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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DATA SHARING

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

BACKGROUND

- CBV/ABC was a randomised double-blind trial conducted in two clinical centres in Uganda as a second substudy within the DART trial.
- 402 previously untreated symptomatic HIV-infected adults initiating ART with CD4<200 cells/mm³ were randomly allocated to combinations plus either stavudine (ABC) (300 mg bd) or tenofovir (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 (DOD) (DOD).

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.

METHODS

- HIV RNA (VL) results were obtained from 2811 of a potential 3000 samples (94%)
- VL (c/ml) results were available for 93 (97%) baseline and 91 (94%) week 48 samples.
- There was no association between week 48 CD4 count and VL change from baseline in the ABC arm (p=0.2).
- Table 1: Prevalence of individual and class specific mutations at week 48

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

<table>
<thead>
<tr>
<th>Mutation</th>
<th>CBV</th>
<th>ABC</th>
<th>p-value</th>
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<tr>
<td>M184V</td>
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<td>16</td>
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<tr>
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<tr>
<td>TAMs</td>
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</tr>
<tr>
<td>NNRTI</td>
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<td>16</td>
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</tr>
</tbody>
</table>

CONCLUSIONS

- Our study used an association network to determine the independent effect of the presence of the network to identify differing patterns of resistance across the mutation classes.
- Resistance may be affected by the treatment arm and baseline VL.
- Only CBV/NVP in the presence of mutations was significant.
- There was a higher rate of clinical events in the NVP arm in the first 48 weeks, despite better virological suppression and CD4 count recovery.

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)
- CBV/ABC is associated with an approximately 1.5 log higher VL compared with no mutations
- NORA substudy of DART Trial uncovered the absence of viral load monitoring in real-time

RESISTANCE AT WEEK 48

- CBV/NVP was the most prevalent mutation, present in 72 (83%) participants (Table 1).
- There was no observed effect of the number of TAMs & M184V mutations on the probability of baseline VL being >50 copies/ml at 48 weeks (all p=0.3).

RESISTANCE AT WEEK 48

1. CBV/NVP: 207 2 2 12 7
2. ABC: 179 18 27 1 3

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

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
- The effect of baseline VL and the probability of VL<50 copies/ml (Figure 2) was significant
- Participants with high baseline VL had a significantly higher probability of being >50 copies/ml at 48 weeks (all p<0.001) compared to lower VL, but the response was similar in both treatment arms when baseline HIV RNA was less than 5 copies/ml, regardless of CD4.
- TAMs & M184V only 1 (2%) 0
- M184V & NNRTI 1 (2%) 12 (39%)
- TAMs only 1 (2%) 0
- TAMs were more common in the ABC arm (31 (55%) vs 18 (32%) in the NVP arm). There was no observed effect of the number of TAMs.
- There was no effect of treatment arm after accounting for these class mutations (p=0.2).

EFFECT OF MUTATIONS ON WEEK 48 VL

- In both treatment arms when baseline HIV RNA was less than 5 log copies/ml, the addition of either a TAM or NNRTI mutation to M184V has a similar effect, and increases this further by approximately 0.7-1 log copies/ml compared with no mutations
- The presence of 3 mutations of TAMs reduces VL by a further 0.5 log copies/ml.