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

C Kityo Mutuluuza, AS Walker, P Kaleebu, V Robertson, R Enzama, A Burke, D Yirrell, A Reid, P Munderi, DM Gibb, C Gilks, P Muggyeniyi, H Grosskurth, J Hakim, and D Pillay

on behalf of the DART Trial Team
Development of AntiRetroviral Therapy In Africa: DART

Joint Clinical Research Centre, Kampala, Uganda & Academic Alliance, Mulago Hospital, Uganda

MRC/Uganda Virus Research Institute Programme on AIDS, Entebbe, Uganda & TASO, Uganda

University of Zimbabwe, Harare, Zimbabwe

MRC Clinical Trials Unit, UK & Imperial College, UK

Rockefeller Foundation

MRC, UK

DFID, UK

GlaxoSmithKline Gilead Boehringer-Ingelheim

CROI 2005
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 increase in CD4 (95% CI)

Mean decrease in HIV-1 RNA (95% CI)

Number

0 4 12 24

0 10 20 30 40 50 60 70 80 90 100 110 120

-4.0 -3.0 -2.0 -1.0 0.0 1.0 2.0 3.0 4.0

297 285 282 281

-2.43 -3.52 -3.70 +98 +106
Viral suppression at week 24

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
<th>Mean log drop</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (n=281)</td>
<td>57%</td>
<td>3.70</td>
</tr>
<tr>
<td>ITT M=F (n=300)</td>
<td>53%</td>
<td>3.67</td>
</tr>
<tr>
<td>OT (n=244)</td>
<td>61%</td>
<td>3.95</td>
</tr>
</tbody>
</table>

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

CROI 2005
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

#### (ITT: n=274)

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>32%</td>
</tr>
<tr>
<td>50-399</td>
<td>7%</td>
</tr>
<tr>
<td>400-1000</td>
<td>3%</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>5%</td>
</tr>
</tbody>
</table>

#### 12 versus 24 week HIV-1 RNA response

- 37 patients had considerably poorer response at 24 weeks
- 15 patients had considerably better response 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/mm³
  - 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>
</tr>
</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
Acknowledgments

- We thank all the patients and staff from all the centres participating in the DART trial.
- **Virology Group:** P Kaleebu, D Pillay, V Robertson, D Yirrell, R Enzama, S Tugume, M Chirara, F Lyagoba, C Gale.
- **Academic Alliance, Mulago Hospital, Uganda:** E Katabira, J Oyugi, A Ronald, A Kambungu, J Martin, R Nalumenya, R Nairubi, E Bulume, M Teopista, C Twijukye, F Sematala, H Byakwaga.
- **The AIDS Support Organisation (TASO), Uganda:** A Coutinho, B Etukoit.
- **Imperial College:** C Gilks, L Colquhoun, K Boocock, C Puddephatt.
- **MRC Clinical Trials Unit:** J Derbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, A Rauchenberger, S Sheehan, C O’Brien.
- **Trial Steering Committee:** I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Derbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, E Loeliger (observer), M Imperiale (observer), O Mugurungi, P Mugyenyi, P Naidoo (observer), M Palmer (observer), J Rooney (observer), J-M Steens (observer).
- **Data and Safety Monitoring Committee:** A McLaren (Chair), C Hill, J Matenga, A Pozniak, D Serwadda
- **GlaxoSmithKline** donated first-line drugs for DART and provided funding for this virology substudy. **Gilead** and **Boehringer-Ingelheim** also donated first-line drugs.
- **Funding:** DART is funded by the **UK Medical Research Council**, the **UK Department for International Development (DFID)**, and the **Rockefeller Foundation**.

CROI 2005
Viral suppression over time (ITT)

Weeks from ART initiation

- <50 c/ml
- <400 c/ml

0% 1%
11%
40%
48%
86%
57%
76%

(n=297) (n=285) (n=282) (n=281)