Body composition changes on Darunavir/Ritonavir (DRV/r) + either Raltegravir (RAL) or Tenofovir/Emtricitabine (TDF/FTC) as first-line antiretroviral therapy. NEAT 001/ANRS 143. Body composition sub-study

Bernardino JI[1], Mocroft A[2], Wallet C[3], Molina JM[4], Knobell H[5], Reynes J[6], Babiker A[7], Raffi F[8], Arribas JR[1] and NEAT 001/ANRS143 Study Group

[1]Hospital Universitario La Paz. IdiPAZ. Spain; [2]University College London, UK; [3]INSERM U897, University Bordeaux, France; [4]Hopital Saint-Louis, Paris, France; [5]Hospital del Mar, Barcelona, Spain; [6]Montpellier University Hospital, France; [7]MRC Clinical Trials Unit at UCL, UK; [8]University of Nantes, France.

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Abstract # 16-381

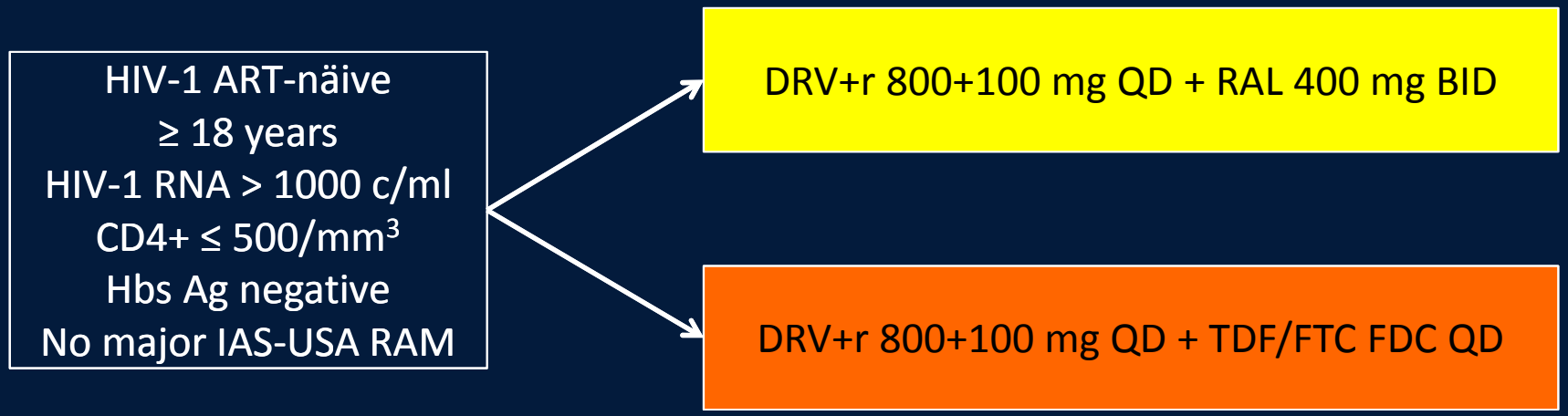
BACKGROUND

- HIV-infected patients receiving currently ART rarely develop alterations in fat distribution.
- In ACTG 5224s patients were randomized to either abacavir/lamivudine or tenofovir/emtricitabine with either efavirenz or Atazanavir/ritonavir both NRTI similarly decreased mitochondrial DNA in fat.
- In ACTG 5260s initiation of either raltegravir, atazanavir/ritonavir or darunavir/ritonavir (with Tenofovir/emtricitabine) led to similar increases in limb fat and central adiposity, although there was a trend for increased fat gain with PI.
- Data are scarce regarding body composition changes with nuke-sparing regimens in ART-naïve patients.

Guaraldi G HIV Medicine 2014, McComsey GA JID 2013, McComsey GA CROI 2015 #140,

NEAT 001/ANRS 143 Study Design

Phase III, randomised, open-label, multicenter, parallel-group, non-inferiority trial
78 sites, 15 European countries



Randomisation 1:1
Stratified by country and participation in virology/immunology substudy

Week 96

- Bone & body composition substudy: patients randomised at same time main study
- Whole body dual-energy x-ray absorptiometry (DXA) scans assessed BMD and body composition (lean and fat mass in total body, trunk and limb)
- Hologic and Lunar devices used. No central reading

Raffi et al. Lancet 2014; 384:1942-51

Objectives

Compare % changes in body composition between treatment arms

Evaluate predictors of % total body fat change over 96 weeks

Primary endpoint:

Mean percentage change of limb fat mass at 96 weeks

Secondary:

- Predictors of % total body fat change over 96 weeks
- Explore associations between BMD and changes in body composition
- Compare inflammatory and metabolic markers between treatment arms (IL-6, insulin, leptine, adiponectine and FGF-23)
- Relationships between body composition changes and biomarkers changes

Methods

- Total body Dual-energy x-ray absorptiometry (DXA) scans were obtained at baseline, week 48, and week 96.
- Metabolic and inflammatory markers (IL-6, Insulin, Leptin, Adiponectin and Fibroblast Growth Factor-23) at baseline and week 48 were analyzed.
- Mean percentage changes in body composition were assessed with unpaired t-tests or non parametric tests.
- Linear regression and analysis of variance were used to explore associations between changes in BMD and changes in total and regional fat. Low BMD defined as t-score <-1.0 in persons aged <40, z-score <-2 in persons aged >40 at either femoral neck, spine or total hip

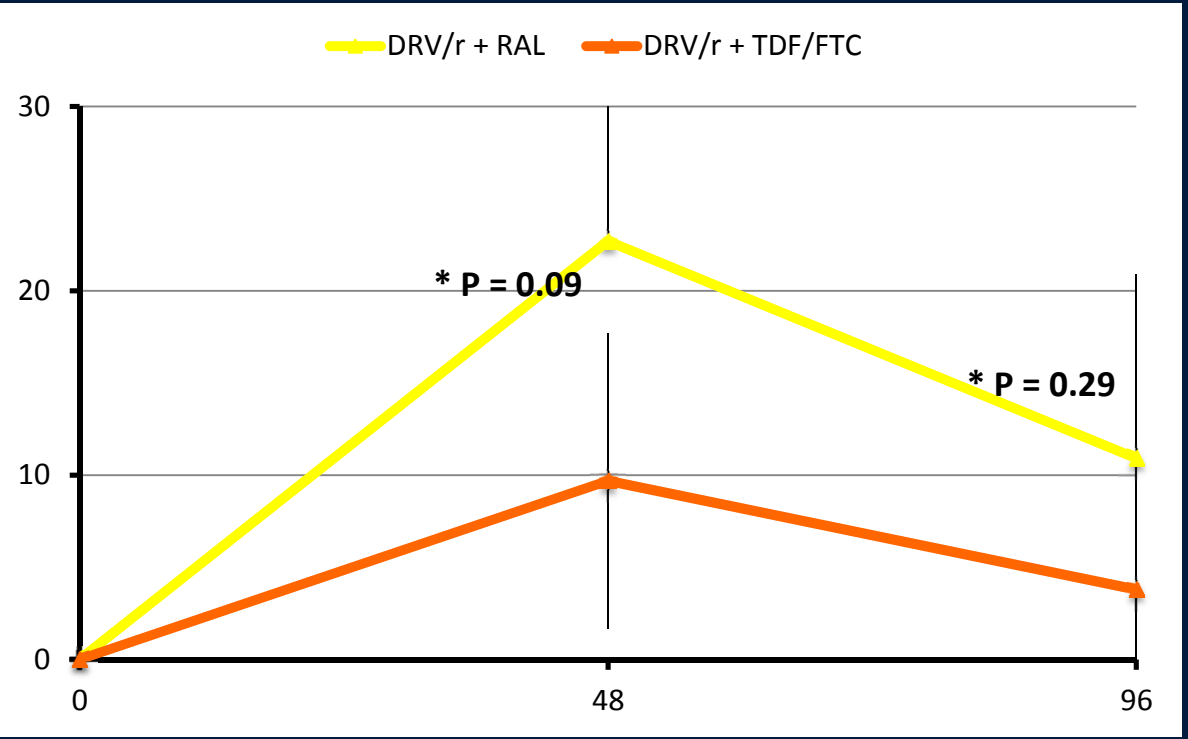
Baseline Characteristics

	DRV/r + RAL N = 61	DRV/r + TDF/FTC N = 65	Total N = 126
Gender Male, n (%)	53 (86.9%)	61 (93.9%)	114 (90.5%)
Age years, median (IQR)	39 (31-45)	40 (32-46)	40 (31-46)
Ethnic group, caucasian n(%)	50 (82%)	53 (81.5%)	103 (88.8%)
HIV duration, years, median (IQR)	1.9 (0.7-4.6)	2 (0.3-3.5)	1.9 (0.5-3.8)
HIV-1 RNA $\log_{10}$ cp/ml median (IQR)	4.8 (4.3-5.2)	4.7 (4.4-5.0)	4.7 (4.3-5.1)
CD4 cells/mm^3, median (IQR)	347 (280-393)	331 (278-414)	338 (279-407)
CD4 nadir cells/mm^3, median (IQR)	327 (236-370)	327 (268-374)	327 (260-374)
BMI Kg/m^2, median (IQR)	22.4 (20.9-26.1)	23.4 (21.7-26.3)	23.2 (21.4-26.2)
Waist circumference cm, median (IQR)	82 (77-89)	84 (79-93)	84 (78-91)
Hip circumference cm, median (IQR)	92 (86-99)	94 (87-99)	93 (86-99)

Baseline Characteristics

	DRV/r + RAL N = 61	DRV/r + TDF/FTC N = 65	Total N = 126
Limb fat Kg, median (IQR)	6.7 (4.7-10.3)	6.4 (5.2-9.1)	6.7 (4.7-9.7)
Trunk lean mass Kg, median (IQR)	25.4 (22.1-28)	25.8 (23.8-27.4)	25.6 (23.2-28)
Trunk fat mass Kg, median (IQR)	7.8 (4.6-11.9)	8.8 (5.4-11.6)	8.5 (4.5-11.7)
Total body lean mass Kg, median (IQR)	49.2 (45.1-52.5)	50.5 (46.8-54.4)	50.1 (46.1-54.2)
Total body fat mass Kg, median (IQR)	66.4 (58-71.3)	66.5 (58.8-71.6)	66.5 (58.8-71.6)

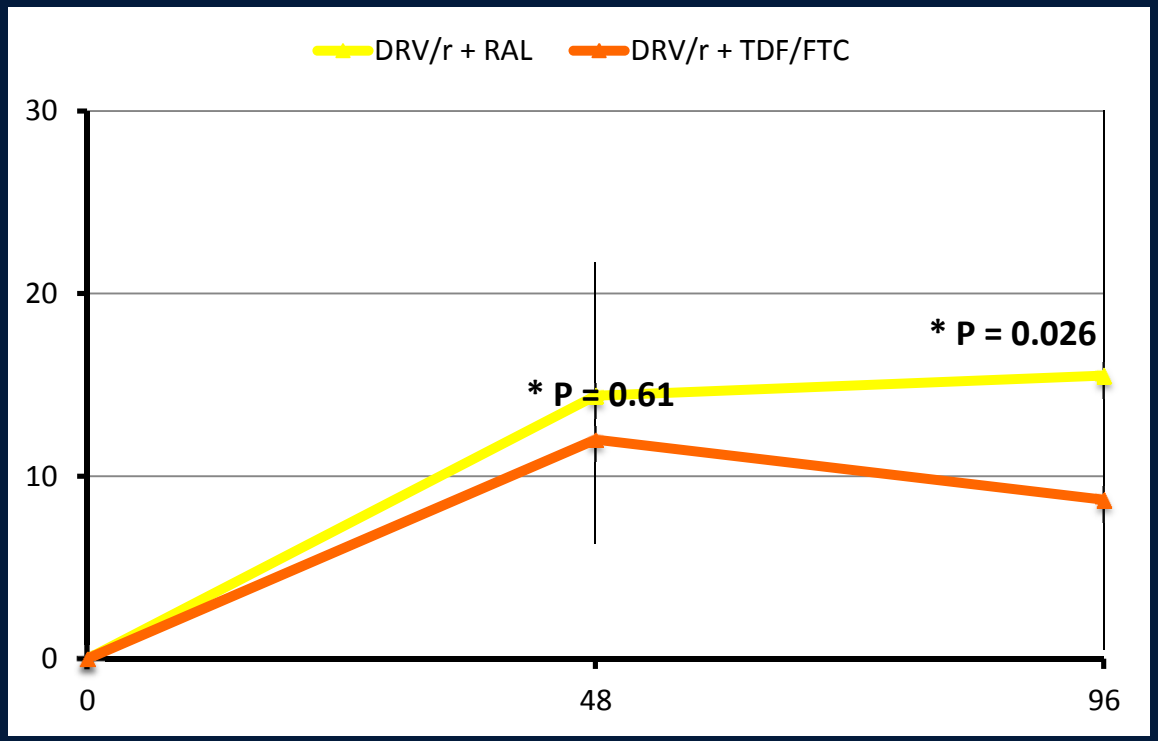
Mean percentage change in limb fat mass



*P values from mean differences between arms (unadjusted)

	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =61	53	22.7 (9.6, 35.8)	49	10.9 (0.9, 20.9)
DRV/r + TDF/FTC n = 65	62	9.7 (1.7, 17.7)	55	3.8 (-4.4, 12)
Mean difference (95% CI); p	**-13.0 (-27.9, 1.9); p 0.09**		**-7.1 (-20.0, 5.8); p = 0.29**	

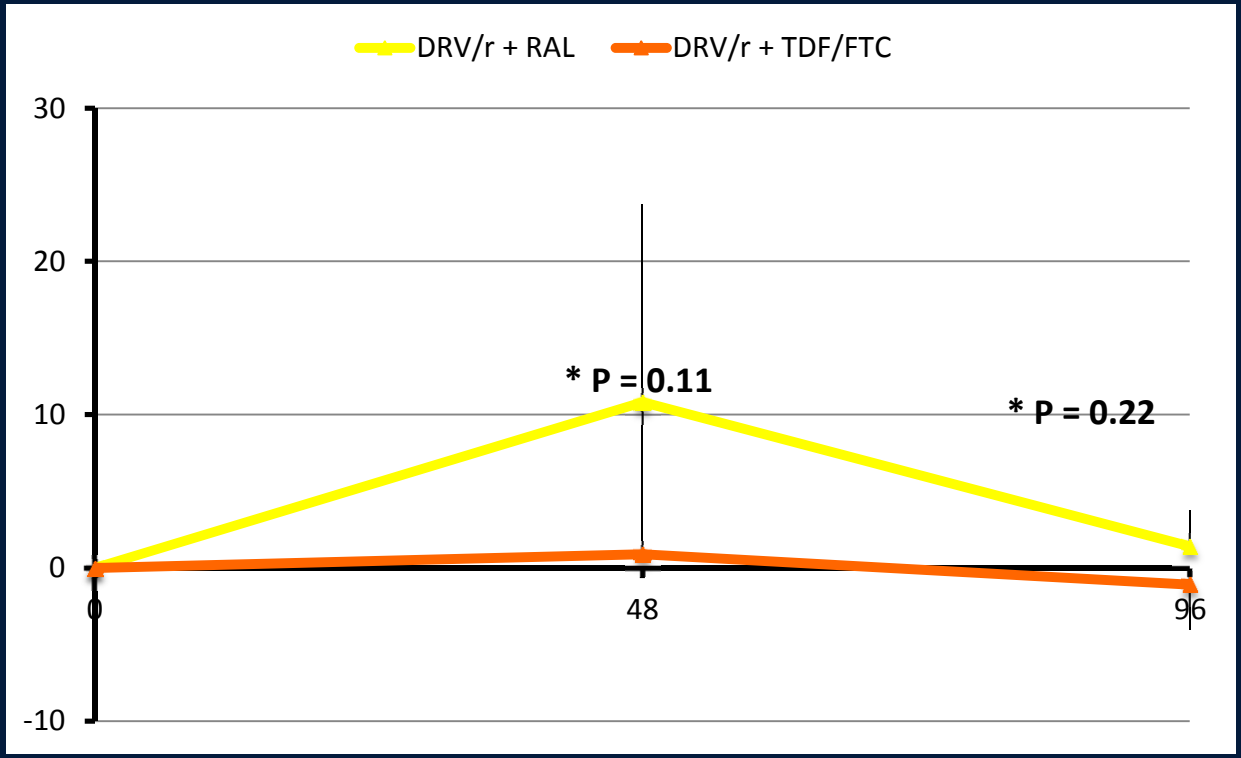
Mean percentage change in trunk fat mass



*P values from mean differences between arms (unadjusted)

	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =61	49	14.4 (7.2, 21.7)	50	15.5 (-2.9, 35.7)
DRV/r + TDF/FTC n = 65	62	12 (6.3, 17.7)	55	8.7 (0.5, 16.9)
Mean difference (95% CI); p	**-2.4 (-11.6, 6.8); p 0.61**		**-6.9 (-31.0, 2.8); p = 0.026**	

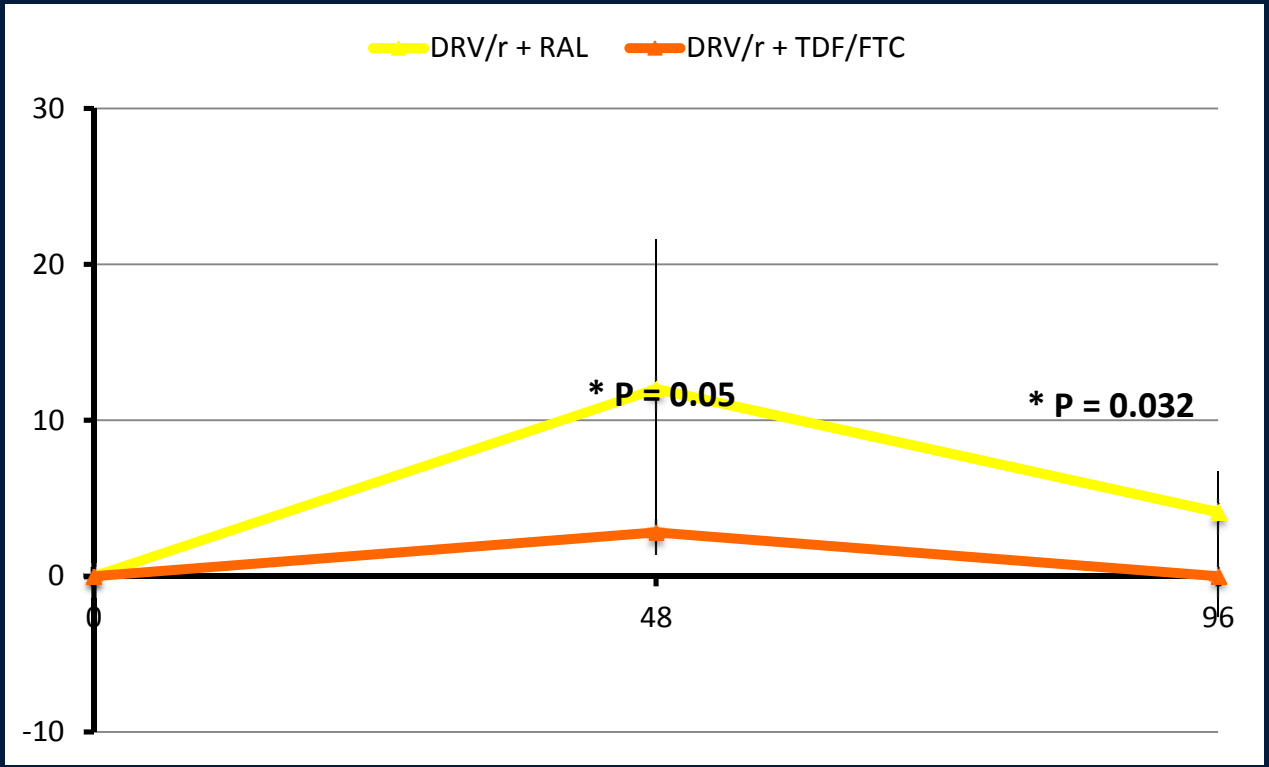
Mean percentage change in total body lean mass



*P values from mean differences between arms (unadjusted)

	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =61	53	10.8 (-2.1, 23.7)	49	1.4 (-1.0, 3.8)
DRV/r + TDF/FTC n = 65	62	0.9 (- 0.7, 2.5)	55	-1.1 (-4, 1.8)
Mean difference (95% CI); p	**-9.3 (-22.0, 2.4); p 0.11**		**-2.4 (-6.1, 1.3); p = 0.22**	

Mean percentage change in total body fat mass



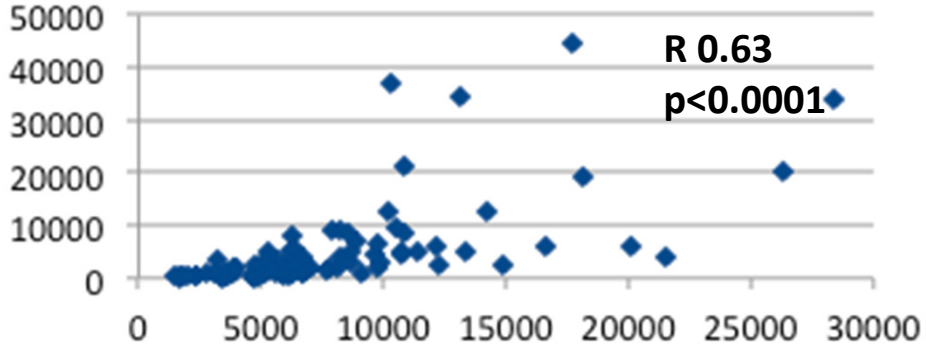
*P values from mean differences between arms (unadjusted)

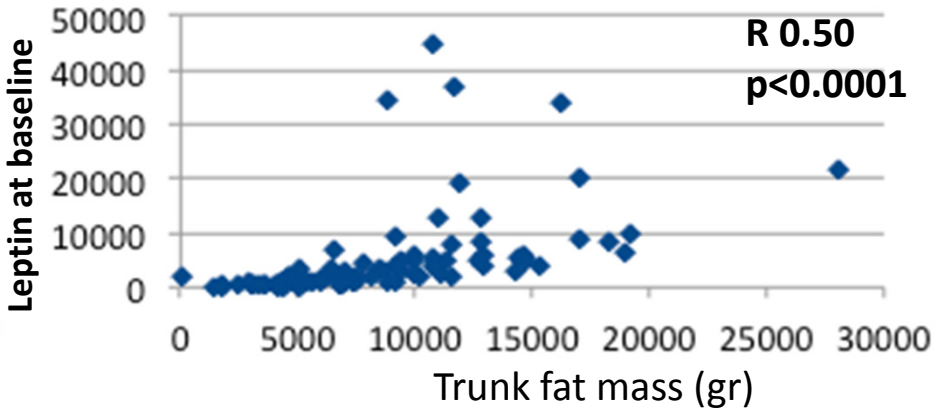
	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n =61	53	12 (2.4, 21.6)	49	4.1 (1.6, 6.7)
DRV/r + TDF/FTC n = 65	62	2.8 (1.4, 4.2)	55	0 (-2.6, 2.6)
Mean difference (95% CI); p	**-9.1 (-18.1,- 0.1); p = 0.05**		**-4.1 (-7.8,- 0.4); p = 0.032**	

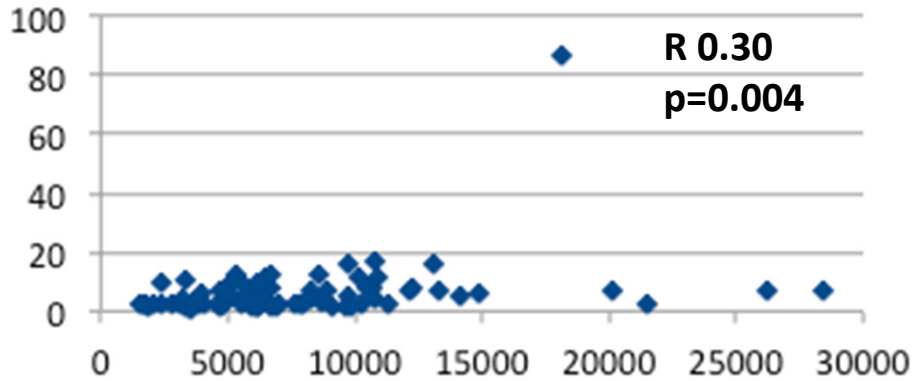
Proportion of subjects with body fat changes

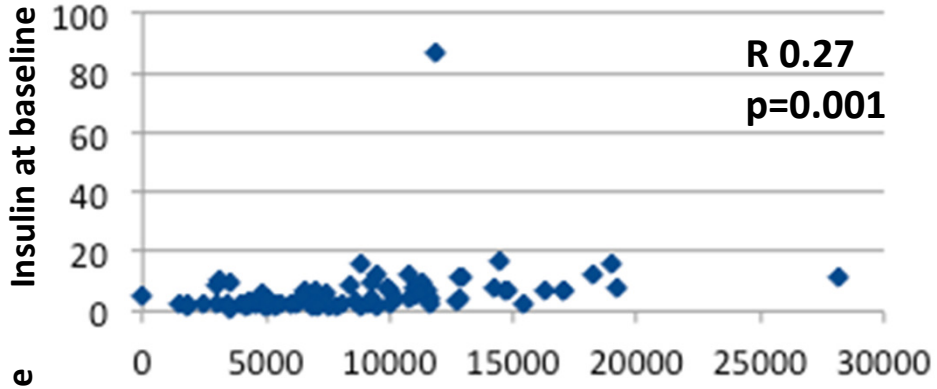
	DRV/r + RAL	DRV/r + TDF/FTC	Total N =126	P value
Proportion of subjects with limb fat loss from baseline to 96W				
≥ 10% (n=49/55)	20.4	30.9	26.0	0.22
≥ 20% (n=49/55)	12.2	16.4	14.4	0.55
Proportion of subjects with trunk fat gain from baseline to 96W				
≥ 10% (n=50/55)	58.0	38.2	47.6	**0.042**
≥ 20% (n=50/55)	44.0	32.7	38.1	0.23

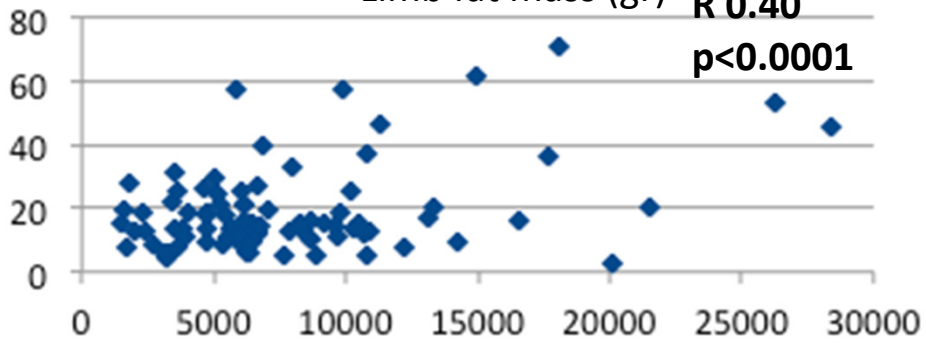
Correlation between inflammatory markers and body composition at baseline

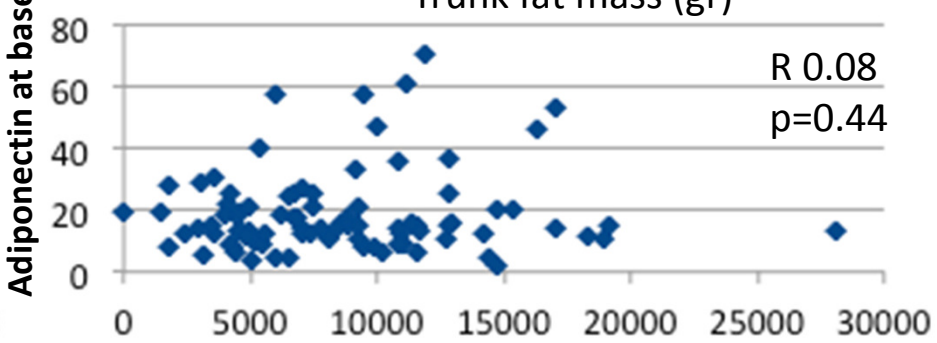




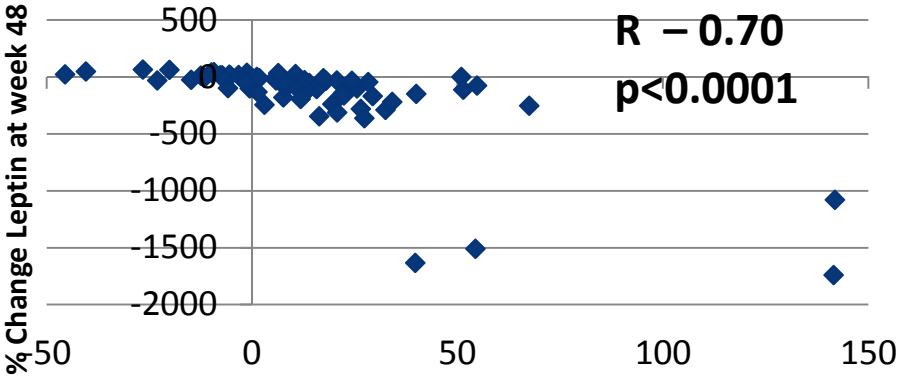




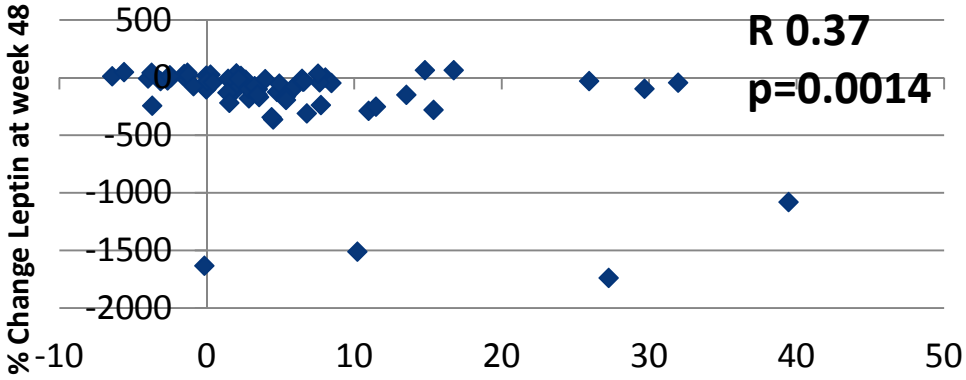




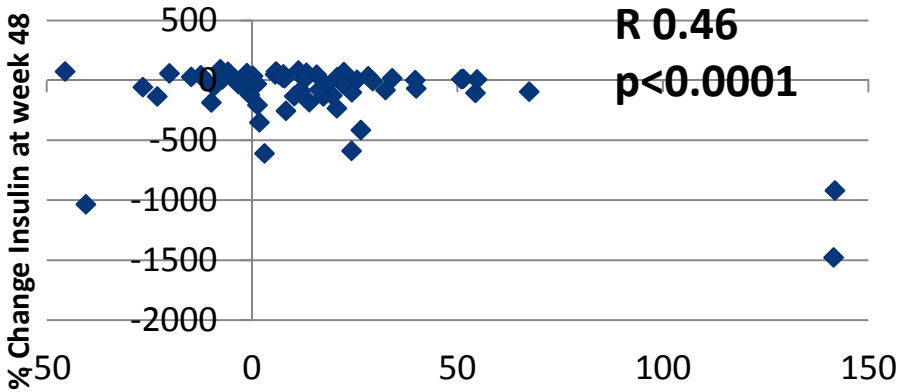
Correlation between % change in inflammatory markers and % change in body composition at 48 weeks



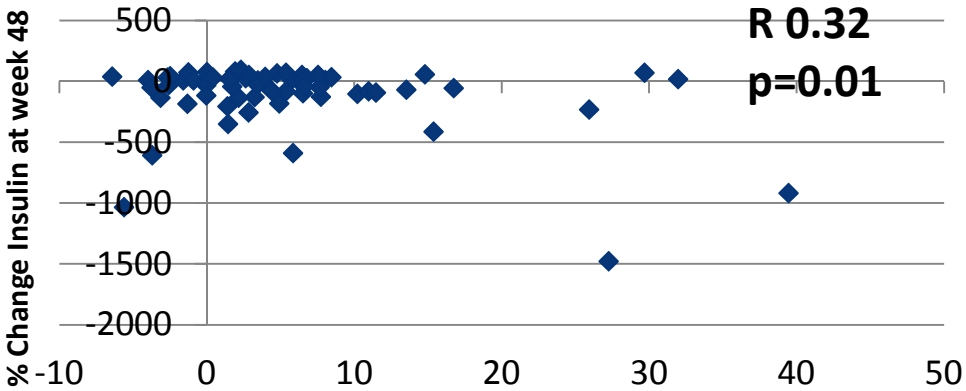
Percentage change in limb fat at week 48



Percentage change in total body fat at week 48



Percentage change in limb fat at week 48



Percentage change in total body fat at week 48

Association between % change in markers and % change in body composition at 48 weeks

		Univariate			Multivariate		
% change at week 48		Mean diff	95% CI	p	Adjusted* mean diff	95% CI	p
Limb fat mass	Insulin[1]	0.5	0.3, 0.8	<0.0001	0.2	-0.1, 0.4	0.17
	Leptin[1]	0.6	0.5, 0.8	<0.0001	0.5	0.3, 0.7	<0.0001
	TDF/FTC + DRV/r vs RAL + DRV/r	-13	-27.9, 1,9	0.09	-2.0	-13.5, 9.5	0.74
Trunk fat mass	Insulin[1]	-0.3	-0.7, 0.0	0.07	-0.3	-0.6, 0.0	0.07
	Leptin[1]	0.3	0.1, 0.6	0.03	0.2	-0.6, 0.0	0.17
	TDF/FTC + DRV/r vs RAL + DRV/r	-3	-12, 6	0.51	2.8	-10.3, 16	0.68
Total Body fat mass	Insulin[1]	0.1	0.0, 0.2	0.01	0.0	-0.1, 0.1	0.37
	Leptin[1]	0.1	0.0, 0.1	0.0014	0.0	-0.1, 0.1	0.27
	TDF/FTC + DRV/r vs RAL + DRV/r	-9.4	-18.3, 0.0	0.043	-3.7	-7.9, 0.4	0.08

[1] Per 10% higher change from baseline to week 48

* Adjusted additionally for fractures at baseline, nadir CD4, CD4 count and viral load at randomisation

Association between % change in markers at 48 weeks and % change in body composition at 96 weeks

		Univariate			Multivariate		
% change at week 96		Mean diff	95% CI	p	Adjusted* mean diff	95% CI	p
Limb fat mass	Insulin[1]	0.5	0.2, 0.8	0.0017	0.3	-0.1, 0.7	0.13
	Leptin[1]	0.5	0.3, 0.6	<0.0001	0.3	0.1, 0.6	0.013
	TDF/FTC + DRV/r vs RAL + DRV/r	-4.9	-17.8, 8,0	0.46	3.5	-12.1, 19.2	0.66
Trunk fat mass	Insulin[1]	0.6	0.2, 0.9	0.002	0.4	0.0, 0.8	0.08
	Leptin[1]	0.5	0.3, 0.7	<0.0001	0.4	0.1, 0.6	0.014
	TDF/FTC + DRV/r vs RAL + DRV/r	-14.4	-29.1, 0.3	0.056	-4.0	21.5, 13.5	0.66
Total Body fat mass	Insulin[1]	0.2	0.1, 0.3	0.0018	0.1	0.0, 0.2	0.17
	Leptin[1]	0.1	0.1 0.2	0.0012	0.1	0.0, 0.14	0.13
	TDF/FTC + DRV/r vs RAL + DRV/r	-4.3	-9.0, -0.6	0.023	-0.8	-6.0, 4.3	0.75

[1] Per 10% higher change from baseline to week 48

* Adjusted additionally for fractures at baseline, nadir CD4, CD4 count and viral load at randomisation

Other results

- There was not a strong correlation between low BMD at any site (hip, spine, femoral neck) at baseline, 48 and 96 weeks and body composition changes
- Correlations between baseline inflammatory and metabolic parameters with body composition (limb, trunk ant total body fat) were weak as were correlations between changes in body composition and inflammatory markers
- Baseline insulin and leptin levels were correlated with baseline limb fat/trunk fat mass [$r=0.31$ ($p=0.0043$)/$r=0.28$ ($p=0.0011$); $r=0.63$ ($p<0.0001$)/$r=0.50$($p<0.0001$), respectively]. Adiponectin was correlated with baseline limb fat mass only [$r=0.40$ ($p<0.0001$)]

CONCLUSIONS

- Use of the nucleos(t)ide sparing regimen DRV/r + RAL produced a higher increase in total and trunk fat mass than the TDF/FTC containing regimen.
- Higher baseline leptin levels were associated with higher limb fat mass and lower trunk fat mass.
- These changes in body composition were modulated by changes in leptin levels after ART initiation.

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Toxicity substudies Working Group: Arribas JR, Bernardino JI, Katkama C, Mallon PW, Mocroft A, Reiss P, de Wit S,
Trial Development Team: C. Allavena, A. Antinori, J. Arribas, B. Autran, A. Babiker, M. Boffito, G. Chêne, N. Dedes, A. Horban, R. Murri, D. Pillay, A. Pozniak, F. Raffi, L. Richert, S. Vella,

Study Coordination: HIV CTU, INSERM U897 Coordinating Unit, Bordeaux, France; MRC Clinical Trials Unit at UCL, London, UK; CHIP Coordinating Unit, Copenhagen, Denmark; Amsterdam Medical Center Coordinating Unit, Amsterdam, The Netherlands; ISS, Rome, Italy; Local CTUs: GESIDA, Madrid, Spain, University of Athens Medical School, Greece

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