



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

P Kaleebu
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



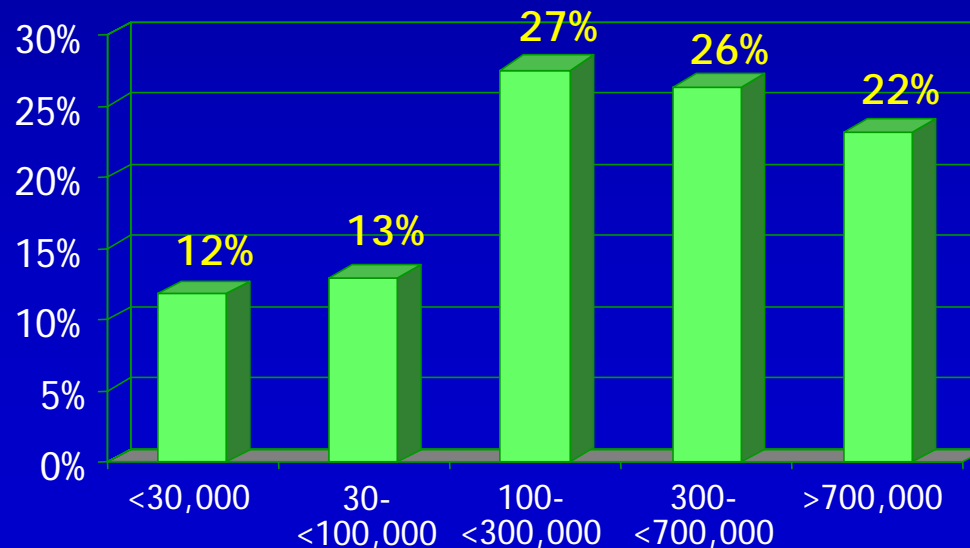
- Viral Load
 - Measured using the Roche™ amplicor 1.5 ultrasensitive assay in Uganda
- Resistance Testing
 - Measured using an in-house method with appropriate sets of primers in Uganda and UK
 - Beckman capillary sequencer



Baseline characteristics

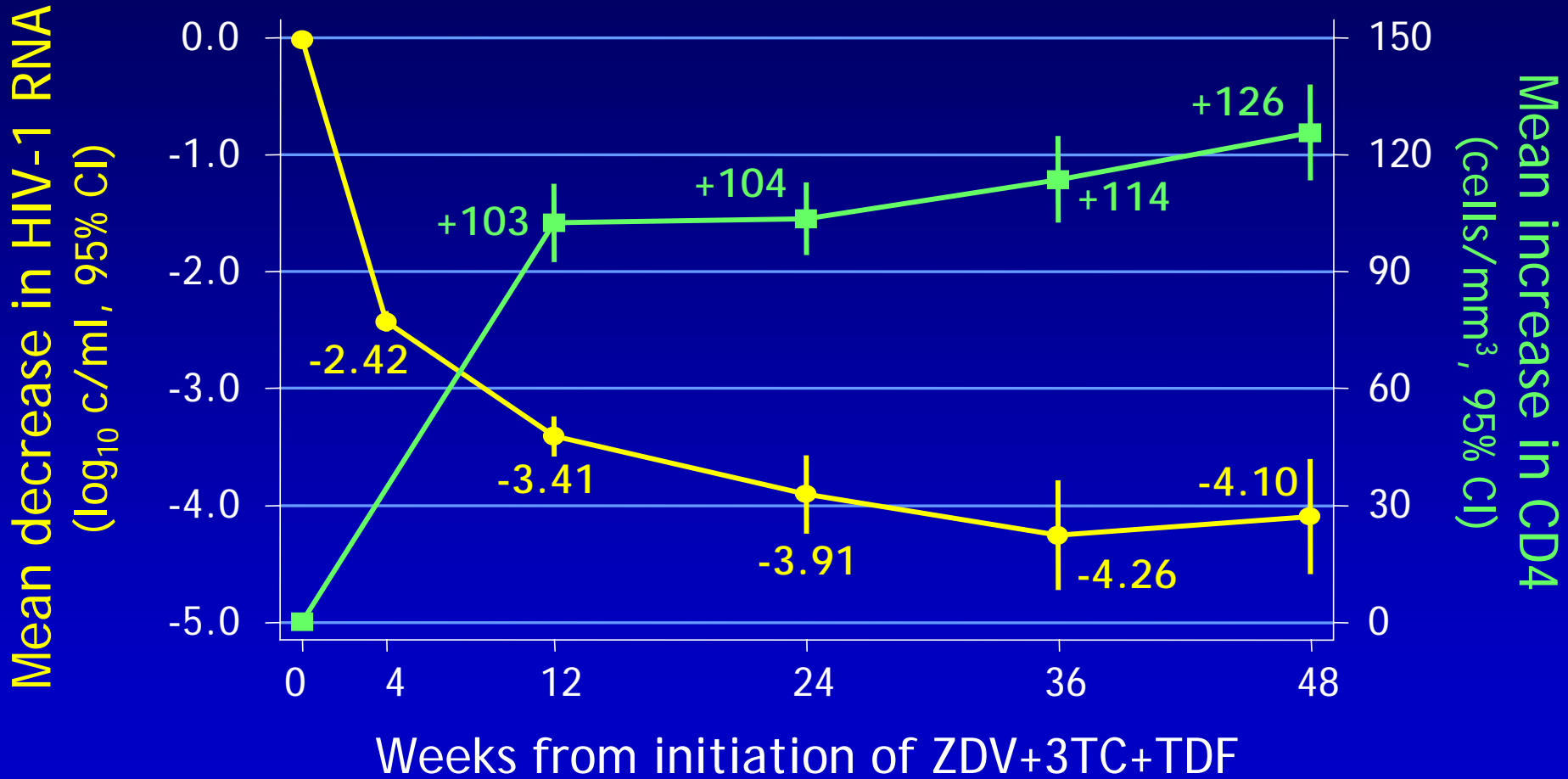


- 66% women
- Age: median 37.3 years (range 20-62 years)
- CD4: median 100 cells/mm³, 30% <50 cells/mm³
- WHO stage: 2 (23%), 3 (51%), 4 (25%)
- HIV-1 RNA: median 279,910 c/ml





Change in HIV-1 RNA & CD4



Number

300

283

279

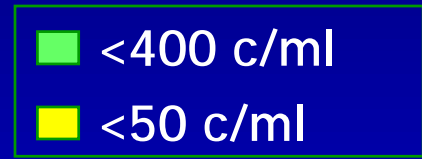
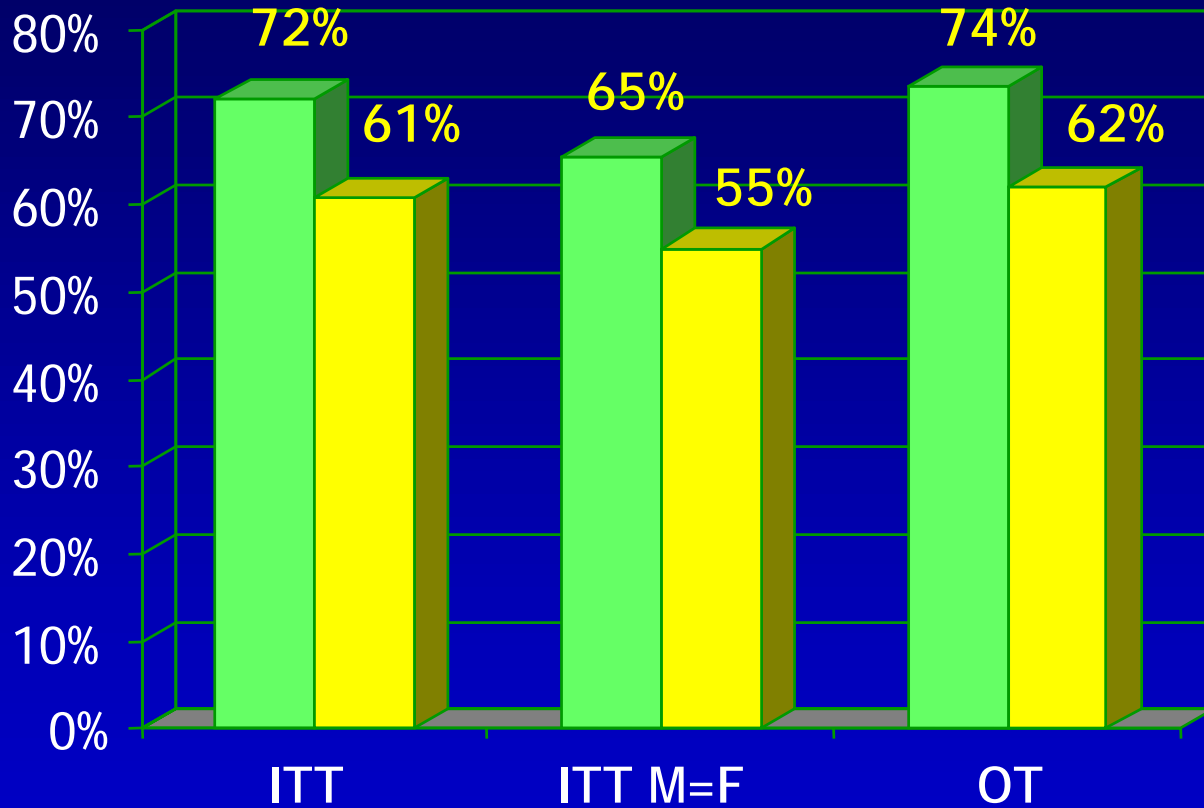
281

274

272



Viral suppression at week 48



Mean log drop:	4.10	3.72	4.20
Number:	272	300	231



HIV genotype at 24 weeks



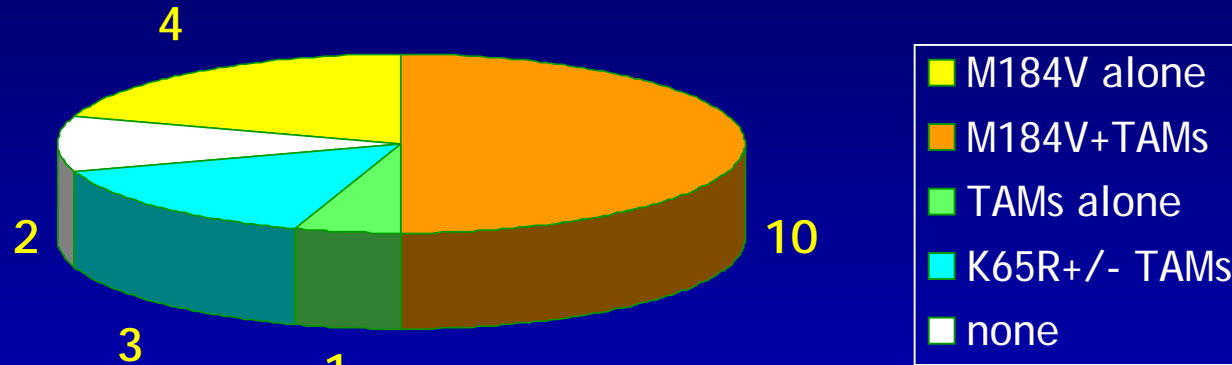
- 48 patients had HIV-1 RNA >1000 c/ml at 24 weeks
 - 10 insufficient sample for genotyping
- Genotypes obtained from 20 of the remaining 38 samples
 - 18 could not amplify both PR and RT even with primers optimised for subtype
 - 12/18 had HIV-1 RNA <5000 c/ml
- **Subtypes (STAR): 6 A, 8 C (all Zim), 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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- **Trial Steering Committee:** I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, E Loeliger (observer), M Imperiale (observer), O Mugurungi, P Mugenyi, P Naidoo (observer), M Palmer (observer), J Rooney (observer), J-M Steens (observer).
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Resistance mutations (modified IAS 2004)



- NRTIs:
 - M41L, E44D, A62V, K65R, D67N, T69N/D, K70R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, K219Q, K219E, T215any, any 69 insertion
 - V118I not included
- NNRTIs:
 - L100I, K103N, V106M/A, V108I, Y181C/I, Y188C/L/H, P225H, M230L, P236L, G190any
- TAMs:
 - M41L, E44D, D67N, T69N/D, K70R, L210W, K219Q, K219E, T215any, any 69 insertion