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Poster
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Prospective randomised comparison of Nevirapine and Atazanavir/ritonavir both combined with Tenofovir DF/Emtricitabine in treatment-naïve HIV-1 infected patients: ARTEN Study week 48 results

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ARTEN
The Viramune® ARTEN Study

Abstract

Objectives: Nevirapine (NVP) and atazanavir/ritonavir (ATZ/r) are effective antiretrovirals (ARVs) with favourable lipid profiles. The ARTEN study compares the efficacy and safety of the two ARVs, both combined with tenofovir DF and emtricitabine (TDF/FTC).

Methods: ARTEN is a randomised, international, non-inferiority (12% margin) study comparing ATZ/r 300mg/100mg QD vs. NVP 200mg BID or 400mg QD, each combined with fixed-dose TDF 300mg/FTC 200mg QD. Treatment-naïve men and women with CD4+ counts <400 and <250 cells/mm³, respectively, were eligible. The primary endpoint for the comparison of the combined NVP groups with the ATZ/r group was treatment response (TR), defined as plasma HIV-RNA <50 copies/mL at two consecutive visits prior to Week 48 (e.g. at weeks 24 and 36) and without subsequent rebound or change of ARVs prior to Week 48. ANCOVA was performed controlling for screening viral load (≤100,000 or >100,000 copies/mL) and screening CD4+ count (<50 or ≥50 cells/mm³).

Results: 569 patients were randomised and treated. Baseline demographics and HIV-related characteristics were similar between groups: mean HIV-RNA was 5.1 $\log_{10}$ copies/mL (64% of patients >100,000 copies/mL); mean CD4+ count was 184.1 cells/mm³. At Week 48, more patients achieved and maintained TR in the combined NVP group compared with the ATZ/r group (66.8% versus 65.3%; ANCOVA difference in proportions 1.9% [95% CI -5.9% to 9.8%]; p=0.63). Non-inferiority of the primary endpoint was established between NVP and ATZ/r (lower limit of the CI was above the pre-defined -12% non-inferiority margin) at Week 48.

Overall, the proportion of patients with adverse events (AEs) was similar between groups (85.9% versus 86.5% in NVP and ATZ/r groups, respectively); of these, 12.5% and 16.1% were DAIDS grade 3 and 5.3% and 3.1% were DAIDS grade 4 in NVP and ATZ/r groups, respectively. The incidence of AEs leading to treatment discontinuation was lower with ATZ/r than with NVP (3.6% versus 13.6%). The most frequently reported AE leading to discontinuation in the NVP arms was rash (5.1% of all NVP treated patients).

Among NVP patients, mean change from baseline to Week 48 (LOCF) in total cholesterol (TC)/high density lipoprotein (HDL) ratio was -0.24 compared to +0.13 for ATZ/r patients (p=0.0001). Mean HDL levels increased by 9.7 mg/dL among NVP patients and by 3.9 mg/dL among ATZ/r patients (p<0.0001). Finally, the increase in mean triglyceride levels was significantly higher with ATZ/r than with NVP (28.1 mg/dL versus -0.2 mg/dL, p≤0.0001).

Conclusions: NVP shows non-inferior efficacy at Week 48 versus ATZ/r (both combined with fixed-dose TDF/FTC). Despite similar rates of AEs, discontinuations were more frequent in NVP than in ATZ/r patients. NVP demonstrated a more favourable lipid profile than ATZ/r.

Introduction

- First-line HAART regimens, currently recommended by international guidelines for the treatment of ARV-naïve HIV-1-infected patients, comprise two nucleoside reverse transcriptase inhibitors (NRTIs) combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir (RTV)-boosted protease inhibitor (PI).[1-4] Preferred NRTIs include emtricitabine co-formulated with tenofovir (FTC/TDF). This combination has become the most frequently used backbone for NNRTI and PI-based HAART in HIV-1-infected treatment naïve patients in Western countries[5]
- Nevirapine (NVP) is widely used in treating HIV-1 infection. However, until now, only limited trial data on NVP used in combination with FTC/TDF, as well as the use of NVP in accordance with the guideline-recommended CD4+ count thresholds,[1-4] have been available
- Guidelines for RTV-boosted PI regimens currently recommend a more recent PI, atazanavir/RTV (ATZ/r), for first-line therapy in ARV-naïve patients[1-4]
- Both NVP and ATZ/r have previously demonstrated favourable lipid profiles in ARV-naive patients,[6,7,8,9] and may therefore limit the need for lipid-lowering strategies to reduce the risk of cardiovascular disease
- The **A**tazanavir/**R**itonavir on a background of **T**enofovir and **E**mtricitabine vs. **N**evirapine on same background (ARTEN) Phase IIIb trial compared the virologic efficacy and safety of these two regimens in ARV-naïve patients with HIV-1-infection

Methods

ARTEN is 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. This is the first prospective clinical trial to apply the guideline-recommended CD4+ count thresholds, of <250 cells/mm³ in women and <400 cells/mm³ in men, to the administration of NVP.[1-4]

Week 48 primary efficacy and safety data from the ARTEN trial (NCT00389207) are reported here.

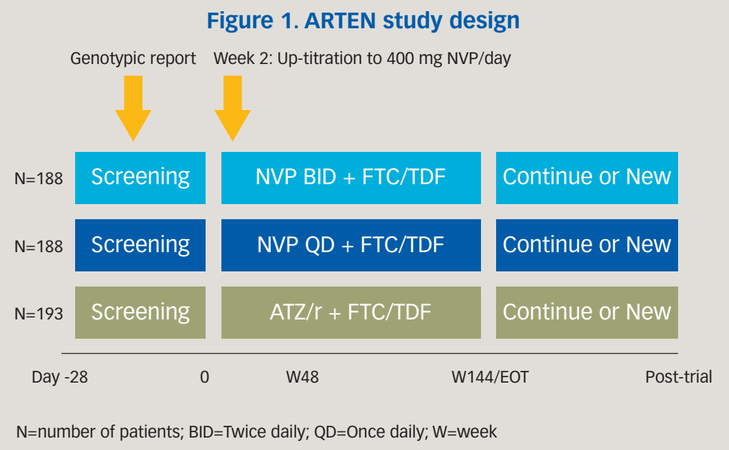
Inclusion/exclusion criteria

Key inclusion criteria:
- HIV-1-infected
- Aged ≥18 years
- Adequate renal function (creatinine clearance ≥50 mL/min)
- Not previously treated with ARVs for >7 days
- Male patients: CD4+ counts <400 cells/mm³
- Female patients: CD4+ counts <250 cells/mm³

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), each given 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+ count (≥50 cells/mm³ or <50 cells/mm³) at screening. During the first 14 days of the study, the protocol required that 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

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
- Changes in lipid parameters
- Change in CD4+ count from baseline through to Week 48
- 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.

In order to evaluate the differences in the lipid levels after 48 weeks of treatment, the mean change from baseline in total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride values (last observation carried forward [LOCF]) was compared between the treatment groups. ANCOVA, controlling for screening viral load and CD4+ categories was performed. In addition, the ratio of total cholesterol to HDL cholesterol (mean change from baseline) was compared between the groups.

Results

Demographic data and HIV baseline characteristics

Overall, 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 QD/BID	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)
Mean HIV-1 RNA ($\log_{10}$ copies/mL)	5.1	5.1	5.1
HIV-1 RNA (copies/mL), N (%) >100,000 $\log_{10}$ copies/mL	236 (62.8)	127 (65.8)	363 (63.8)
Mean CD4+ count (cells/mm³)	182.1	187.8	184.1
CD4+ count <50 cells/mm³, 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.

Efficacy results

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 (66.8% versus 65.3%; ANCOVA difference in proportions 1.9% [95% CI -5.9% to 9.8%]) (Table 2, Figure 2). When the definition of TR as patients with HIV-RNA <50 copies/mL at two consecutive visits up to Week 48 without subsequent rebound or change of ARVs (TLOVR algorithm) was applied, 70.2% and 73.6% of NVP and ATZ/r patients, respectively [ANCOVA difference -2.9% (95% CI -10.4% to 4.5%)] achieved this endpoint (Table 2, Figure 2).

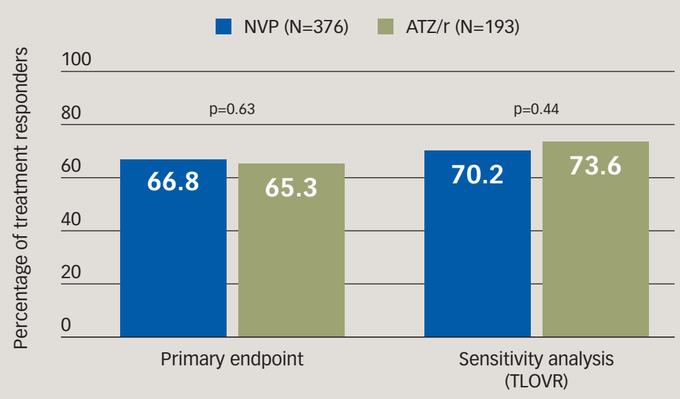
Non-inferiority of NVP vs. ATZ/r was established in the primary analysis (lower limit of the CI was above the pre-defined -12% non-inferiority margin at Week 48), and was confirmed by the sensitivity analysis (TLOVR algorithm) (Table 2).

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)
Primary endpoint (PPS)	248/371 (66.9)	118/181 (65.2)	2.3% (-5.7 to 10.4)
Sensitivity analysis (TLOVR-FAS)	264/376 (70.2)	142/193 (73.6)	-2.9% (-10.4 to 4.5)
Sensitivity analysis (TLOVR-PPS)	261/371 (70.4)	134/181 (74.0)	-3.1% (-10.7 to 4.5)
VL<50 copies/mL at Week 48 among observed cases on-treatment	256/274 (93.4)	154/175 (88.0)	5.1% (-0.4 to 10.6)

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

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



Treatment response by NVP dose schedule (primary endpoint [ITT analysis]) is shown in Figure 3 and a comparison of virologic failure rates is shown in Table 3.

Figure 3. Percentage of patients with Week 48 treatment response (primary endpoint, ITT analysis) by NVP dose schedule

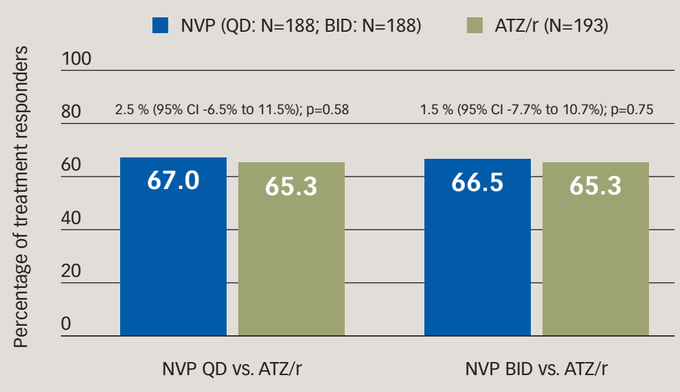


Table 3. Comparison of virologic failure rates between groups

	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 virologic failure), n (%)	11 (5.9)	21 (11.2)	3 (1.6)
Without confirmed response at Week 48, n (%)	10 (5.3)	3 (1.6)	24 (12.4)

CD4+ count

The mean change in CD4+ count from baseline to Week 48 (OT analysis) was not statistically different between the combined NVP group and ATZ/r. The mean CD4+ count increased by 170 cells/mm³ and by 185 cells/mm³ from baseline to Week 48 in the NVP and ATZ/r groups, respectively (p=0.18, ANCOVA difference 95% CI -39.3 to 7.4).

Lipids

At Week 48, a more favourable lipid profile was observed among NVP recipients than among ATZ/r recipients (Figures 4 and 5).

Figure 4. Mean change from baseline to Week 48 in TC:HDL ratio (LOCF)

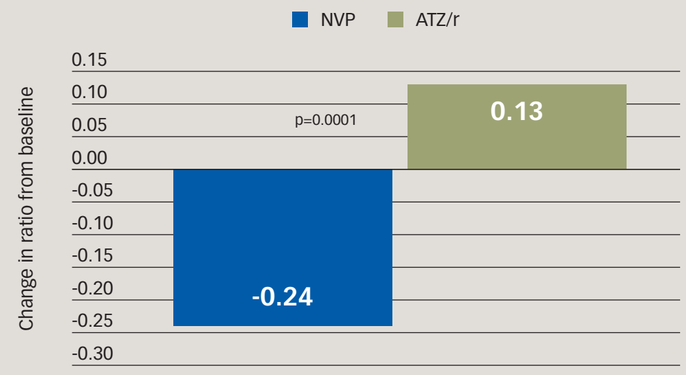
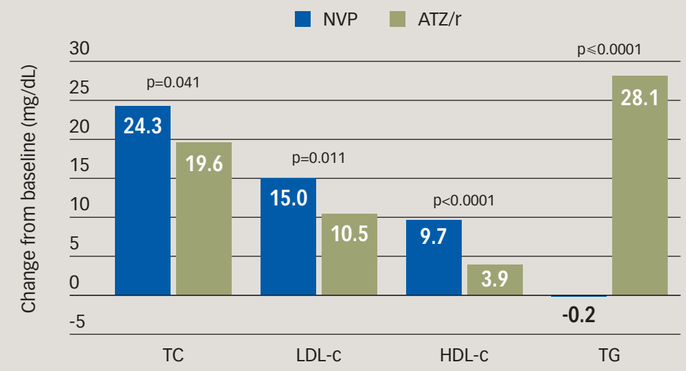


Figure 5. Mean change in lipid parameters from baseline to Week 48 (LOCF)



To convert mg/dL of HDL-c or LDL-c to mmol/L divide by 39.
To convert mg/dL of TG to mmol/L divide by 89.

Safety Results

Overall, AE rates were similar between groups (85.9% among NVP patients and 86.5% among ATZ/r patients) (Figure 6). DAIDS grade 3/4 AEs occurred in 12.5%/5.3% of NVP recipients and 16.1%/3.1% of 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%).

Figure 6. Overall AE rates at Week 48

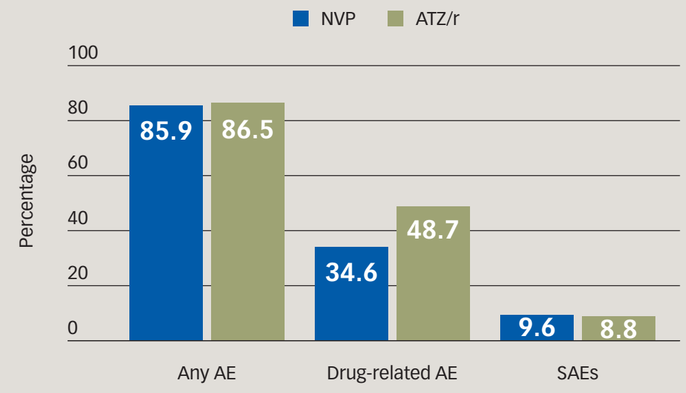


Table 4. Incidence of rash and hepatic events at Week 48

	Any Grade			DAIDS 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*	14.9	17.0	12.4	1.6	1.6	0.0	3.7	6.4	0.0
Hepatitis**	1.6	2.1	0.0	1.0	1.6	0.0	1.6	2.1	0.0
LEE**	5.9	7.4	1.6	3.2	4.8	1.5	2.1	3.2	1.0

*In 39 of these 60 NVP patients (65%) rash occured during the lead-in phase
** Hepatitis (excluding viral) and liver enzyme elevations (LEE) (double coding possible), excluding hyperbilirubinaemia, coded as adverse events

Most nevirapine-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.

Table 5. The percentage of patients with Grade 3 and 4 liver enzyme elevations at Week 48

	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	0.0
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

ALT=alanine aminotransferase, AST=aspartate aminotransferase
* leading to discontinuation in 0.5% of patients (n=1)

Conclusions

- Non-inferiority between NVP and ATZ/r (both combined with fixed-dose TDF/FTC) with regard to efficacy at Week 48 was established
- NVP demonstrated a more favourable lipid profile than ATZ/r
- Both NVP dosing regimens were similar in terms of virological response and safety
- ARTEN study data confirm that the combination of NVP and TDF/FTC is effective in treatment-naïve patients, including those with high viral load at baseline
- Despite similar rates and severity of AEs, discontinuations were more frequent in NVP than in ATZ/r patients
- The ARTEN study demonstrates that NVP is an effective ARV, which is well tolerated when administered as first-line therapy in accordance with the guideline-recommended CD4+ count thresholds for NVP of <250 cells/mm³ in women and <400 cells/mm³ in men

References

1. Gazzard BG. *HIV Med* 2008 **9** (8): 563-608.
2. 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.
3. 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.
4. Hammer SM *et al*. *JAMA* 2008 **300** (5): 555-570.
5. Jimenez-Nacher I *et al*. *J Antimicrob Chemother* 2008 **62** (4): 816-822.
6. Molina JM *et al*. *Lancet* 2008 **372** (9639): 646-655.
7. Cahn PE *et al*. *J Int Assoc Physicians AIDS Care (Chic Ill)* 2004 **3** (3): 92-8.
8. van Leth F *et al*. *Plos Med* 2004; **1** (1): e19.
9. Sankatsing R *et al*. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, 22-25 Jul 2007 (Poster).

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