Immunological response to boosted PI (LPV/r)-Containing Second-line ART after Switching for Clinical/immunological Criteria is Comparable to Response to First-line in Patients with low CD4 Counts in Africa

C Chimbetete[1], C Kityo[2], P Munderi[3], AS Walker[4], A Reid[1], F Ssali[2], H Grosskurth[3], J Darbyshire[4], C Gilks[5] and the DART Trial Team

[1]University of Zimbabwe, Harare, Zimbabwe; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]MRC/UVRI Program on AIDS, Entebbe, Uganda; [4]MRC Clinical Trials Unit, London, UK; [5]Imperial College, London, UK

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www.ctu.mrc.ac.uk/dart
Email: dart@ctu.mrc.ac.uk

ABSTRACT (updated)

Background: Immunological response to boosted PI-containing second-line has rarely been compared to response to first-line therapy in adults who initiated ART with low CD4 counts.

Methods: In the DART trial 3316 ART-naive adults with CD4<200 cells/mm^3 from Uganda and Zimbabwe initiated first-line ART with combivir (ZDV/3TC) plus tenofovir (n=2469), abacavir (n=300) or nevirapine (n=547). WHO-defined failure (new/recurrent WHO 4 events in all; CD4<100 cells/mm^3 in the 50% randomised to laboratory monitoring) triggered switch to second-line ART.

Results: After median follow-up of 4.0 years, 495 (15%) participants had failed first-line; rates were 0.3, 4.0, 7.2, 7.1 and 8.3/100 person-years during the first, second, third, fourth and fifth years on ART respectively. 477 (96%) patients initiated second-line with bPI (LPV/r, Kaletra/Aluvia)-containing regimens: 417/477 (87%) received LPV/r+NNRTI±NRTIs (following 3NRTIs first-line) and 60 (12%) LPV/r+NRTIs (following NNRTI+NRTIs first-line). Median (IQR) CD4 at first-line failure was 46 (23-84) cells/mm^3 (n=477); increasing substantially to 190 (n=405), 199 (n=358), 237 (n=310) and 245 (n=261) cells/mm^3 12, 24, 36 and 48 weeks respectively after switch to bPI(LPV/r)-containing second-line. This represented a mean increase of 10.8 and 1.7 cells/mm^3 per week in the first 12 weeks and thereafter (heterogeneity p<0.001). In contrast, in these 477 patients median (IQR) CD4 at initiation of first-line ART was 39 cells/mm^3 (13-82), increasing to 121, 142, 134 and 142 cells/mm^3 after 12, 24, 36 and 48 weeks (a poorer first-line response than overall), and representing a mean change of 8.8 and -0.4 cells/mm^3 per week in the first 12 weeks and thereafter. Second-line response was also excellent in the 72/477 (15%) patients who had not achieved a 50 cell/mm^3 CD4 increase on first-line: median CD4 increase was +78, +89, +109 and +155 cells/mm^3 12, 24, 36 and 48 weeks after starting second-line and 78% achieved a 50 cell/mm^3 increase on second-line.

Conclusions: Immunological response to bPI (LPV/r, Kaletra/Aluvia)-containing second-line therapy is excellent in patients switching for clinical/immunological failure with low CD4.

RATIONALE

- In resource-constrained settings, many patients receiving antiretroviral therapy are not monitored using HIV RNA viral loads, but using CD4 cell counts or clinical signs/symptoms alone
- Failure of first-line therapy is therefore defined in WHO guidelines by
  - low CD4 cell counts (<100 cells/mm^3)
  - new WHO stage 4 (AIDS) events
- **The immunological response to second-line therapy in these patients with advanced failure at switch has rarely been investigated**
  - **particularly in comparison to their first-line response**

THE DART TRIAL

- **DART** (**D**evelopment of **A**nti**R**etroviral **T**herapy in Africa) is a randomised controlled trial comparing laboratory and clinical (LCM) versus clinical monitoring only (CMO) in 3316 previously untreated symptomatic HIV-1 infected participants initiating ART with CD4 <200 cell/mm^3 in Uganda (2 sites plus 1 satellite site) and Zimbabwe (1 site)
  - all participants see a nurse every 4 weeks and a doctor every 12 weeks, and have full blood count, biochemistry and CD4 count routinely measured every 12 weeks
    - for LCM participants these routine results are automatically returned
    - for CMO participants, routine haematology/biochemistry results are returned only if the treating physician has requested them for clinical reasons (or if they have not been requested but are a Grade 4 toxicity). CD4 counts are not returned for CMO participants
    - other blood tests can be requested in CMO and LCM participants at any time, and full blood counts and biochemistry tests can also be requested for clinical reasons at any time outside of the routine visit timepoints in CMO and LCM participants
    - no real-time viral load monitoring in either CMO or LCM
  - criteria for first-line failure after 48 weeks on ART include
    - new or recurrent WHO stage 4 events
    - multiple new or recurrent WHO stage 3 events
    - CD4 <100 cells/mm^3 (<50 cells/mm^3 early in the trial) (LCM only)
- 3316 previously untreated patients initiated ART with Combivir (co-formulated zidovudine+lamivudine) plus either tenofovir DF (TDF, 2469, 74%); nevirapine (NVP , 547, 16%) or abacavir (ABC, 300, 9%)
  - most regimen allocation was non-randomised: only 600 patients were randomised to NVP versus ABC in the NORA substudy

AIM

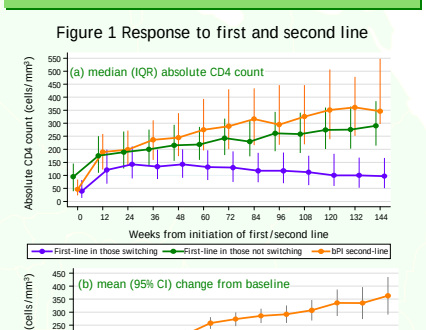
To compare immunological responses to boosted PI-containing second-line regimen versus non-PI containing first-line regimens in adults initiating ART with low CD4 counts in the DART trial and switching according to immunological/clinical criteria

METHODS

- We compared the median CD4 and change in CD4 following switch to second-line therapy in DART with
  - median CD4 and change in CD4 following ART initiation in these patients before they switched to second-line
  - median CD4 and change in CD4 following ART initiation in patients who have not yet switched to second-line
- We used data merged on 18 December 2007`

IMMUNOLOGICAL RESPONSES

Figure 1 Response to first and second line

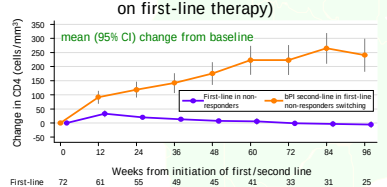


Numbers

First-line switchers	477	466	468	467	469	450	433	407	381	350	314	275	227
First-line not switched	2821	2665	2617	2574	2569	2536	2523	2489	2467	2454	2461	2435	2427
bPI second-line	477	405	358	310	261	228	184	150	110	90	79	49	27

Note: Excluding completely the 17 patients switching to a non-bPI-containing second-line regimen. bPI might be expected to lead to greater CD4 count increases in similar patients (Bartlett JA, AIDS 2007; ACTG 5142)

Figure 2 Responses in first-line non-responders (not achieving a 50 cell/mm^3 CD4 increase on first-line therapy)



First-line	72	61	55	49	45	41	33	31	25
Second-line	72	70	68	68	70	64	56	46	40

Note: clinicians wanted to give patients who had started ART with very low CD4s sufficient opportunity to respond immunologically to first-line, as they were uncertain whether such patients would respond at all to second-line

RESULTS - switch to second-line

- Median (IQR) follow-up to 18 December 2007 was 4.0 (3.5-4.2) years
- 495 (15%) participants had switched to second-line
  - 18 (4%) patients initiated second-line without using a bPI and are not considered further
    - this mostly occurred early on (2004-5) when a clinical tuberculosis diagnosis contraindicated bPI: later (2006-) tuberculosis was treated whilst maintaining the first-line regimen with switch to bPI-containing second-line after the induction phase

  - 477 (96%) patients initiated second-line with bPI (LPV/r, Kaletra/Aluvia)-containing regimens: 417/477 (87%) received LPV/r+NNRTI±NRTIs (following 3NRTIs first-line) and 60 (12%) LPV/r+NRTIs (following NNRTI+NRTIs first-line)
- **Rates of switching to second-line were 0.3, 4.0, 7.2, 7.1 and 8.3 per 100 person-years during the first, second, third, fourth and fifth years on ART respectively**

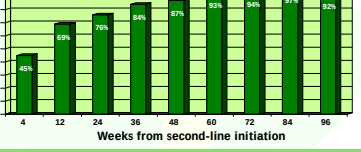
RESULTS - response to LPV/r-containing ART

- The 477 patients switching to LPV/r (Kaletra/Aluvia) containing second-line therapy had a median (IQR) CD4 count of 46 (23-84) cells/mm^3
  - in these 477 patients, median (IQR) CD4 at initiation of first-line ART was 39 (13-82) cells/mm^3
  - compared to 95 (39-145) cells/mm^3 in patients who had not switched to second-line
- Patients had a median 55 weeks follow-up after switch (IQR 24-92) [range 0-191]
- Switch to bPI(LPV/r)-containing second-line therapy led to a substantial increase in CD4 cell count (Figure 1(a) and (b))
  - a mean increase of 10.8 and 1.7 cells/mm^3 per week in the first 12 weeks and thereafter (heterogeneity p<0.001)
  - compared to a mean change of 8.8 and -0.4 cells/mm^3 per week in the first 12 weeks and thereafter after initiating first-line ART
- The 477 patients switching to bPI(LPV/r)-containing second-line had better responses to second-line than to their first-line regimen
  - the fact that their first-line response was poorer than average suggests that poor adherence may have contributed to failure of first-line
    - ★second-line regimens were considerably more complex than the 3-4 pills per day on first-line, so adherence was re-inforced at switch
  - their excellent response to second-line suggests that other factors may also have contributed to their poorer than average first-line response
    - ? undisclosed prior receipt of ART before DART enrolment ?
    - ★6/83 with resistance tests had NNRTI and/or NRTI resistance at baseline

RESULTS - non-responders

- 77 (16%) of the 495 patients switched to second-line in DART had not achieved a 50 cell/mm^3 increase in CD4 count on their first-line therapy
  - 128/495 (26%) were still >50 cells/mm^3 above pre-ART CD4 at switch
  - 290/495 (59%) had increased CD4 by >50 cell/mm^3 but then dropped below this before switching to second-line
- Second-line response was also excellent in the 72/477 (15%) patients who never achieved a 50 cell/mm^3 CD4 increase on first-line and initiated bPI(LPV/r)-containing second-line therapy (Figure 2 and below)
  - 69%, 76%, 84%, and 87% had achieved a 50 cell/mm^3 increase 12, 24, 36 and 48 weeks respectively after switching to second-line

Percentage achieving a >50 cell/mm3 CD4 increase



SUMMARY

- After median follow-up of 4.0 years, the rate of first-line failure among DART participants (who were predominantly on triple NRTI regimens) was low (~7-8% per annum)
- Participants who failed first-line therapy had an excellent CD4 response on bPI second-line therapy with LPV/r (Kaletra/Aluvia), despite low CD4s at switch
- Most importantly, patients who had not achieved an immunological response on first-line did very well immunologically when switched to a bPI(LPV/r)-containing second-line regimen
  - this suggests that clinicians should proactively consider switching patients who have not responded well to first-line if they do not have concerns about adherence
- Further follow-up of patients on second line therapy will be important to monitor overall second-line response over time
- **Conclusion:** Immunological response to bPI (LPV/r) containing second line therapy is excellent in patients switching for clinical or immunological failure with low CD4

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