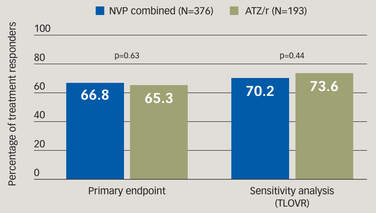


Figure 2. Percentage of patients with Week 48 treatment response (ITT-NCF analysis)



Methods

ARTEN was an open-label, randomised, international, non-inferiority clinical trial comparing the efficacy and safety of NVP versus ATZ/r in a total of 569 ARV-naïve patients with HIV-1-infection. It was the first prospective clinical trial to apply the guideline-recommended CD4+ cell count thresholds, of <250 cells/mm^3 in women and <400 cells/mm^3 in men, to the administration of NVP.[5–7] The ARTEN study included one arm with patients treated with NVP once-daily dosing. NVP is not indicated for once-daily dosing. The efficacy and safety of NVP once-daily dosing have not been established.

Results of subanalyses of the ARTEN study are reported here on early viral decay (log_{10}), the percentage of patients with HIV-RNA <50 copies/mL at each visit, and CD4+ cell count increase within the first 12 weeks of treatment.

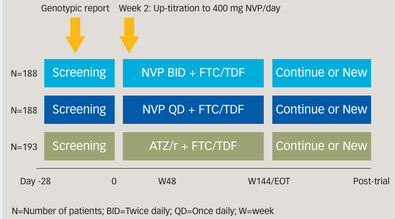
Inclusion/exclusion criteria

Key inclusion criteria:
- HIV-1-infected patients aged ≥18 years
- Adequate renal function (creatinine clearance ≥50 mL/min)
- Not previously treated with ARVs for >7 days
- CD4+ cell counts <400 cells/mm^3 or <250 cells/mm^3 for male and female patients respectively

Key exclusion criteria:
- Hepatic cirrhosis stage Child-Pugh B or C
- DAIDS grade >2 laboratory parameters (DAIDS grade >3 triglycerides)
- Active hepatitis B or C, defined as HBsAg-positive or HCV-RNA positive with AST/ALT >2.5x ULN (DAIDS grade 1)

Study design and randomisation

Figure 1. ARTEN study design



N=Number of patients; BID=Twice daily; QD=Once daily; W=week

Patients were randomised (1:1:1) to receive i) NVP 200 mg BID, ii) NVP 400 mg QD or iii) ATZ 300mg QD plus RTV 100mg QD (ATZ/r), in combination with fixed-dose FTC 200mg QD/TDF 300mg QD. Randomisation was stratified according to HIV-1 RNA (>100,000 copies/mL or ≤100,000 copies/mL) and CD4+ cell count (≥50 cells/mm^3 or <50 cells/mm^3) at screening. During the first 14 days of the study both NVP BID and NVP QD dose groups started out with a lead-in dose of NVP 200mg QD according to the product label.

Study endpoints

Primary endpoint at Week 48:
- Treatment response (TR) was defined as the proportion of patients with HIV-1 RNA <50 copies/mL measured at two consecutive visits **prior** to Week 48 and without subsequent rebound or change of ARV therapy prior to or at Week 48. This was based on recommendations from the EACS and DHHS guidelines at the time of the trial design.

Secondary endpoints at Week 48 included:
- A sensitivity analysis: a time to loss of virologic response (TLOVR) algorithm was applied, which defined TR as the proportion of patients with HIV-RNA <50 copies/mL at two consecutive visits **up to** Week 48 and without subsequent rebound or change of ARV therapy prior to or at Week 48
- Virologic failure
- Proportions of patients with VL <50 copies/mL at Week 48 (single measurement) among observed cases on treatment
  - Proportion of patients with VL <50 copies/mL at each study visit
- Time to treatment response, defined as time from start of treatment until the first measurement of the first confirmed virological response evaluated among the responders
- Changes in lipid parameters
- Change in CD4+ cell count from baseline through to Week 48
  - Mean CD4+ cell count increase within the first 12 weeks of treatment
- Rate of liver enzyme elevations

Safety endpoints included the incidence of adverse events (AEs), serious adverse events (SAEs) and discontinuations due to AEs, DAIDS grade ≥2 laboratory abnormalities and changes from baseline in laboratory tests over time.

Statistics

The statistical analysis of efficacy and safety was performed on all randomised patients receiving at least one dose of study medication. For the primary efficacy analysis, an intention-to-treat, non-completers considered failures (ITT-NCF) analysis was performed.

The primary analysis was the test of non-inferiority of the combined NVP arms compared to ATZ/r. The non-inferiority test was performed by calculating the two-sided 95% confidence interval (CI) for the difference in the proportions of responders between the combined NVP groups and ATZ/r. Non-inferiority of NVP was established if -12% was excluded from the CI.

Analysis of covariance (ANCOVA), controlling for screening VL and CD4+ cell count categories was performed.

Results

Demographic data and HIV baseline characteristics

A total of 576 patients were enrolled and randomised to treatment; 569 received study medication (70.8% in Western Europe, 21.4% in Latin America and 7.7% in Eastern Europe).

Table 1. Demographic data and HIV baseline characteristics

	NVP combined	ATZ/r	Total
Number of patients	376	193	569
Male, N (%)	315 (83.8)	162 (83.9)	477 (83.8)
Race, N (%)			
White	301 (80.1)	154 (79.8)	455 (80.0)
Black	28 (7.4)	17 (8.8)	45 (7.9)
Asian	47 (12.5)	22 (11.4)	69 (12.1)
Mean age (SD)	39.2 (10.1)	37.6 (9.5)	38.6 (9.9)
HIV-1 RNA (copies/mL), N (%) >100,000 log_{10} copies/mL	236 (62.8)	127 (65.8)	363 (63.8)
CD4+ cell count <50 cells/mm^3, N (%)	31 (8.2)	12 (6.2)	43 (7.6)

N=Number of patients, SD=Standard deviation

By Week 48, 41/188 (21.8%) patients treated with NVP QD, 53/188 (28.2%) patients treated with NVP BID and 18/193 (9.3%) patients treated with ATZ/r discontinued their study medication.

Primary efficacy and safety results

Primary efficacy and safety data have been presented previously[1] and are summarised below. At Week 48, a comparable proportion of patients achieved and maintained a TR (primary endpoint, ITT-NCF analysis) in the NVP group compared with the ATZ/r group (Table 2).

Non-inferiority of NVP vs. ATZ/r was established in the primary analysis (lower limit of the CI was above the pre-defined -12% non-inferiority margin at Week 48), and was confirmed by the sensitivity analysis (TLOVR algorithm) (Table 2).

Table 2. Analysis of treatment response at Week 48: primary analysis and sensitivity analyses

	Treatment response rates		
	NVP combined n/N (%)	ATZ/r n/N (%)	Difference NVP-ATZ/r (95% CI)
Primary endpoint (FAS)	251/376 (66.8)	126/193 (65.3)	1.9% (-5.9 to 9.8)
Sensitivity analysis (TLOVR-FAS)	264/376 (70.2)	142/193 (73.6)	-2.9% (-10.4 to 4.5)
VL<50 copies/mL at Week 48 among observed cases on-treatment	253/271 (93.4)	151/175 (86.3)	5.8% (-0.0 to 11.6)

n=number of responders, N=number of analysed patients, FAS=full analysis set, TLOVR=time to loss of virologic response

Overall, AE rates were similar between groups (85.9% among NVP patients and 86.5% among ATZ/r patients). However, despite similar AE rates, the incidence of AE-related treatment discontinuations was lower with ATZ/r than with NVP (3.6% vs. 13.6%). Rash was reported in 16.0% of NVP and 12.4% of ATZ/r patients, but more NVP patients were discontinued due to rash compared with ATZ/r (5.1% vs. 0%).

Most NVP-associated rashes developed during the lead-in phase. No Grade 4 rashes were observed. No cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or deaths due to liver or skin toxicity occurred.

Early virological and immunological response data

Percentage of patients with HIV-RNA <50 copies/mL

At baseline, >60% of patients in both the combined NVP arm and ATZ/r arm had a VL >100,000 copies/mL. At weeks 8 and 12, a comparable proportion of all patients achieved VL<50 copies/mL in the combined NVP group compared with the ATZ/r group (Table 3, Figure 4).

Table 3. Percentage of patients achieving VL <50 copies/mL

	Treatment response rates	
Proportion of patients achieving VL <50 copies/mL	NVP combined (N=376)	ATZ/r (N=193)
Week 4 [n(%)]	39 (9.6)	16 (8.3)
Week 8 [n(%)]	100 (26.6)	46 (23.8)
Week 12 [n(%)]	167 (44.4)	76 (39.4)

N=number of patients, VL=viral load

Figure 4. Proportion of patients with treatment response according to the TLOVR algorithm at each visit

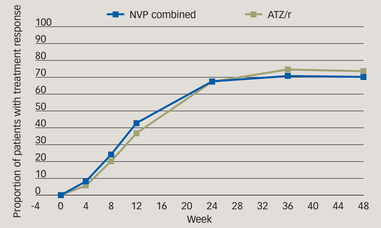
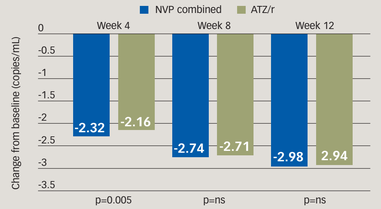


Figure 5. Mean change from baseline in HIV-RNA

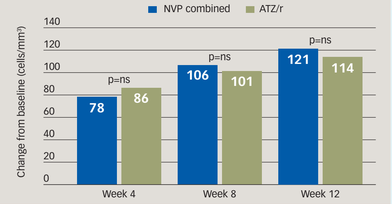


Mean HIV-RNA (log_{10}) at baseline was 5.12 copies/mL in the combined NVP arm and 5.12 copies/mL in the ATZ/r arm. Among NVP patients, mean change from baseline to Week 4 in HIV-RNA (log_{10}) was -2.32 copies/mL compared with -2.16 copies/mL for ATZ/r patients (p=0.045, ANCOVA difference 95% CI). Changes in HIV-RNA from baseline to Week 12 were not significantly different (Figure 5).

CD4+ cell counts

The baseline CD4+ cell count was 193 cells/mm^3 for both the combined NVP and ATZ/r treatment groups. The mean changes in CD4+ cell counts from baseline to Weeks 4 and 12 were not statistically different between the combined NVP and ATZ/r groups (Figure 6).

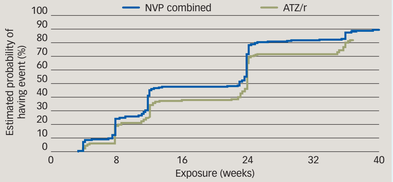
Figure 6. Mean change from baseline in CD4+ cell count



Time to treatment response

The Kaplan-Meier distributions of time to treatment response were significantly better for combined NVP than for ATZ/r. (Cox hazard ratio 0.74; Cox regression p=0.003 [95% CI 0.60 to 0.90]) (Figure 7).

Figure 7. Time to treatment response (first confirmed VL <50 copies per mL)



Conclusions

- In general, early virological and immunological responses were comparable between NVP and ATZ/r
- However, VL decay within the first 4 weeks and time to treatment response were significantly better for NVP compared with ATZ/r
- Non-inferiority between NVP and ATZ/r (both combined with fixed dose TDF/FTC) with regard to TR at Week 48 was established
- The ARTEN study confirms that the combination of NVP and TDF/FTC is effective in treatment-naïve patients, including those with high VL at baseline
- The ARTEN study demonstrates that NVP is an effective and well tolerated ARV for first-line therapy, when used in accordance with the guideline-recommended CD4+ cell count thresholds for NVP of <250 cells/mm^3 in women and <400 cells/mm^3 in men

References

1. Soriano V *et al.* 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, 19–22 Jul 2009 (Poster LBPEB07). **2.** Huang W *et al. J Infect Dis* 2001; **183**(10): 1455-1465. **3.** Powderly WG *et al. AIDS* 1999; **13**(14): 1873-1880. **4.** Raffi F *et al. Clin Infect Dis* 2006; **42**(6): 870-877. **5.** Polis MA *et al. Lancet* 2001; **358**(9295): 1760-1765. **6.** Gazzard BG. *HIV Med* 2008; **9**(8): 563-608. **7.** DHHS. Panel on Guidelines for Adults and Adolescents (November 2008). Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last accessed 15 November 2008. **8.** EACS Guidelines for the clinical management and treatment of HIV infected adults in Europe. Available at http://www.eacs.eu/guide/index.htm. Last accessed 08 February 2009. **9.** Hammer SM *et al. JAMA* 2008; **300**(5): 555-570.

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