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# Lopinavir-ritonavir plus Abacavir and Lamivudine versus Lopinavir-ritonavir Monotherapy for Recovery of Lipoatrophy in HIV-infected Patients with Sustained Virological Suppression while Receiving Zidovudine/Lamivudine/Abacavir

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## BACKGROUND

- Prevalence of lipoatrophy varies from 50% in early cohort studies to 25% in recent studied cohorts[1,2].
- Thymidine analogues (both d4T and AZT) have been clearly associated with lipoatrophy[3].
- Discontinuation of thymidine nucleoside reverse transcriptase inhibitors (NRTIs) is the only proven strategy for lipoatrophy based on antiretroviral regimen change[4-6].
- Clinical trials of nuke-sparing regimens have shown similar increases in limb fat but with worsening dyslipidemia[7].
- Four studies in different scenarios suggest a role of protease inhibitors (PI) monotherapy for limb fat recovery[8-11].

## HYPOTHESIS

Switching from ZDV/3TC/ABC to LPV/r monotherapy would result in more limb fat recovery than ABC/3TC + LPV/r in virologically suppressed HIV-infected patients with moderate to severe lipoatrophy

## OBJECTIVES

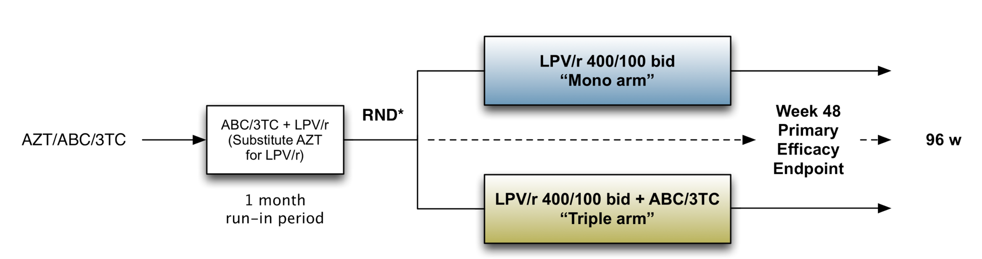
**Primary objective:**

- Absolute change in limb fat mass measured by DEXA from baseline to W48

**Secondary objectives:**

- Absolute change in limb fat at 96 weeks from baseline
- Percentage change in limb fat mass at 48/96 weeks from baseline
- Changes in lipid profiles (Total, HDL and LDL cholesterol, triglycerides) at 24, 48 and 96 weeks
- Safety and tolerability
- Incidence of virologic failures (>400 HIV-RNA copies/mL)

## KRETA STUDY DESIGN


AZT/ABC/3TC
ABC/3TC + LPV/r (Substitute AZT for LPV/r)
1 month run-in period
RND*
LPV/r 400/100 bid "Mono arm"
LPV/r 400/100 bid + ABC/3TC "Triple arm"
Week 48 Primary Efficacy Endpoint
96 w

* RND: Randomization

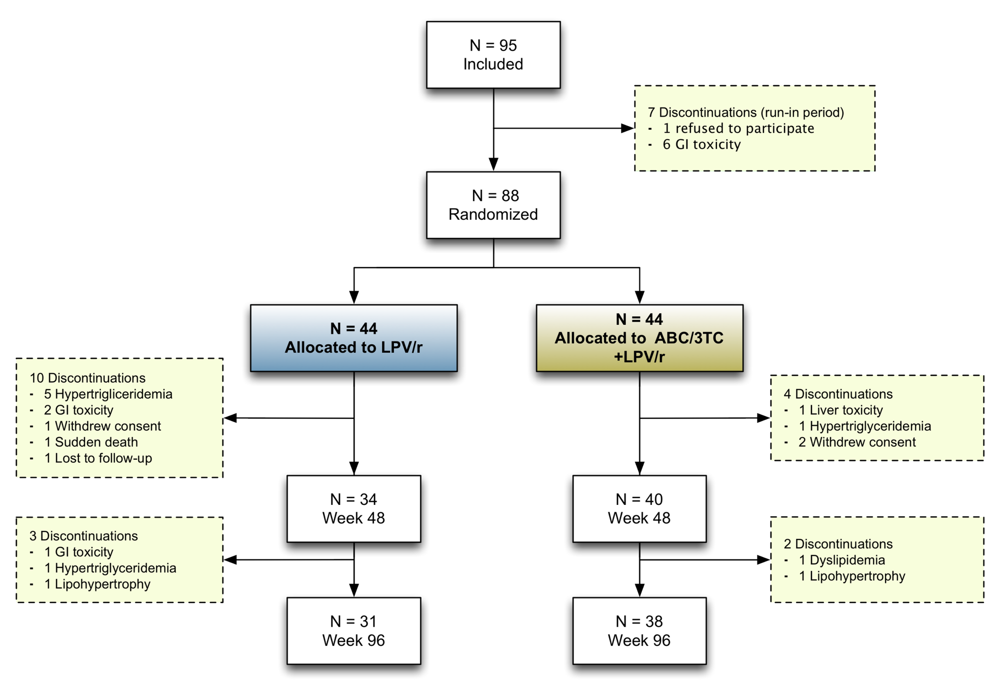
| Stratified by: | |
|---|---|
| Nadir CD4 cell count (< or ≥ 100 cells/mm3)<br>Months with zidovudine (< or ≥ 3 years).<br>DEXA center | |
| **Inclusion criteria:** | **Exclusion criteria:** |
| Stable Trizivir® (AZT/3TC/ABC)<br>Moderate-severe lipoatrophy (LSGS)<br>VL < 50 copies/ml for at least 6 month<br>No prior virological failure of a PI containing regimen | Pregnancy<br>Presence of serum hepatitis B surface antigen<br>Chemotherapy for malignancy<br>Insulin-sensitizing agent, anabolic steroids or GH in the last 16 weeks |

## METHODS

- 96 week multicentre, prospective, open label, randomized (1:1) study
- 10 sites in Spain
  - » Visits: Baseline, 4, 12, 24, 36, 48, 72, 96 weeks
  - » DEXAs: Baseline, 48, 96 week.
  - » Severe-Moderate Lipoatrophy (LSGS* grade 2-3 in at least 2 localizations)
- Primary Endpoint:
  - » Absolute change in limb fat mass measured by DEXA scan from baseline to 48 weeks

*** Lichtenstein KA, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. Aids 2001;15(11):1389-1398**

## SUBJECT DISPOSITION


N = 95
Included
7 Discontinuations (run-in period)
- 1 refused to participate
- 6 GI toxicity
N = 88
Randomized
N = 44
Allocated to LPV/r
N = 44
Allocated to ABC/3TC +LPV/r
10 Discontinuations
- 5 Hypertriglyceridemia
- 2 GI toxicity
- 1 Withdrew consent
- 1 Sudden death
- 1 Lost to follow-up
4 Discontinuations
- 1 Liver toxicity
- 1 Hypertriglyceridemia
- 2 Withdrew consent
N = 34
Week 48
N = 40
Week 48
3 Discontinuations
- 1 GI toxicity
- 1 Hypertriglyceridemia
- 1 Lipohypertrophy
2 Discontinuations
- 1 Dyslipidemia
- 1 Lipohypertrophy
N = 31
Week 96
N = 38
Week 96

## BASELINE: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

| | Mono arm N = 44 | Triple arm N = 44 | Total N = 88 | P value |
|---|---|---|---|---|
| **Age [years (IQR)]** | 44.7 (41.5-52) | 45 (42.1-50.8) | 44.8 (41.8-51.1) | NS |
| **Male sex [No. (%)]** | 26 (59.1) | 33 (75) | 59 (67) | NS |
| **Mode of HIV transmission [No. (%)]** | | | | |
| **Men sex with men** | 8 (18.2) | 17 (38.6) | 25 (28.4) | 0.03 |
| **Heterosexual** | 22 (50) | 14 (31.8) | 36 (40.9) | 0.08 |
| **IDU** | 11 (25) | 15 (3 4) | 26 (29.5) | NS |
| **Other** | 3 (6.8) | 2 (4.5) | 5 (5.7) | NS |
| **Duration HIV infection [years (IQR)]** | 11 (8.7-13.7) | 11.8 (10.5-16.7) | 11.4 (9.3-15) | 0.09 |
| **CDC category AIDS [No. (%)]** | 26 (59.1) | 20 (45.5) | 46 (52.3) | NS |
| **HCV + Antibody [No. (%)]** | 16 (36.4) | 22 (50) | 38 (43.2) | NS |
| **Nadir CD4+ [cells/µL (IQR)]** | 189 (40-298) | 233 (128-285) | 222 (104-291) | NS |
| **Total CD4+ [cells/µL (IQR)]** | 675 (512-885) | 766 (543-1002) | 697 (524-946) | NS |
| **Median time on Zidovudine [years (IQR)]** | 6.7 (5.2-7.9) | 8.5 (6.4-11.3) | 7.4 (5.4-9.2) | 0.003 |
| **Median time on thymidine analogues [years (IQR)]** | 7.9 (5.5-10.3) | 10.5 (7.7-11.7) | 9.4 (6.3-11) | 0.006 |

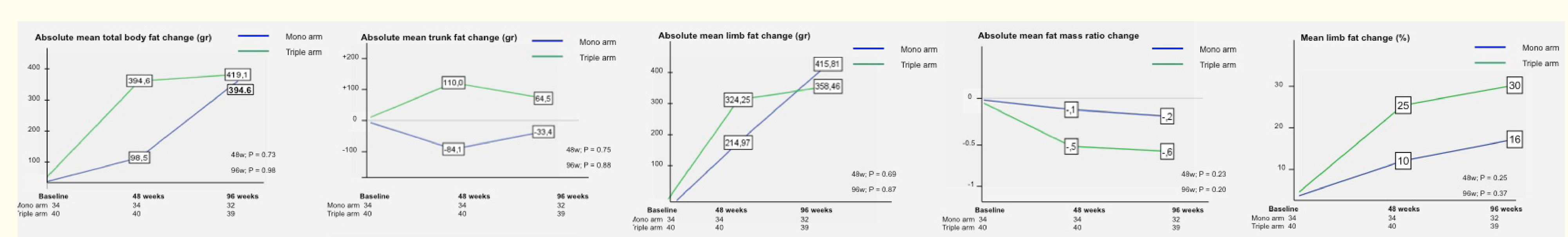
## BASELINE CHARACTERISTICS: ANTHROPOMETRICS, BODY COMPOSITION, LIPIDS

| | Mono arm N = 44 | Triple arm N = 44 | Total N = 88 | P value |
|---|---|---|---|---|
| **Body mass index [Kg/m2 (IQR)]** | 24 (20.9-25.8) | 23.3 (21-25) | 23.5 (21-25) | NS |
| **Waist circumference [cm (IQR)]** | 83.5 (75.9-91.3) | 86 (80-91.5) | 85 (78-91.5) | NS |
| **Hip circumference [cm (IQR)]** | 91 (87-95.5) | 89.5 (86-96) | 90 (86-96) | NS |
| **Total body fat [Kg (IQR)]** | 12.9 (8.9-16.5) | 9.8 (7.4-15.4) | 11.6 (8-15.7) | NS |
| **Trunk fat [Kg (IQR)]** | 8.5 (5.6-11.1) | 8.2 (5.1-10.8) | 8.4 (5.4-10.8) | NS |
| **Limb fat [Kg (IQR)]** | 2.5 (1.9-5.3) | 2.5 (1.6-3.6) | 2.5 (1.7-4.2) | NS |
| **Fat mass ratio [median (IQR)]** | 1.9 (1.4-2.9) | 2.1 (1.6-3.1) | 2.0 (1.5-3.1) | NS |
| **Total Cholesterol [mg/dL (IQR)]** | 247.5 (195-268) | 214.2 (179.5-263) | 224 (187-268) | 0.075 |
| **HDL- Cholesterol [mg/dL (IQR)]** | 43.8 (38-58.5) | 40 (36-49.5) | 41.5 (37-53) | NS |
| **LDL-Cholesterol [mg/dL (IQR)]** | 136 (98-167) | 112 (86-142) | 120 (94-160) | NS |
| **Triglycerides [mg/dL (IQR)]** | 270 (156-398) | 246 (134-342) | 254 (151-378) | NS |
| **Total /HDL-Cholesterol ratio [median (IQR)]** | 5.3 (4.1-6.7) | 5.2 (3.8-6.3) | 5.2 (3.9-6.5) | NS |

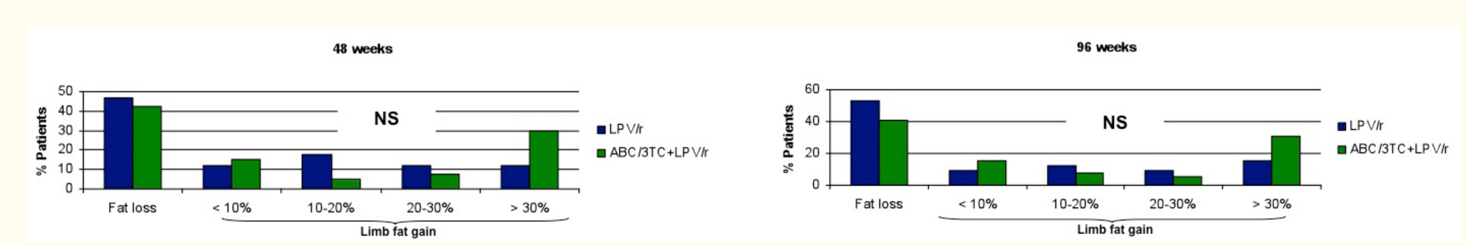
## MEAN CHANGE IN TOTAL, TRUNK, LIMB FAT AND FAT MASS RATIO

| | Mean (SD) change over 48 weeks | | | | Mean (SD) change over 96 weeks | | | |
|---|---|---|---|---|---|---|---|---|
| | Mono arm N =34 | Triple arm N =40 | Mean (95% CI) difference between arms* | P value | Mono arm N=32 | Triple arm N=39 | Mean (95% CI) difference between arms* | P value |
| **Total fat (gr)** | 98.5 (3814) | 394.6 (3628) | - 296 (-2032, 1440) | 0.73 | 394 (4243) | 419 (3830) | -25 (-1961, 1911) | 0.98 |
| **Limb fat (gr)** | 215 (1161) | 324.2 (1205) | - 109 (-659, 440) | 0.69 | 416 (1670) | 358.5 (1207) | 57 (-650, 765) | 0.87 |
| **Trunk fat (gr)** | - 84 (2737) | 110 (2533) | -194 (-1425, 1037) | 0.75 | -33 (2762) | 64.5 (2601) | -98 (-1380, 1184) | 0.88 |
| **Fat mass ratio †** | -1 (0.5) | -0.5 (2.1) | 0.42 (-0.28, 1.12) | 0.23 | -0.2 (0.5) | -0.6 (1.9) | 0.4 (-0.23, 1.04) | 0.20 |
| **Limb fat (%)** | 10 (44.6) | 25 (64.6) | - 14.8 (-40.2, 10.7) | 0.25 | 15.7 (62.7) | 30.1 (72.9) | - 14.4 (-46.5, 17.7) | 0.37 |

*** mean value in LPV/r minus ABC+3TC+LPV/r**
**† Statistically significant difference intra-group for FMR in Mono arm at 96 w: -0.2 (95% CI -0.37, -0.02); p =0.026**


Absolute mean total body fat change (gr)
Absolute mean trunk fat change (gr)
Absolute mean limb fat change (gr)
Absolute mean fat mass ratio change
Mean limb fat change (%)
Mono arm
Triple arm
Baseline
48 weeks
96 weeks

## LIMB FAT GAIN < 10%, 10-20%, 20-30%, >30%


48 weeks
96 weeks
% Patients
NS
LPV/r
ABC/3TC+LPV/r
Fat loss
< 10%
10-20%
20-30%
> 30%
Limb fat gain

## LIPID CHANGES FROM BASELINE TO WEEK 48 AND 96

| | Mean (SD) change run-in period | Mean (SD) change from BL to W48 | | | | Mean (SD) change from BL to W96 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N =87 | Mono arm N =44 | Triple arm N =43 | Mean (95% CI) difference between arms* | P value | Mono arm N =44 | Triple arm N =43 | Mean (95% CI) difference between arms* | P value |
| **Total Cholesterol (mg/dl)** | 44 (38) | - 7 (36) | 10.2 (46) | -17.1 (-34.7, 0.49) | 0.057 | -8.7 (38.8) | 4.7 (44) | -13.37 (-31, 4.3) | 0.136 |
| **HDL cholesterol (mg/dl) †** | -1.9 (9.4) | 5 (10.5) | -0.6 (19.2) | 5.6 (-1.02, 12.28) | 0.096 | 6.6 (12.1) | 2.7 (23.2) | 3.8 (-4.1, 11.8) | 0.342 |
| **LDL cholesterol (mg/dl)** | 19.4 (31.6) | 0.3 (30.4) | 16.6 (41) | -16.3 (-32.74, 0.11) | 0.052 | -3.4 (28.6) | 8.2 (44) | -11.6 (-28.6, 5.4) | 0.178 |
| **Triglycerides (mg/dl)**** | 151.6 (202) | - 74 (149) | -13 (129) | -61 (-121.5, 0.57) | 0.048 | -45.6 (261) | -27.6 (172.7) | -18 (-114.2, 78.1) | 0.711 |
| **Total/HDL cholesterol †** | 1 (1.1) | - 0.5 (1.1) | 0.3 (1.5) | -0.81 (-1.38, 0.23) | 0.006 | - 0.6 (1.4) | 0.0 (2) | -0.62 (-1.37, 0.13) | 0.104 |

*** mean value in LPV/r minus ABC+3TC+LPV/r**
**† Statistically significant difference intra-group in HDL cholesterol and total/HDL cholesterol in mono arm at 48 w and 96 w:**
**HDL cholesterol: 48 week [5 (95% CI 1.7, 8.1); p =0.03], 96 week [6.5 (95% CI 2.8, 10.2); p =0.01]**
**Total/HDL cholesterol: 48 week [-0.53 (95% CI -0.85, -0.21); p =0.002], 96 week [ -0.6 (95% CI -1.02, -0.17); p =0.007]**
**** Statistically significant difference intra-group in triglycerides in mono arm at 48w: -74 (95% CI -119.5, -28.6); p =0.002**

## VIROLOGIC FAILURES

- 3 virologic failures (2 mono arm/ 1 triple arm).
- The 82A mutation was detected in one patient in the monotherapy arm

## PERCENTAGES OF PATIENTS WITH ADVERSE EVENTS 96 WEEKS

| | Mono arm (N=44) n (%) | Triple arm (N=44) n (%) | P value |
|---|---|---|---|
| **Any Adverse Event** | 42 (95.4) | 35 (79.5) | 0.024 |
| **Drug related Adverse Event** | 30 (68.2) | 30 (68.2) | 1 |
| **Serious Adverse Event*** | 8 (18.2) | 5 (11.4) | 0.367 |
| **Discontinuation due to any Adverse Event †** | 11 (25) | 4 (9) | 0.047 |

*** Serious Adverse Events:**
**Mono arm: 1 cardiac arrest, 4 hospitalizations due to infectious diseases, 2 traumatic fractures, 1 paranoid disorder**
**Triple arm: 2 hospitalizations due to infectious diseases, 1 pneumothorax, 1 uterine mioma and 1 abdominal obesity surgery**
**† Most AE related discontinuations occurred before W24. The difference between arms is statistically significant at W48**

## DISCUSSION

- In previous studies, switching thymidine analogues for tenofovir or abacavir led to a median increase of limb fat mass between 300-480 gr at 48 weeks [4,5].
- Switching studies with PI monotherapy showed a limb fat increase between 160-340 gr at 48 weeks [10,12].
- Although limb fat increases in this trial are concordant with previous studies we didn't find differences between switching to LPV/r monotherapy or ABC/3TC + LPV/r. This could be explained by the following:
  - » Median baseline limb fat extremely low compared to other similar studies.
  - » Compared to previous studies longer prior exposure to thymidine analogues.
- Limitations:
  - » DEXA scans were not centrally read and different equipments (Lunar, Hologic, Norland) were used.
  - » Small number of patients that lead to misbalanced baseline characteristics although after adjustment main results didn't change (data not shown).
  - » Excessive numbers of discontinuations specially in the monotherapy arm which had an impact on the virological efficacy analysis.

## CONCLUSIONS

- In moderate to severe lipoatrophic patients treated with AZT/ABC/3TC, with a long history of of thymidine analogues treatment, switching to LPV/r monotherapy had no benefit in limb fat recovery relative to switching to ABC/3TC + LPV/r.
- There were no differences in limb fat gain and no clinically relevant differences in lipid profile between both strategies.
- There were more discontinuations in the LPV/r monotherapy arm during the first 48 weeks
- These data suggest that non-thymidine nucleosides such as ABC/3TC do not represent themselves an obstacle for limb fat recovery.

### ACKNOWLEDGEMENTS

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