Phenotypic data to guide selection of reverse transcriptase inhibitors in second-line therapy following extended virological failure in Uganda

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INTRODUCTION

- Quantitative phenotypic resistance information interpreted via clinical cut-off can facilitate optimization of combination antiretroviral therapy.
- Resistance to efavirenz (TMC125), a new non-nucleoside reverse transcriptase inhibitor (NNRTI), develops through the accumulation of multiple NNRTI resistance associated mutations (RAMs).
- Associated factors and frequency of efavirenz cross-resistance among patients infected with non-subtype B HIV-1 failing Combivir®/abacavir and Combivir®/nevirapine based regimens requires examination.
- Viral load and resistance testing to guide individual patient management is rarely available in resource-limited settings, where switch to second-line therapies are often triggered by clinical failure alone.
- WHO guidelines recommend a change in the entire regimen to one with minimal (expected) cross-resistance with first-line drugs. However, data for cross resistance patterns emerging in those treated without viral load monitoring is still accumulating, and phenotypic data are scarce.

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® (fixed dose combination of lamivudine (3TC) 300mg BID) 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.

AIM

- To determine drug susceptibility (fold resistance for specific NRTI and NNRTI) in both the ABC and NVP arms of NORA at wk48 in patients with plasma samples taken at weeks 0, 48 and 96 were retrospectively assayed for HIV-1 RNA.
- The analysis included samples where HIV-1 RNA exceeded 1000 copies/ml.
- Phenotypic resistance testing results were available (Antivirogram ver5.2.01, Virco BVBA).
- Patients remained on first-line therapy at week 96.
- No genotypic baseline resistance was detected.
- Samples at week 96 were classified as phenotypically sensitive/resistant using biological cut-offs for candidate second-line RTI drugs proposed in WHO 2006 guidelines (Table 1).
- Efavirenz, a second-generation NNRTI.
- Fold-change values greater than 30 are displayed as 30 exactly in Figure 1 for nevirapine, efavirenz and efavirenz.

RESULTS

Phenotypic results were available for 73 patients at baseline and 55 patients at week 96 - 17 NVP, 38 ABC.

Of these, the majority of patients (13 NVP, 20 ABC) had VL>1000 at week 48.

Median (IQR) viral load at week 96 was 41,000 (8,000-77,000) and 33,000 (9,000-98,000) for nevirapine and abacavir groups, respectively.

The distribution of fold-change values for each drug are shown in Figure 1. The percentage of samples which are phenotypically sensitive are given in Table 2.

All baseline samples were sensitive to 3TC; at week 96 resistance was present in 34/38 ABC and 16/47 NVP samples.

Table 1: Number phenotypically sensitive using biological cut-offs

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>NVP (n=17)</th>
<th>ABC (n=38)</th>
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<tbody>
<tr>
<td>Abacavir</td>
<td>11 (65%)</td>
<td>17 (45%)</td>
</tr>
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<td>Didanosine</td>
<td>16 (94%)</td>
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<tr>
<td>Nevirapine</td>
<td>1 (6%)</td>
<td>31 (82%)</td>
</tr>
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<td>Efavirenz</td>
<td>4 (24%)</td>
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<td>Efavirenz</td>
<td>8 (47%)</td>
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CONCLUSIONS

- Isolates from the majority of patients with prolonged viroasia up to 96 weeks on either of these two first-line NORA regimens maintain susceptibility to didanosine and tenofovir.
- Abacavir resistance was present in only 55% of patients who failed on Combivir®/abacavir; 35% of patients in the NVP arm also developed abacavir resistance.
- Nevirapine, efavirenz and etravirine are all predicted to have significant activity in patients failing in the ABC arm, who received triple NRTI (class sparing) first-line ART.
- Efavirenz is predicted to have significant activity in approximately half of the NORA participants with prolonged virological non-suppression on Combivir®/nevirapine.
- These values may be conservative estimates as they are based on biological (i.e. based on the distribution for untreated patients) rather than clinical cut-offs.
- These findings should help inform selection of second-line regimens in resource-limited settings.

Figure 1: Distribution of Fold-Change at Baseline and at Week 96 by Randomised Group, for each ARV Drug.

Table 2: Number phenotypically sensitive using biological cut-offs

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