



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

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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-naïve adults with CD4<200 cells/mm³ 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/mm³ 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 NNRTI first-line) and 60 (12%) LPV/r-NRTIs (following NNRTI-NRTI first-line). Median (IQR) CD4 at first-line failure was 46 (23-84) cells/mm³ (n=477); increasing substantially to 190 (n=405), 199 (n=358), 237 (n=310) and 245 (n=261) cells/mm³ 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/mm³ 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/mm³ (13-82), increasing to 121, 142, 134 and 142 cells/mm³ 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/mm³ 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/mm³ CD4 increase on first-line: median CD4 increase was +78, +89, +109 and +155 cells/mm³ 12, 24, 36 and 48 weeks after starting second-line and 78% achieved a 50 cell/mm³ 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/mm³) – 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 (Development of **A**ntiretroviral **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/mm³ 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/mm³ (<50 cells/mm³ 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 NORBA study

AIM

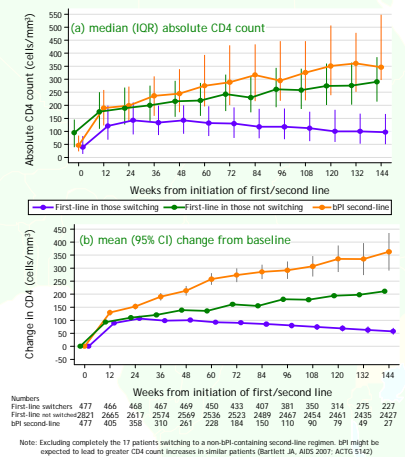
To compare immunological responses to boosted PI-containing second-line regimen versus non-PI containing first-line regimens in adults initiating ART with low CD4 counts in the DART trial and switching according to immunological/clinical criteria

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



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 NNRTI first-line) and 60 (12%) LPV/r-NRTIs (following NNRTI-NRTI first-line)



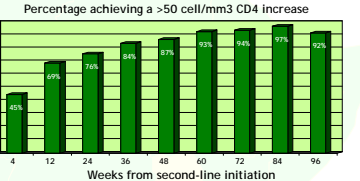
- Rates of switching to second-line were 0.3, 4.0, 7.2, 7.1 and 8.3 per 100 person-years during the first, second, third, fourth and fifth years on ART respectively

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/mm³
 - in these 477 patients, median (IQR) CD4 at initiation of first-line ART was 39 (13-82) cells/mm³
 - compared to 95 (29-145) cells/mm³ 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/mm³ 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/mm³ 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-enforced at switch
 - their excellent response to second-line suggests that other factors may also have contributed to their poorer than average first-line response
 - undoesed 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/mm³ increase in CD4 count on their first-line therapy
 - 128/495 (26%) were still >50 cells/mm³ above pre-ART CD4 at switch
 - 290/495 (59%) had increased CD4 by >50 cell/mm³ 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/mm³ 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/mm³ increase 12, 24, 36 and 48 weeks respectively after switching to second-line



SUMMARY

- After median follow-up of 4.0 years, the rate of first-line failure among DART participants (who were predominantly on triple NNRTI 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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