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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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/mm³ were randomly allocated to combivir 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).

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.

PATIENT CHARACTERISTICS

		ABC (n=300)	NVP (n=300)
BASELINE CHARACTERISTICS			
Women		72%	71%
Prior ART to prevent MTCT (most sdNVP) (% of women)		2%	5%
Age median (years)		37.6	36.3
CD4 (cells/mm³)	median (IQR)	99 (49-199)	100 (45-145)
HIV RNA (copies/ml) (N=586)	median mean $\log_{10}$ (SD)	292,300 5.4 (0.7)	283,000 5.4 (0.7)
WHO stage	2 3 4	28% 58% 15%	25% 52% 22%
FOLLOW-UP			
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* substituted ABC/NVP for another drug		279 (93%) 21 (7%)	266 (89%) 34 (11%)

* allowing substitution of ZDV to d4T

VIROLOGICAL RESPONSES

- HIV RNA (VL) results were obtained from 2811 of a potential 3000 samples (94%).
- All participants had ≥1.0 $\log_{10}$ decreases between baseline and week 4; median change was -2.72 (IQR -3.20, -2.33) $\log_{10}$ 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=0.004 at both week 24 & 48, chi-squared test).
- In those with VL ≥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.

BASELINE PREDICTORS OF VL≥50 COPIES/ML AT WEEK 48

- Logistic regression models were used to identify baseline factors associated with VL≥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≥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 $\log_{10}$ copies/ml.

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 $\log_{10}$ 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 1: Distribution of VL over time

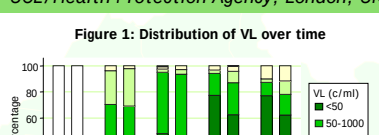


Figure 2: Relationship between baseline VL and the probability of VL failure at week 48

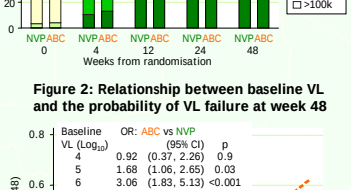
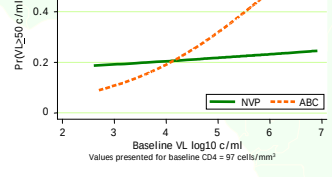


Figure 3: Relationship between change in CD4 cell count to week 48 and week 48 VL



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 baseline NNRTI resistance (3 ABC,1 NVP). None reported previously taking ART for treatment or MTCT. 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 ≥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 ≥1 TAM and ≥1 NNRTI mutation.

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) $\log_{10}$ c/ml
  - any NNRTI mutation +0.98 (95% CI: 0.60, 1.36) $\log_{10}$ c/ml
  - M184V +1.42 (95% CI: 1.11, 1.73) $\log_{10}$ 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.

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

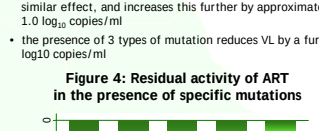
		ABC (n=56)	NVP (n=31)
Individual Mutations*			
M41L		3 (5%)	2 (6%)
D67NG		21 (38%)	6 (19%)
K70R		24 (43%)	3 (10%)
K103N		3 (5%)	7 (23%)
Y181CI		0	6 (19%)
M184V		49 (88%)	23 (74%)
G190AS		1 (2%)	9 (29%)
T215FY		11 (20%)	4 (13%)
K219QEN		8 (14%)	1 (3%)
Type of mutations			
TAMs	none	25 (45%)	22 (71%)
	1-2	23 (41%)	7 (23%)
	3+	8 (14%)	2 (6%)
NNRTI	none	52 (93%)	9 (29%)
	1+	4 (7%)	22 (71%)
Permutations of Mutations			
None[3]		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
[3] 3 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 $\log_{10}$ 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 $\log_{10}$ copies/ml
  - the presence of 3 types of mutation reduces VL by a further 0.5 log10 copies/ml

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



Treatment arms combined. TAMs only and NNRTI only categories with small numbers are excluded from the Figure.

CONCLUSIONS

- Virological efficacy of the ABC arm was inversely related to the baseline VL, despite equal 4 week VL decline.
  - ⇨CBV/ABC has less antiviral efficacy compared to CBV/NVP.
- In those with suppressed VL the CD4 recovery is better for those in the CBV/NVP arm
  - ⇨CBV/NVP may drive VL to lower levels within the range of undetectability than CBV/ABC
- CD4 cell count response was strongly related to viral suppression on CBV/NVP but no relationship was seen for CBV/ABC
  - ⇨the use of CD4 cell count as a surrogate of virological efficacy (to guide treatment changes) may be drug dependent
- As expected, K103N +/- M184V was the most common pattern in the NVP arm and M184V +/- TAMS in the ABC arm.
- Patients with these patterns still had >1 $\log_{10}$ lower VL at week 48 compared with baseline.
- ABC retains a similar degree of activity in the presence of TAMS to NVP in the presence of NNRTI mutations.
- This analysis only considers data up to 48 weeks and the continual evolution of resistance to therapy may reduce the observed differences between the arms. Data up to 96 weeks are being studied.

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