Emergence and evolution of drug resistance in the absence of viral load monitoring during 48 weeks of Combivir/Tenofovir within the DART Trial

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ABSTRACT

Background: DART is a randomized trial comparing clinical trials of zidovudine plus lamivudine to lamivudine plus Tenofovir in Uganda and Zimbabwe. The study aimed to compare the impact of baseline resistance on viral load and CD4 outcomes in patients with HIV-1 infection treated with Tenofovir and Combivir.

Methods: Von level measurements at baseline, weeks 24 and 48 were undertaken retrospectively by Phakamile Simukelwa. 144 weeks of patients initiating ART with lamivudine plus Tenofovir. Patients were assigned to two groups: 1) patients with detectable viral load at baseline and 2) patients without detectable viral load at baseline. The study was conducted at the University of Harare and the University of Kampala.

Results: Of the 144 patients initiating ART with lamivudine plus Tenofovir, 94 patients had detectable viral load at baseline, 50 patients had undetectable viral load at baseline. Overall, prevalence of resistance was higher at 48 compared to 24 weeks. The proportion of samples with 4-6 TAMS at 24 and 48 weeks was 4% and 39% respectively, all with co-existing M184V. Although a small excess of TAM-1 pathway mutations at 24 weeks compared to 48 weeks, the most notable finding was that most viruses by week 48 did not reach the 0-4 TAMS area under the curve (0-24 weeks) as a possible correlate (Table 4).

Overall, prevalence of resistance was higher at 48 compared to 24 weeks. The proportion of samples with 4-6 TAMs at 24 and 48 weeks was 4% and 39% respectively, all with co-existing M184V (Table 1). Although there was a small excess of TAM-1 pathway mutations at 24 weeks compared to 48 weeks, the most notable finding was that most viruses by week 48 did not reach the 0-4 TAMS area under the curve (0-24 weeks) as a possible correlate (Table 4). We now describe the resistance patterns emerging in those with detectable viral load at 24 and/or 48 weeks.

VL and CD4 OUTCOMES TO 48 WEEKS

<table>
<thead>
<tr>
<th>Week</th>
<th>VL (log_10 c/ml)</th>
<th>CD4 (cells/mm^3)</th>
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<tr>
<td>24</td>
<td>-2.6 (0.8)</td>
<td>370 (110)</td>
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<tr>
<td>48</td>
<td>-2.2 (0.7)</td>
<td>520 (120)</td>
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PREDICTORS OF RESISTANCE

In an attempt to identify specific predictors of the EXTENT OF RESISTANCE, we studied the association between viral load at baseline, weeks 4, 12, and 24, and the numbers of resistance mutations. For this analysis we only used viral loads for patients with week 48 resistance data in addition with continuous data. The extent of 0-4 TAMs was associated with higher viral load at baseline (Table 1).

DISCUSSION

- 36% of those with VL=1000 c/ml at 48 weeks of therapy had 4-6 TAMs, severely limiting future drug options within the NNRTI class.
- In this population initiating ART with NNRTI, this must be balanced against the potential benefits of maintaining 2 further active classes, including boosted PI.
- The majority of patients enrolld into the virology substudy had undetectable viral load at week 24 and 48. We assume this reflects the lack of resistance at these timepoints.
- 10% of this DART population have evidence of drug resistance prior to initiating ART (treatment naive). This likely reflects prior partial response with NNRTI and NNRTI classes of drugs, although we cannot exclude resistance.
- Pre-existing drug resistance should be considered as a potential cause of drug failure in ART-naive populations.

The viral load at 48 weeks predicted the extent of TAMs at week 48 (p<0.01), which is probably explained by pre-existing drug resistance. This may be facilitating continual evolution of more complex resistance patterns. Indeed, the VL at 48 weeks may be a marker of number and severity of mutations, but we did not reach statistical significance. TAM pattern may also be determined by a number of specific risk factors that were not all available.

Despite recent observations of more rapid emergence of K65R in subtype C, we found no evidence that CBV/TDF selected different sets of mutations, although we were not able to rule out that the two partners in some subtypes than others, although numbers were small. This does not exclude different patterns of being observed for other drug combinations, or over longer follow-up.

Of interest, we find that the traditional classification of nucleoside analogue drug resistance as TAMs and TAM-pathway drugs loses relevance during prolonged viremia. This suggests that resistance studies in the context of ART rollover with limited virological monitoring will identify novel sets of resistance mutations which are rarely observed in the resource-rich setting.

HIV sequence data were obtained in only approximately half of eligible samples from 24 and 48 weeks, due to sample exhaustion and/or technical problems. Hence, similar analyses were not possible with regard to the viral loads in samples which yielded sequences compared to those which did not, and therefore we are confident that our results are representative of the population with detectable viral loads at these time points.

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

REFERENCES