Short-term Virological Response to a Triple Nucleoside/Nucleotide Analogue Regimen in Adults with HIV Infection in Africa within the DART Trial

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Development of AntiRetroviral Therapy In Africa: DART
DART trial design: main randomisation

3315 previously untreated HIV-infected patients stage WHO 2, 3 or 4 and CD4<200 cells/mm³

randomise to initiate triple drug ART with

Clinical and Laboratory Monitoring (12 weekly biochemistry, FBC & CD4; no virology)

Clinical Monitoring Only (biochemistry and/or FBC if clinically indicated)

• 2468 (74%) received Combivir (CBV) plus tenofovir DF (TDF) first-line

• 300 patients enrolled into virology substudy (retrospective)
Rationale for first-line regimen

- Potential advantages of initial regimens containing only nucleoside or nucleotide RTIs
  - avoid drug interactions eg TB therapy
  - class sparing
  - low pill burden
  - good tolerability and toxicity profile

- Concerns
  - suboptimal virological potency (eg ACTG 5095)
  - development of resistance (eg ESS30009)

- Limited data on CBV+TDF as a combination
  - ZDV may reduce emergence of K65R (eg Winston 2004)
Objectives of virology substudy

• Primary objective
  - determine early virological response to CBV+TDF

• Secondary objectives
  - investigate predictors of virological suppression and failure
  - compare virological response to CBV+TDF with other triple combinations in similar populations with low CD4 counts
Methods

- 300 patients
  - 100 from each of 3 clinical sites in Uganda (2) and Zimbabwe (1)
  - half with baseline CD4 <100 cells/mm³
  - consecutive patients enrolled in each CD4 strata after first 2 months of the trial, excluding the first 20 patients in each site

- Plasma HIV-1 RNA assayed on stored specimens at 0, 4, 12 and 24 weeks after initiation of CBV+TDF
  - maximum possible 1200 results

- All assays (Roche Amplicor 1.5) performed locally with cross-site QA programme
Baseline characteristics

- 65% women
- age: median 37.5 years (range 20-62 years)
- CD4: median 100 cells/mm³, 29% <50 cells/mm³
- WHO stage: 2 (23%), 3 (48%), 4 (29%)
- HIV-1 RNA: median 289,400 c/ml
Follow-up to week 24

• 1148 (95.7%) results were obtained
  - ITT analysis (based on all available results)

• 52 missing results due to
  - 11 (4%) patients died before week 24
    • 4 died before week 4
    • 7 had last HIV-1 RNA <1500 c/ml (4 <50 c/ml)
  - missed visit or sample not taken
  - ITT M=F analysis (missing results due to death, missed visit, or no sample included as “failure”)
Follow-up to week 24 (ctd)

- 249 (83%) patients known to be alive at 24 weeks having been prescribed CBV+TDF without interruption
  - on treatment (OT) analysis (based on all available results when patient had been taking CBV+TDF without interruption)

- 15 (5%) patients had substituted d4T for ZDV

- 33 (11%) patients interrupted ART for 3+ days
  - median 12 days (range 3-78 days)
Change in HIV-1 RNA & CD4 (ITT)

Weeks from initiation of CBV/TDF

Mean decrease in HIV-1 RNA (95% CI)
-4.0
-3.0
-2.0
-1.0
0.0

Mean increase in CD4 (95% CI)
0.0
30.0
60.0
90.0
120.0

Number
297
285
282
281

CROI 2005
Viral suppression at week 24

<table>
<thead>
<tr>
<th></th>
<th>% &lt;50 c/ml</th>
<th>% &lt;400 c/ml</th>
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<tbody>
<tr>
<td>ITT (n=281)</td>
<td>57%</td>
<td>76%</td>
</tr>
<tr>
<td>ITT M=F (n=300)</td>
<td>53%</td>
<td>71%</td>
</tr>
<tr>
<td>OT (n=244)</td>
<td>61%</td>
<td>80%</td>
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</table>

Mean log drop: 3.70  3.67  3.95

NOTE: 8 values <100 or <400 due to insufficient sample volume are conservatively counted as ≥50c/ml (3%)
Predictors of suppression
<50 or <400 c/ml at week 24

- Patients who spent more time off ART before 24 weeks were less likely to suppress
  - <400 c/ml: OR = 0.68 per week off ART (p=0.007)
  - <50 c/ml: OR = 0.59 per week off ART (p=0.009)

- No effect of baseline HIV-1 RNA
  - <400 c/ml: OR = 1.01 per 1 log higher (p=0.98)
  - <50 c/ml: OR = 1.00 per 1 log higher (p=0.99)

- Non-significant trends in expected direction for
  - age
  - baseline CD4
  - HIV-1 RNA response at 4 weeks
  - self-reported adherence to prescribed medication
12 versus 24 week HIV-1 RNA response

<table>
<thead>
<tr>
<th>(ITT: n=274)</th>
<th>Week 24</th>
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<tbody>
<tr>
<td></td>
<td>&lt;50</td>
</tr>
<tr>
<td>&lt;50</td>
<td>32%</td>
</tr>
<tr>
<td>50-399</td>
<td>22%</td>
</tr>
<tr>
<td>400-1000</td>
<td>2%</td>
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<tr>
<td>&gt;1000</td>
<td>2%</td>
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- 37 patients had considerably poorer response at 24 weeks
- 15 patients had considerably better response at 24 weeks
HIV-1 RNA >1000 c/ml at 24 weeks

- 47/281 (17%) patients had HIV-1 RNA >1000 c/ml at 24 weeks
  - 18 (6%) >10000 c/ml
- 12 had never achieved suppression <400 c/ml
- 29 had HIV-1 RNA <400 c/ml at 12 weeks
  - 18/29 had one or more factors in the preceding 12 weeks possibly contributing to rebound
    - off ART for >1 week (n=2)
    - incomplete adherence (n=15)
    - SAE, Grade 3/4 AEs, or other ART-modifying AEs (n=3)
    - malaria (n=6)
Cohort comparison: UK CHIC

- **UK CHIC: 1997 - 2002**
  - starting HAART naïve (3+ drugs, 94% PI/NNRTI based)
  - 1971 patients with baseline CD4<200 cells/mm$^3$
  - median HIV-1 RNA 161,600 c/ml
  - 24% women, 37% heterosexually infected, 32% Black African

- Suppression rates varied across year of starting HAART

<table>
<thead>
<tr>
<th>At 24 weeks (ITT)</th>
<th>1998</th>
<th>2000</th>
<th>2002</th>
<th>DART</th>
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</thead>
<tbody>
<tr>
<td>&lt;400 c/ml</td>
<td>68%</td>
<td>90%</td>
<td>87%</td>
<td>76%</td>
</tr>
<tr>
<td>&lt;50 c/ml</td>
<td>[16%]</td>
<td>56%</td>
<td>56%</td>
<td>57%</td>
</tr>
</tbody>
</table>
Summary and future work

• Good virological response to CBV+TDF at 24 weeks
  - high baseline viral load, co-morbidities
  - tolerability is also good

• Comparable to populations with low CD4 counts initiating PI/NNRTI based regimens

• Genotyping of samples with HIV-1 RNA >1000 c/ml at 24 weeks is currently ongoing

• Extension of viral load testing to 36 and 48 week samples is in progress
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Viral suppression over time (ITT)

- Weeks from ART initiation:
  - 0 weeks: 0% (<50 c/ml), 1% (<400 c/ml)
  - 4 weeks: 11% (<50 c/ml), 40% (<400 c/ml)
  - 12 weeks: 48% (<50 c/ml), 86% (<400 c/ml)
  - 24 weeks: 57% (<50 c/ml), 76% (<400 c/ml)

Sample sizes:
- 0 weeks: n=297
- 4 weeks: n=285
- 12 weeks: n=282
- 24 weeks: n=281