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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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ABSTRACT

Introduction: There are few viral load (VL) data on ZDV+3TC+TDF (tenofovir DF) as first-line therapy. We therefore evaluated VL response through 48 weeks, and emergence of genotypic mutations in those with VL>1000 c/ml at 24 weeks, in naive adults initiating ART in the DART trial.

Methods: Plasma HIV-1 RNA was assayed retrospectively in 300 adults with baseline CD4 <200 cells/mm^3 from 3 sites in Uganda and Zimbabwe using the Roche Amplicor assay v1.5. All assays were performed in Africa with cross-site QA. Samples with VL >1000 c/ml at 24 weeks were sequenced.

Results (updated): Median baseline CD4 was 100 cells/mm^3 (IQR 37-150) and VL was 279,910 c/ml (IQR 102,820-647,160). At 48 weeks, 61% had VL <50 c/ml and 72% <400 c/ml (ITT M=F 55% and 65% respectively), compared to 59% and 79% at 24 weeks (ITT M=F 56% and 74%). At 24 and 48 weeks, 15% and 24% had VL >1000 c/ml (6% and 17% >10,000 c/ml), and mean CD4 increases were 104 and 126 cells/mm^3 respectively. No patient switched to second-line therapy before 48 weeks (based on clinical/immunological criteria for failure). Genotypes were obtained for 20/38 samples with VL>1000 c/ml at 24 weeks, 12 of the remaining 18 having VL<5,000 c/ml. 18/20 showed key mutations; 14 had M184V, 10 with additional TAMs (mean 2.4, range 1-4); 1 had TAMs alone; and the remaining 3 had K65R, one with T215Y, one with Y115F, and one alone (substituted d4T for ZDV at week 14). Two of the 14 with M184V (1/10 with additional TAMs) had major NNRTI mutations, despite no documented treatment with this class.

Conclusion: ZDV+3TC+TDF maintains good virological efficacy from 24 to 48 weeks in advanced disease. 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.

DART: DESIGN and REGIMENS

- DART is a large randomised trial with clinical endpoints, primarily assessing whether ART can be given safely without routine laboratory monitoring for toxicity (haematology, biochemistry) and efficacy (T cell subsets)
  - all 3315 patients receive triple drug ART
  - viral load monitoring is not performed in real time in any patient
- 2468 (74%) have received zidovudine+lamivudine (as combivir) plus tenofovir DF (ZDV+3TC+TDF) first-line
- 300 patients receiving ZDV+3TC+TDF were enrolled into a virology substudy (retrospective), with, on average, good virological response at 24 weeks
  - 76% <400 c/ml, 57% <50 c/ml (CROI 2005 [Abs 22] www.ctu.mrc.ac.uk/dart/files/pubs.asp)
  - comparable to other populations initiating PI/NNRTI based regimens with low CD4 counts in industrialised countries

OBJECTIVES

1. To determine response to ZDV+3TC+TDF up to 48 weeks
2. To describe the distribution of resistance mutations in those with HIV-1 RNA ≥1000 c/ml at 24 weeks

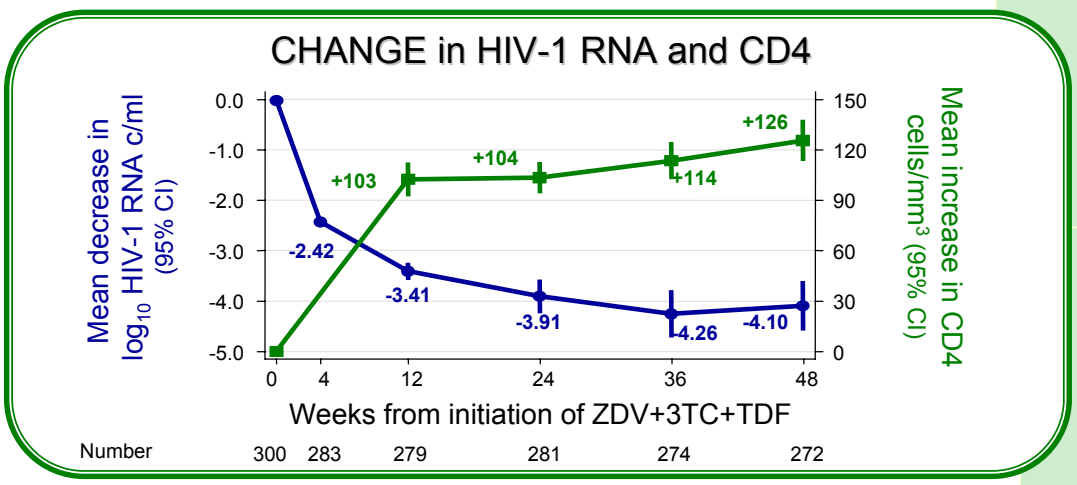
METHODS

- 300 patients
  - 100 from each of 3 sites; 2 in Uganda and 1 in Zimbabwe
  - half with baseline CD4 <100 cells/mm^3
  - consecutive patients enrolled in each CD4 strata (0-99 and 100-199 cells/mm^3) after the first 2 months of the trial, excluding the first 20 patients in each site
- 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: therefore these patients were excluded and replaced with patients matched on baseline and week 24 CD4 who did not interrupt ART before 48 weeks (next patients entering the trial)
- Plasma HIV-1 RNA assayed on stored specimens at 0, 4, 12, 24, 36 and 48 weeks after ZDV+3TC+TDF initiation
- Samples >1000 c/ml at 24 weeks (from the initial week 24 population of 300 patients) were sequenced

POPULATION CHARACTERISTICS (n=300)

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

Follow-up
- ★ 231 (77%) patients known to be alive at 48 weeks having been prescribed ZDV+3TC+TDF without interruption
- ★ 17 (6%) patients had substituted d4T for ZDV
- ★ 38 (13%) patients interrupted ART for 3+ days (median 12 days, range 4-167 days)



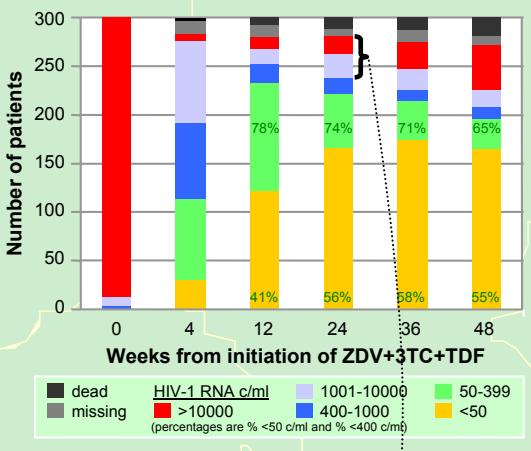
SUMMARY

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

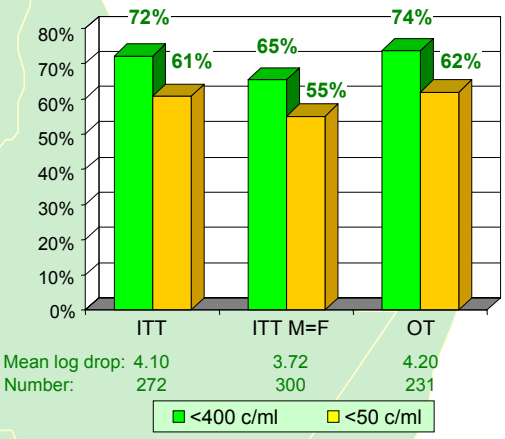
HIV-1 VIRAL LOAD

- ★ **No patient reached clinical/immunological criteria for failure (ie there were no switches to second-line therapy) before 48 weeks**
- ★ The proportion with HIV-1 RNA >1000 and >10,000 c/ml increased over time as expected, but remained low
  - 4%, 6%, 9% and 16% of HIV-1 RNA results were >10,000 c/ml at 12, 24, 36 and 48 weeks
- ★ At 24 weeks, the only important predictor of viral suppression was time off ART before 24 weeks: this was not a predictor at 48 weeks, but far fewer patients had interrupted ART between 24 and 48 weeks
- ★ At 48 weeks, viral suppression was independently (multivariable analysis) significantly more likely in patients
  - with higher baseline CD4
  - who were female
  - who were older
  - ➢ there was a trend towards lower chance of suppressing <400 c/ml with higher baseline RNA, but the effect of baseline viral load was much weaker for suppression <50 c/ml

Viral loads and patient status over time

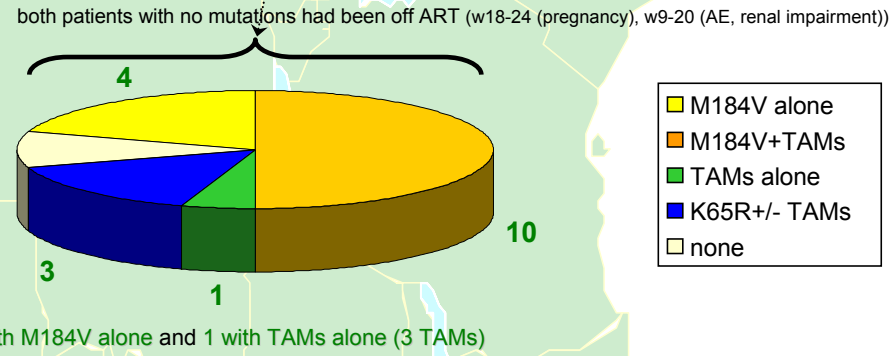


Viral suppression at 48 weeks



HIV GENOTYPE at 24 WEEKS

- ★ 48 patients had HIV-1 RNA >1000 c/ml at 24 weeks
  - 10 had insufficient sample for genotyping
- ★ Genotypes were obtained from 20 of the remaining 38 samples
  - it was not possible to amplify both PR and RT in 18 samples, even with optimised primers: 12 of these 18 samples had HIV-1 RNA <5000 c/ml
- ★ **Subtypes** of the 20 sequenced viruses (STAR[1]): 6 A, 8 C, 5 D, 1 D/A
  - A and D from Uganda, C from Zimbabwe as expected
- ★ 18/20 showed key NRTI resistance mutations
  - both patients with no mutations had been off ART (w18-24 (pregnancy), w9-20 (AE, renal impairment))



- ★ 4 with M184V alone and 1 with TAMs alone (3 TAMs)
- ★ 10 with M184V and additional TAMs (mean 2.4, median 2, 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 (at week 14 for anaemia & neutropenia)
- ★ only 3/20 (15%) patients had ever achieved HIV-1 RNA <50 c/ml (10/20 (50%) ever <400 c/ml)
- ★ PI resistance mutations: no sample had resistance-associated mutations in protease
- ★ NNRTI resistance mutations: two of the 14 with M184V had NNRTI mutations
  - 1 Y181 mixture (also had 3 TAMs), 1 K103N
  - neither had documented treatment with this class eg for MTCT
  - baseline genotypes are currently being sequenced
- ★ no relationship between pattern of NRTI mutations and
  - subtype
  - reporting complete adherence between weeks 4 and 24 (4-weekly questionnaires)
  - ever suppressing <50 c/ml or <400 c/ml

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[1] Gale et al. Development of a novel human immunodeficiency virus type 1 subtyping tool, subtype analyzer (STAR). AIDS Res Hum Ret 2004; 20(5):457-64.