

# Fat Tissue Distribution Changes in HIV-infected Patients with Viral Suppression Treated with Darunavir/ritonavir (DRV/r) monotherapy versus 2 NRTIs + DRV/r in the MONOI-ANRS 136 Randomized Trial : Results at 48 weeks

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### ABSTRACT

**Background:** MONOI-ANRS136 is an ongoing open-label, randomized trial comparing the efficacy of 2 NRTIs+DRV/r vs. DRV/r monotherapy in patients with suppressed HIV viraemia. The primary analysis at week 48 showed non-inferiority of DRV/r compared with 2NRTIs+DRV/r (94% vs 99%, PP population). Whether such single drug strategy could improve fat tissue distribution abnormalities, frequent in HIV-treated patients, is an important clinical issue to be addressed.

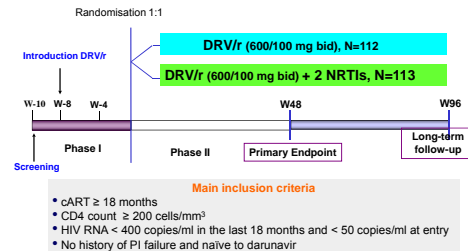
**Methods:** MONOI-ANRS136 included a DEXA sub-study to evaluate changes in body composition between baseline and week 48. Evolution of fat tissue distribution was analyzed as changes in limbs and trunk fat tissue (kg). Lipotrophy was defined as a loss >20% in limb fat lipotrophy as a gain >20% in trunk fat from baseline. Fisher's exact and Wilcoxon tests were used for group comparisons. All analyses were intent-to-treat.

**Results:** Overall 141 patients (67 in the 2 NRTIs+DRV/r arm and 74 in the DRV/r arm) of the 225 patients randomized in MONOI had DEXA-scans data at baseline and W48. There was no difference regarding baseline characteristics between the subgroup with DEXA-scans and the total study population. In the triple therapy arm: backbone NRTIs combined to DRV/r was: 3TC 51%, TDF 49%, FTC 43%, ABC 23%, AZT 22%, and DDI 12%. Median IQR baseline values were not different within arms: age 45 years [39.5-52.4], duration of HIV infection 11.2 years [8.1-16.9], weight 70 kg [64-78], trunk fat 9.4 kg [6.1-13.0], limb fat 5.0 kg [3.2-8.3]. Median changes in limb fat were -0.02kg and 0.34kg in the 2 NRTIs+DRV/r and DRV/r arm, respectively (p=0.011). Lipotrophy was observed at W48 in 87/4 (11%) patients receiving 2 NRTIs+DRV/r in contrast with 167 (1%) patient in the DRV/r arm (p=0.04). In the 8 lipotrophic patients, the NRTIs backbone was: TDF/FTC (n=6), AZT/3TC (n=2), 3TC/ABC (n=1), ABC/3TC (n=1). There was no difference between the two arms neither in the change of trunk fat tissue (+0.6 kg vs +0.73 kg, p=0.40) nor in the proportion of patients with lipotrophy (23% vs 27%, p=0.70).

**Conclusion:** Through 48 weeks, MONOI study shows that the switch to a DRV/r monotherapy leads to a significant gain in limb fat tissue contrasting with no change in the triple-drug arm. Despite a NRTI backbone which included many non-thymidine analogues, lipotrophy was more frequent (11%) in the triple-drug arm compared to the monotherapy arm (1%).

### MONOI DESIGN

MONOI is a prospective, open-label, non-inferiority, randomized, 96-week trial comparing, after introduction of darunavir/ritonavir (600/100 mg bid) for eight weeks, efficacy and safety of maintaining a darunavir/ritonavir triple drug regimen to a switch on darunavir monotherapy in patients with suppressed viral load while receiving triple-drug therapy.



### METHODS

- The primary end point was the proportion of patients in treatment success by week 48, treatment failure was defined as two consecutive HIV RNA > 400 copies/mL (TLOVR).
- Secondary end points included changes in body composition from baseline to week 48 in patients involved in the DEXA sub-study.
- Evolution of fat tissue distribution includes changes in limbs and total fat tissue (kg and %) and the proportion of patients experiencing lipotrophy (>20% loss in limb fat) or lipohypertrophy (>20% gain in trunk fat) between D0 and W48. For these secondary end points missing data due to missed evaluations were simply ignored.
- Body composition was measured by whole body scan using dual x-ray absorptiometry (DEXA) at study entry, week 48 and week 96. All DEXA evaluations were performed according to a standardized protocol and data were centrally analyzed blinded to treatment group. Results at week 48 are presented.

### OBJECTIVE

To compare the effect of DRV/r versus 2NRTIs+DRV/r on body adipose distribution as measured by change in fat tissue levels from baseline to week 48.

DEXA scans were available at baseline for 156 patients (DRV/r + 2 NRTIs n=81; DRV/r n=75), and at baseline and week 48 for 141 patients (DRV/r + 2 NRTIs n=74; DRV/r n=77) of the 225 patients MONOI subjects at 32 participating ANRS sites in France.

### Patient baseline characteristics

Demographics	DRV/r + 2 NRTIs N=81	DRV/r N=75	Total N=156
Age (years) (median [IQR])	45.4 [40.0-55.6]	45.6 [40-51]	45 [40-53]
Weight (kg) (median [IQR])	71 [63-81]	70 [64-77]	70 [64-78]
Female, n (%)	18 (22.2%)	17 (22.7%)	35 (22.4%)
Years since known HIV-infected (median [IQR])	10.3 [4.2-17.9]	12.2 [8.0-16.5]	11.6 [8.0-16.6]
<b>ART history (years)</b>			
NRTI exposure (median [IQR])	8.2 [3.1-11.8]	9.9 [4.6-11.8]	9.0 [3.5-11.8]
NNRTI exposure (median [IQR])	7.5 [3.8-8.4]	8.0 [6.4-8.9]	7.7 [4.6-8.6]
PI exposure (median [IQR])	5.1 [2.5-9.2]	6.2 [3.2-9.9]	5.8 [3.0-9.6]
<b>ART prior screening</b>			
Protease inhibitor-sparing regimen (n, (%))	21 (25.9%)	22 (29.3%)	43
Protease inhibitor-containing regimen (n, (%))	60 (74.1%)	53 (70.7%)	113

### Main combination of NRTIs associated with darunavir/r

Abacavir+lamivudine	15 (18.5%)	NA	NA
Zidovudine+lamivudine	17 (21.0%)	NA	NA
Tenofovir+emtricitabine	33 (40.7%)	NA	NA

### Body composition

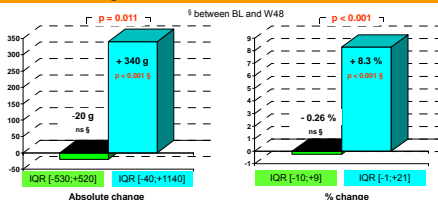
Body Mass Index (kg/m <sup>2</sup> ) (median [IQR])	24.4 [22.3-26.7]	23.5 [22.2-24.9]	23.8 [22.2-26.1]
Limb fat (kg) (median [IQR])	5.2 [2.9-8.3]	4.8 [3.4-8.3]	5.0 [3.2-8.3]
Limb fat (%) (median [IQR])	16.3 [9.9-26.1]	17.1 [11.6-25]	17.0 [10.6-25.0]
Trunk fat (kg) (median [IQR])	8.9 [6.2-14.3]	9.8 [6.0-12.5]	9.4 [6.1-13.0]
Trunk fat (%) (median [IQR])	26.1 [17.5-33.1]	27.7 [18.5-33.1]	26.4 [18.0-33.6]
Total fat (kg) (median [IQR])	15.6 [10.2-25.1]	15.6 [9.9-21.5]	15.6 [10.1-22.8]
Total fat (%) (median [IQR])	21.7 [14.4-30.9]	21.9 [16.3-28.6]	21.7 [15.2-29.9]

### Metabolic values

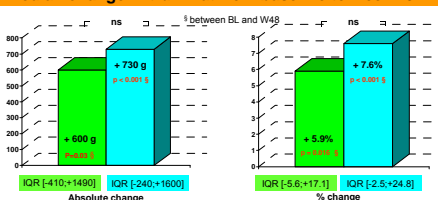
Total-cholesterol (mg/dl) (median [IQR])	208 [177-241]	209 [183-242]	209 [182-241]
LDL-cholesterol (mg/dl) (median [IQR])	123 [98-154]	130 [106-156]	125 [99-155]
HDL-cholesterol (mg/dl) (median [IQR])	43 [37-56]	46 [40-57]	46 [38-56]
Triglycerides (mg/dl) (median [IQR])	147 [98-220]	140 [104-217]	143 [102-218]
Glucose (mg/dl) (median [IQR])	92 [86-97]	88 [83-95]	90 [85-95]

Baseline characteristics were similar between treatment arms, except for glucose (p=0.047)

### Median change in limb fat from baseline to week 48



### Median change in trunk fat from baseline to week 48



### Sensitivity analysis of lipotrophy and lipohypertrophy occurrence at week 48

	DRV/r + 2 NRTIs N=74	DRV/r N=67	p
<b>Lipotrophy</b>			
>10% loss in limb fat n (%)	177/4 (22.9%)	4/67 (5.9%)	p<0.005
>20% loss in limb fat n (%)	87/4 (10.8%)	1/67 (1.5%)	p<0.035
>30% loss in limb fat n (%)	2/74 (2.7%)	0/67	ns
<b>Lipohypertrophy</b>			
>10% gain in trunk fat n (%)	25/74 (33.8%)	32/67 (47.8%)	ns
>20% gain in trunk fat n (%)	17/74 (23.0%)	18/67 (26.9%)	ns
>30% gain in trunk fat n (%)	9/74 (12.2%)	13/67 (19.4%)	ns

### CONCLUSIONS

- In patients with long exposure to NRTI-containing regimen, switch to darunavir/r monotherapy regimen leads to an increase of the limb fat tissue with :
  - a reduced number of patients developing lipotrophy over 48 weeks (1.5% vs 11%).
  - a gain of 340 g (8.3%) of adipose tissue in the darunavir/r monotherapy arm contrasting with a decrease of 20 g in the triple therapy arm even in patients receiving abacavir/lamivudine or tenofovir/emtricitabine.
- There is a significant difference in change of glycemia in the darunavir/r monotherapy compared with the triple-drug therapy. The increase of trunk fat observed in both groups warrants further investigation. Additional data at week 96 are ongoing.