

# Differences in the dynamics of viral rebound and evolution of resistance between CBV/NVP and CBV/ABC (NORA substudy of DART Trial) uncovered in the absence of viral load monitoring in real-time

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Poster #889

Short course  
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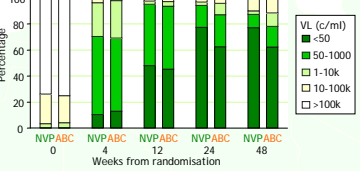
## BACKGROUND

- NORA was a randomised double-blind trial conducted in two clinical centres in Uganda as a nested substudy within the DART trial.
- 600 previously untreated symptomatic HIV-infected adults initiating ART with CD4<200 cells/mm<sup>3</sup> were randomly allocated to combination plus either **abacavir (ABC)** (300 mg bd) or **nevirapine (NVP)** (200 mg bd).
- After 24 weeks, participants were unblinded and continued their allocated regimen with open-label drug.
- We have already reported a higher rate of clinical events in the NVP arm in the first 48 weeks, despite better virological suppression and CD4 count recovery (CROI 2007 #506).

## VIROLOGICAL RESPONSES

- HIV RNA (VL) results were obtained from 2811 of a potential 3000 samples (94%).
- All participants had  $\geq 1.0$  log<sub>10</sub> decreases between baseline and week 4; median change was -2.72 (IQR -3.20, -2.33) log<sub>10</sub> copies/ml.
- Viral suppression at weeks 4 and 12 was similar in the two arms (Figure 1); NVP superiority became apparent at later time-points (p<0.0048 at both week 24 & 48, chi-squared test).
- In those with VL  $\leq 50$  copies/ml at week 48, 58/107 (54%) **ABC** and 39/62 (63%) **NVP** participants had previously attained VL <50 copies/ml before experiencing viral rebound.

Figure 1: Distribution of VL over time



## RESISTANCE TESTING

- 96 participants had week 48 VL >1000 c/ml. Genotypic results were available for 93 (97%) baseline and 91 (95%) week 48 samples.
- 4 patients had no baseline NNRTI resistance (3 ABC, 1 NVP). None reported previously taking ART for treatment or MTC. These 4 patients are excluded from the following analyses.

## RESISTANCE AT WEEK 48

- M184V was the most prevalent mutation, present in 72 (83%) participants (Table 1).
- TAMs were more common in the ABC arm (31 (55%) ABC, 9 (29%) NVP), but were not present in large numbers.
- Two-thirds of those in NVP arm developed  $\geq 1$  NNRTI mutation
- G190AS, K103N, Y181CI most frequent mutations
- 15% of those with any NNRTI mutations had more than one
- 52/87 participants (31 ABC, 21 NVP) had mutations associated with resistance to more than one of the following: 3TC, ZDV/ABC, NVP; of whom 10 participants (3 (5%) ABC, 7 (23%) NVP) had the M184V mutation and  $\geq 1$  TAM and  $\geq 1$  NNRTI mutation.

Table 1: Prevalence of individual and class specific mutations at week 48

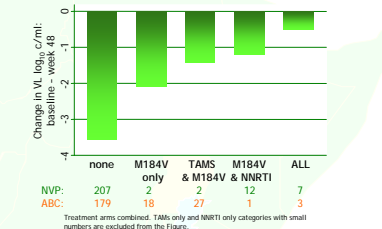
	ABC (n=56)	NVP (n=31)
<b>Individual Mutations*</b>		
M41L	3 (5%)	2 (6%)
D67NG	21 (38%)	6 (19%)
K70R	24 (43%)	3 (10%)
K103N	3 (5%)	7 (23%)
Y181CI	0	6 (19%)
M184V	49 (88%)	23 (74%)
G190AS	1 (2%)	9 (29%)
T215FY	11 (20%)	4 (13%)
K219QEN	8 (14%)	1 (3%)
<b>Type of mutations</b>		
TAMs	none	25 (71%)
	1-2	23 (41%)
	3+	8 (14%)
NNRTI	none	52 (93%)
	1+	4 (7%)
<b>Permutations of Mutations</b>		
None*	6 (11%)	5 (16%)
TAMs only	1 (2%)	0
M184V only	18 (32%)	2 (6%)
NNRTI only	0	3 (10%)
TAMs & M184V	27 (48%)	2 (6%)
TAMs & NNRTI	0	0
M184V & NNRTI	1 (2%)	12 (39%)
TAMs & M184V & NNRTI	3 (5%)	7 (23%)

\*occurring with >5% prevalence  
 †ABC: 5 NVP with VL>100,000 & likely non-adherent

## RESIDUAL ACTIVITY

- Predicted change in VL from baseline from the previous model can be interpreted as the "residual activity" of the drugs in the presence of the observed mutations (Figure 4):
- M184V is associated with an approximately 1.5 log<sub>10</sub> higher VL compared with no mutations
- the addition of either a TAM or NNRTI mutation to M184V has a similar effect, and increases this further by approximately 0.7-1.0 log<sub>10</sub> copies/ml
- the presence of 3 types of mutation reduces VL by a further 0.5 log<sub>10</sub> copies/ml

Figure 4: Residual activity of ART in the presence of specific mutations



## AIM

To describe a detailed retrospective study of participants in the NORA study that aims to understand the relationship between

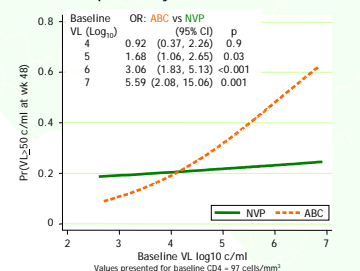
- virological response
- immune recovery
- emergence of resistance

and to explore whether these relationships differed between the 2 drug combinations studied.

## BASELINE PREDICTORS OF VL $\geq 50$ COPIES/ML AT WEEK 48

- Logistic regression models were used to identify baseline factors associated with VL  $\geq 50$  copies/ml at 48 weeks.
- No association was observed with sex (p=0.6), age (p=0.8), or WHO stage at ART initiation (p=0.5) but pre-ART CD4 count, HIV RNA, and treatment arm were all strongly predictive.
- Higher baseline CD4 counts were independently associated with lower odds of VL  $\geq 50$  copies/ml: OR 0.64 (95% CI: 0.57, 0.79) per 50 cells higher (p<0.001).
- The effect of baseline HIV RNA on the probability of VL <50 c/ml was significantly different between the treatment arms (p<0.04) (Figure 2). Patients with high baseline HIV RNA had a significantly higher probability of being >50 copies/ml at 48 weeks on ABC compared to NVP, but the response was similar in both treatment arms when baseline HIV RNA was less than 5 log<sub>10</sub> copies/ml.

Figure 2: Relationship between baseline VL and the probability of VL failure at week 48



## PATIENT CHARACTERISTICS

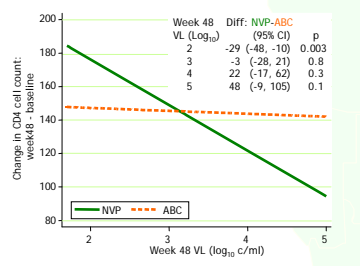
	ABC (n=300)	NVP (n=300)
<b>BASELINE CHARACTERISTICS</b>		
Women	72%	71%
Prior ART to prevent MTCT (most sdNVP) (% of women)	2%	5%
Age median (years)	37.6	36.3
CD4 (cells/mm <sup>3</sup> ) median (IQR)	99 (49-119)	103 (45-145)
HIV RNA (copies/ml) median (N=586)	292,300 (5.4 (0.7))	283,000 (5.4 (0.7))
WHO stage		
1	28%	25%
2	58%	52%
3	15%	22%
<b>FOLLOW-UP</b>		
Died before 48 weeks	9 (3%)	16 (5%)
Lost to follow-up before 48 weeks	5 (2%)	7 (2%)
Alive and in follow-up at 48 weeks	286 (95%)	277 (92%)
At last alive or 48 weeks		
still on randomised drug-2NRTI*	279 (93%)	266 (89%)
substituted ABC/NVP for another drug	21 (7%)	34 (11%)

\* allowing substitution of ZDV to d4T

## RELATIONSHIP BETWEEN BASELINE VL AND CD4

- A linear regression model was used to investigate the relationship between week 48 VL and the change in CD4 cell count from baseline to week 48.
- This was found to differ significantly in the two treatment arms (p<0.01).
- NVP: 27 cell lower week 48 CD4 (95% CI: 13-42 cells, p<0.001) per 1 log<sub>10</sub> greater HIV RNA at week 48
- ABC: no significant association between week 48 CD4 count change and VL at week 48
- A low week 48 VL was associated with a significantly greater increase in CD4 count in the NVP arm (Figure 3). This relationship remained after adjusting for baseline HIV RNA levels.
- Although a high week 48 VL was associated with a smaller increase in CD4 count from baseline on the NVP arm the difference between the arms was not significant.

Figure 3: Relationship between change in CD4 cell count to week 48 and week 48 VL



## EFFECT OF MUTATIONS ON WEEK 48 VL

- A multivariate regression model was used to determine the independent effect of the presence of TAMs, NNRTI-associated mutations and M184V on change in VL between week 48 and baseline.
- 8 participants (3 ABC, 5 NVP) with VL>100,000 c/ml and no mutations were considered non-adherent and excluded.
- Each type of mutation had an independent significant effect on VL (p<0.001):
  - any TAM +0.67 (95% CI: 0.31, 1.03) log<sub>10</sub> c/ml
  - any NNRTI +0.98 (95% CI: 0.60, 1.36) log<sub>10</sub> c/ml
  - M184V +1.42 (95% CI: 1.11, 1.73) log<sub>10</sub> c/ml
- There was no effect of treatment arm after accounting for these class mutations (p=0.2).
- There was no observed effect of the number of TAMs.

We thank all the patients and staff from all the centres participating in the DART trial.