48 week virological response to a triple nucleoside/nucleotide analogue regimen in adults with HIV infection in Africa within the DART trial

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on behalf of the DART Trial Team
DART trial design and regimens

• DART is a large randomised trial with clinical endpoints
  - all 3315 patients receive triple drug ART
  - NO viral load monitoring

• 2468 (74%) have received zidovudine (ZDV) + lamivudine (3TC) as combivir plus tenofovir DF (TDF) first-line

• 300 patients enrolled into virology substudy (retrospective)

• Good virological response to ZDV+3TC+TDF at 24 weeks reported at CROI 2005
Objectives & Methods

- **Objectives**
  - determine 48 week virological response to ZDV+3TC+TDF
  - describe the distribution of mutations in those with HIV-1 RNA >1000 c/ml at 24 weeks

- **300 patients**
  - 100 from each of 3 sites; 2 in Uganda and 1 in Zimbabwe
  - half with baseline CD4 <100 cells/mm³

- **77 of the original 300 patients entered a pilot STI study at 28 weeks (based on their week 24 CD4 response) and interrupted all ART for 12 weeks**
  - excluded and replaced with patients matched on baseline and week 24 CD4 who did not interrupt ART before 48 weeks
Laboratory Methods

• Viral Load
  - Measured using the Roche™ amplicor 1.5 ultrasensitive assay in Uganda

• Resistance Testing
  - Measured using an in-house method with appropriate sets of primers in Uganda and UK
  - Beckman capillary sequencer
Baseline characteristics

- 66% women
- Age: median 37.3 years (range 20-62 years)
- CD4: median 100 cells/mm³, 30% <50 cells/mm³
- WHO stage: 2 (23%), 3 (51%), 4 (25%)
- HIV-1 RNA: median 279,910 c/ml
Change in HIV-1 RNA & CD4

Mean decrease in HIV-1 RNA (log$_{10}$ c/ml, 95% CI)

Mean increase in CD4 (cells/mm$^3$, 95% CI)

Weeks from initiation of ZDV+3TC+TDF

Number 300 283 279 281 274 272

Mean decrease in HIV-1 RNA:
-2.42, +103, +104, +114, +126

Mean increase in CD4:
+104, +103, -3.41, -3.91, -4.26, -4.10

Number of patients:
300, 283, 279, 281, 274, 272
Viral suppression at week 48

- ITT: 72% <400 c/ml, 61% <50 c/ml
- ITT M=F: 65% <400 c/ml, 55% <50 c/ml
- OT: 74% <400 c/ml, 62% <50 c/ml

Mean log drop:
- ITT: 4.10
- ITT M=F: 3.72
- OT: 4.20

Number:
- ITT: 272
- ITT M=F: 300
- OT: 231
HIV genotype at 24 weeks

- 48 patients had HIV-1 RNA >1000 c/ml at 24 weeks
  - 10 insufficient sample for genotyping

- Genotypes obtained from 20 of the remaining 38 samples
  - 18 could not amplify both PR and RT even with primers optimised for subtype
    - 12/18 had HIV-1 RNA <5000 c/ml

- Subtypes (STAR): 6 A, 8 C (all Zim), 5 D, 1 D/A

NRTI resistance mutations

• 18/20 showed key mutations
  - both with no mutations had been off ART (pregnancy and AE)

• 4 with M184V alone and 1 with TAMs alone (3 TAMs)
• 10 with M184V and additional TAMs (mean 2.4, range 1-4)
• 3 with K65R
  - one with T215Y, one with Y115F, and one K65R alone
• TAMs: M41L (8), D67N (6), K70R (5), T215F (1), T215N (3), T215Y (6)
• only the patient with K65R alone had substituted d4T for ZDV
Summary and future work

• ZDV+3TC+TDF maintains good virological efficacy from 24 to 48 weeks
  - this population has high baseline viral load, advanced disease, co-morbidities
  - tolerability is also good

• In this population infected with HIV-1 subtypes A, C or D, M184V with or without TAMs was the most common route to resistance, whereas K65R was identified infrequently
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Resistance mutations (modified IAS 2004)

• NRTIs:
  - V118I not included

• NNRTIs:

• TAMs: