

Discussion

- A limitation of our study is that not all subjects (61 out of 108) received DEXA scans at Baseline and Week 48. Furthermore, only 13 of these 61 subjects underwent DEXA scans at Week 96.
 - These data should be interpreted with caution. Possible bias in who received DEXA scans and why.
- Given that patients are expected to take ARV therapy for many years, DEXA scans after longer follow up are required to further define risks of developing lipoatrophy and lipohypertrophy with LPV/r therapy.
- TDF- or ABC- based NRTI backbones may have less potential for lipoatrophy with LPV/r than AZT-, D4T-, or DDI- containing regimens.
- These findings are consistent with the findings of ACTG 5142 and M03-613 where LPV/r therapy was found to have a low potential to cause lipoatrophy.
- Data from the MONARK, M03-613, and ACTG 5142 studies challenge the previously held notion that protease inhibitor therapy (including LPV/r) was a major cause of lipodystrophy with a mixed phenotype of fat loss in the limbs and central fat accumulation.

Conclusion

- **LPV/r monotherapy induced significantly less limb lipoatrophy compared to LPV/r + AZT/3TC.**
 - Only treatment arm was associated with lipoatrophy.
- **Trunk fat accumulation did not differ between the 2 treatment arms.**

References

- 1) Riddler SA, Haubrich R *et al.*, XVI IAC, Toronto 2006, #THLB0204
- 2) Cameron DW *et al.*, XVI IAC, Toronto, August 2006, #THLB0201
- 3) Delfraissy JF. *et al.*, XVI IAC, Toronto, 2006, #THLB0202

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• Principal Investigator & Scientific Coordination

Pr. Jean-François DELFRAISSY Le Kremlin Bicêtre Hospital - Paris, France.

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Poster WEPEB118LB

One-year Fat Tissue Distribution Changes in Antiretroviral Naïve HIV-infected Patients Treated with Lopinavir/ritonavir (LPV/r) monotherapy *versus* LPV/r with zidovudine/lamivudine (AZT/3TC) in the MONARK Trial

JF. Delfraissy¹, P. Flandre², P. Ngo Van³, I. Cohen-Codar³, MA. Valantin⁴, C. Lascoux⁵, P. Morlat⁶, F. Boué⁷, JP. Chauvin⁸, F. Emery Salbert³, I. Gaultier⁸, R. Rode⁸, M. Norton⁸, C. Roux⁹, S. Kolta⁹.

¹Bicêtre Hospital, Le Kremlin Bicêtre, France; ²INSERM Unité 720, CHU Pitié-Salpêtrière, France; ³Abbott France, Rungis, France; ⁴CHU Pitié-Salpêtrière, Paris, France; ⁵CHU St-Louis, Paris, France; ⁶St André Hospital, Bordeaux, France; ⁷A. Beclère. Hospital, Clamart, France; ⁸Abbott Laboratories, North Chicago, USA; ⁹Paris-Descartes University, Medicine Faculty, UPRES-EA 4058, Assistance Publique-Hôpitaux de Paris, Cochin Hospital, Paris, France.

Background

- Lipodystrophy is a long term adverse event of antiretroviral therapy, for which it is difficult to assess the relative contribution of:
 - HIV itself.
 - Different components of the antiretroviral regimen.
- Historically, both Protease Inhibitors (PIs) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs), especially D4T, have been associated with lipodystrophy.
- 2 recent trials provide insight into the relationship between lipodystrophy and LPV/r. These trials examined LPV/r therapy with and without NRTIs. In both trials LPV/r was compared to EFV-anchored triple therapy.^{1,2}
- The MONARK trial was a randomized, open-label, multi-center, 96-week study designed to compare the antiviral activity of LPV/r monotherapy to that of LPV/r + ZDV/3TC in antiretroviral-naïve patients.³ The trial was conducted at 36 sites in 5 countries (France, Germany, Italy, Poland and Spain).
- In a 48-week analysis previously presented³, virologic response rates for the monotherapy and the triple arm were 64% vs. 75% (ITT, p=0.19) and 80% vs. 98% (OT, p=0.02), respectively.
- The current analysis provides an opportunity to further assess the relative contribution of LPV/r in the development of lipodystrophy.

Study Design and Baseline Characteristics

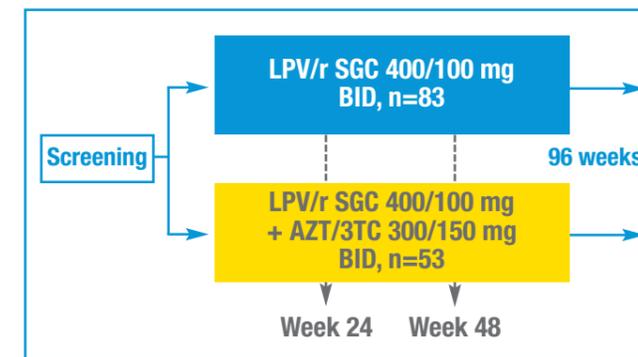
Entry criteria

- Antiretroviral naïve patients.
- HIV-1 RNA <100,000 c/mL.
- CD4 >100 cells/mm³.

Baseline characteristics:

Mean (range)

- HIV-1 RNA (log₁₀ c/mL): 4.39 (1.70-5.87; mono) vs 4.34 (2.85-5.36; Triple).
- CD4 (cell/μL): 257 (86-1247; mono) vs 234 (106-521; Triple).



Primary efficacy analysis

- Proportion of subjects with HIV-1 RNA < 400 copies/mL at Week 24 AND < 50 copies/mL at Week 48.

Secondary analysis

- Changes in fat distribution, obtained via DEXA scans and anthropomorphic measurements at Baseline and Week 48.

Methods

- As a secondary analysis of the MONARK trial, a protocol-defined assessment of fat and lean tissue changes in the limbs and trunk by dual-energy X-ray absorptiometry (DEXA) was performed in France, Poland, Spain, and Italy using standardized procedures. DEXA scans were not performed in Germany.
- DEXA assessment was performed at Baseline and Week 48.
 - Longer-term analysis was performed in a few subjects at Week 96.
- DEXA equipment: Hologic® and Lunar® brand systems were utilized.
- Results were analyzed in a central facility by a single observer blinded to the treatment arms.
- Total body fat and lean tissue mass were measured, with focus on limbs and trunk.
- Mean and median changes between Baseline and Week 48 (and Week 96 for a few subjects) were calculated, and compared between treatment arms, for the following parameters:
 - Total mass of lean and fatty tissues.
 - Mass of lean and fatty tissues in the limbs and trunk.
- Lipohypertrophy was defined as a >20% gain in trunk fat.¹
- Lipoatrophy was defined as a >20% loss in limb fat.¹
- Kruskal-Wallis test and Fisher's exact test were used to perform between-arm comparisons for continuous and categorical variables, respectively. The Wilcoxon signed rank test was used to evaluate within-group changes (evolution) from baseline.

Results

- DEXA results were available:
 - for 63 subjects at Baseline and Week 48: 41 in the LPV/r arm, 22 in the LPV/r+AZT/3TC arm.
 - for 13 subjects at Baseline, Week 48, and Week 96: 8 in the LPV/r arm, 5 in the LPV/r+AZT/3TC arm.
- Subject disposition is shown in Figure 1. Demographics and baseline characteristics for patients with DEXA values at both Baseline and Week 48 are shown in Table 1.
- Tables 2 and 3, as well as Figures 2 through 7 present the changes in limb and trunk fat, between Baseline and Weeks 48 and 96.

Figure 1. Subject Disposition

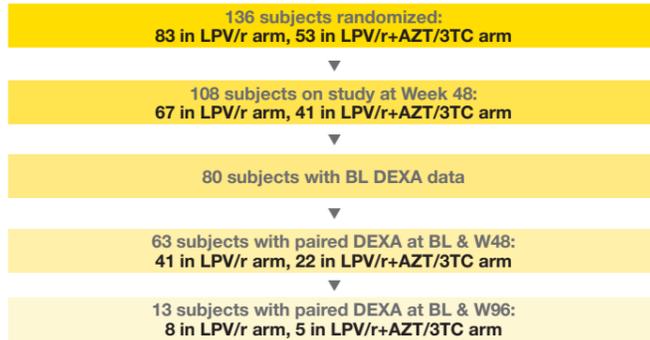


Table 1: Demographics and Baseline Characteristics for Subjects with Paired Baseline and Week 48 DEXA Scans

	LPV/r + AZT/3TC (n=22)	LPV/r (n=41)
Gender		
male	13 (59.1%)	29 (70.7%)
female	9 (40.9%)	12 (29.3%)
Weight (kg, mean ± SD)	71.4 ± 7.65	70.5 ± 13.19
Limb fat (kg, mean ± SD)	8.70 ± 4.711	7.14 ± 4.460
Trunk fat (kg, mean ± SD)	8.79 ± 3.871	8.07 ± 4.830
Age (mean ± SD)	34.5 ± 5.70	36.7 ± 9.14
HIV-1 RNA (log₁₀ c/mL, mean ± SD)	4.34 ± 0.606	4.32 ± 0.491
CD4 (c/mm³, mean ± SD)	228.5 ± 77.30	239.2 ± 65.25

Table 2: Median Change from Baseline in Limb Fat

	LPV/r + AZT/3TC (n=22)	LPV/r (n=41)	P-value (between-arms comparison)
Median change in Limb Fat at W48 - g (IQR)	-703 (-2020; -80)	-63 (-515; +810)	0.014
P-value (evolution from BL)	0.027	0.670	
Median change in Limb Fat at W48 - % (IQR)	-12.43 (-26; -0.6)	-0.90 (-8.2; +14)	0.019
P-value (evolution from BL)	0.047	0.588	
	LPV/r + AZT/3TC (n=5)	LPV/r (n=8)	P-value (between-arms comparison)
Median change in Limb Fat at W96 - g (IQR)	-1930 (-3170; +404)	-400 (-1051; +2063)	0.188
Median change in Limb Fat at W96 - % (IQR)	-24.0 (-27; +4.8)	-6.59 (-24; +36)	0.464

Table 3: Median Change from Baseline in Trunk Fat

	LPV/r + AZT/3TC (n=22)	LPV/r (n=41)	P-value (between-arms comparison)
Median change in Trunk Fat at W48 - g (IQR)	-211 (-1583; +1156)	-579 (-986; +595)	0.665
P-value (evolution from BL)	0.582	0.140	
Median change in Trunk Fat at W48 - % (IQR)	-2.96 (-18; +12)	-2.24 (-16; +11)	0.019
P-value (evolution from BL)	0.539	0.387	
	LPV/r + AZT/3TC (n=5)	LPV/r (n=8)	P-value (between-arms comparison)
Median change in Trunk Fat at W96 - g (IQR)	+346 (-2165; +643)	-859 (-1817; +2958)	0.558
Median change in Trunk Fat at W96 - % (IQR)	-2.57 (-17; +12)	-10.62 (-23; +49)	0.770

Figure 2: Median Change in Limb Fat (g)

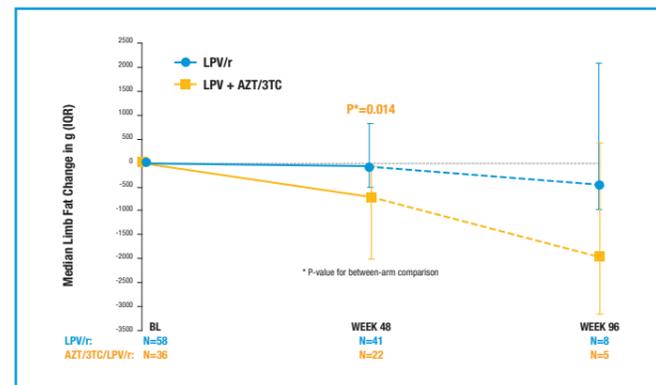


Figure 3: Median Changes in Trunk Fat (g)

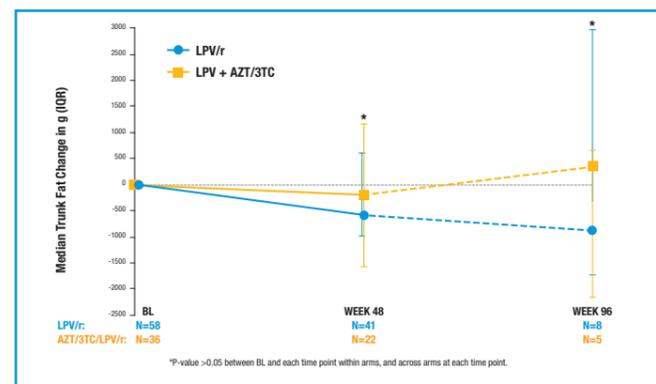
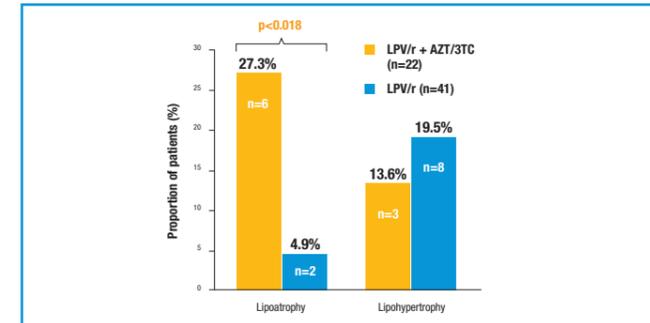


Figure 4: Proportion of Patients with Lipoatrophy or Lipohypertrophy at Week 48

- A higher number of patients in the NRTI-containing arm experienced lipoatrophy than in the monotherapy arm ($p < 0.018$)
- There was no statistically significant difference between arms in proportion of patients experiencing lipohypertrophy ($p = 0.733$)



Category	LPV/r (n=41)	AZT/3TC LPV/r (n=22)	p-value
Lipoatrophy	4.9%	27.3%	0.018
Lipohypertrophy	19.5%	13.6%	0.733
Both	0	0	

- No patient had both lipoatrophy and lipohypertrophy.

Figure 5: Lipoatrophy and Lipohypertrophy at Week 48 for all Patients with Paired DEXA Data

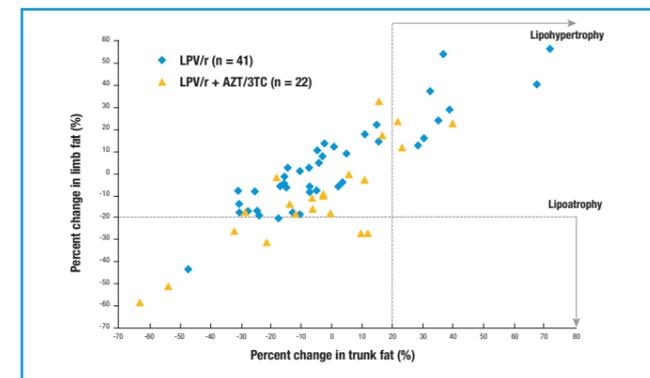


Figure 6: Lipoatrophy and Lipohypertrophy at Week 48 for Patients with DEXA Data at Week 96 (n=13)

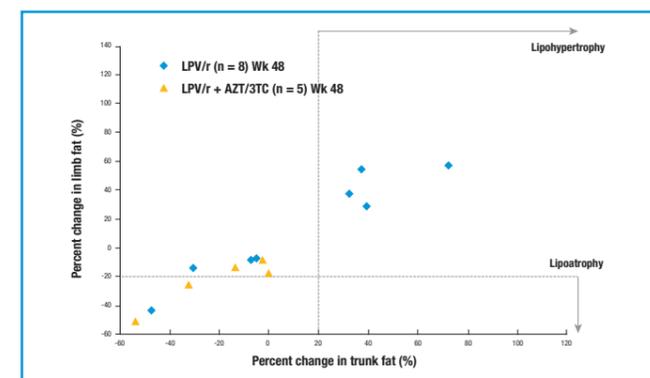
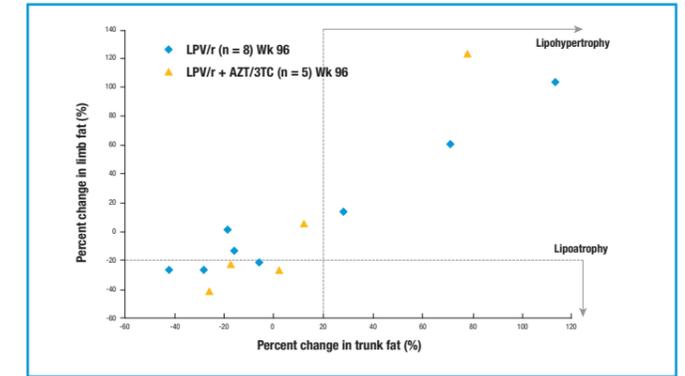


Figure 7: Lipoatrophy and Lipohypertrophy at Week 96 for Patients with DEXA Data at Week 96 (n=13)



Lean Mass Changes from Baseline to Week 48

- A The median decrease in lean arm tissue was greater in the LPV/r + AZT/3TC arm than in the LPV/r monotherapy arm at Week 48: -308 g versus -96 g ($p = 0.015$).
- There were no statistically significant differences between treatment arms for median trunk lean mass or leg lean mass at Week 48 ($p \geq 0.379$).

Table 4. Lipodystrophy Related Terms by Physician Report through 96 Weeks

- 12 patients had a fat redistribution related adverse event (FAE) reported on CRF*.
- 6/11 with FAE also had paired DEXA data
 - 3/6 had concurrence between physician report and DEXA findings.

Reported Adverse Event	Physician Report	# w/ DEXA at BL & W48	Concurrence FAE - DEXA
Lipodystrophy (n)	4 [†]	2	2
Lipoatrophy of the face (n)	2	2	1
Weight loss	4	2	0
Waist circumference increase	1	0	0

*1 patient censored due to weight loss already reported at Baseline
[†]1 patient with concomitant weight loss AE & lipodystrophy

Predictive Factors Associated with Lipoatrophy or Lipohypertrophy

- The presence of lipoatrophy (>20% loss in limb fat) was associated only with the treatment group ($p < 0.02$). There was no association with the other studied variables:
 - Gender/age
 - Baseline weight
 - BMI
 - Time from diagnosis of HIV infection
 - CD4 at BL
 - Viral load at BL
- No difference in lipohypertrophy (>20% gain in trunk fat) was found between the treatment arms.