

Changes in Bone Mineral Density (BMD) over 96 Weeks on Darunavir/Ritonavir (DRV/r) + Raltegravir (RAL) or Darunavir/Ritonavir + Tenofovir/Emtricitabine (TDF/FTC)

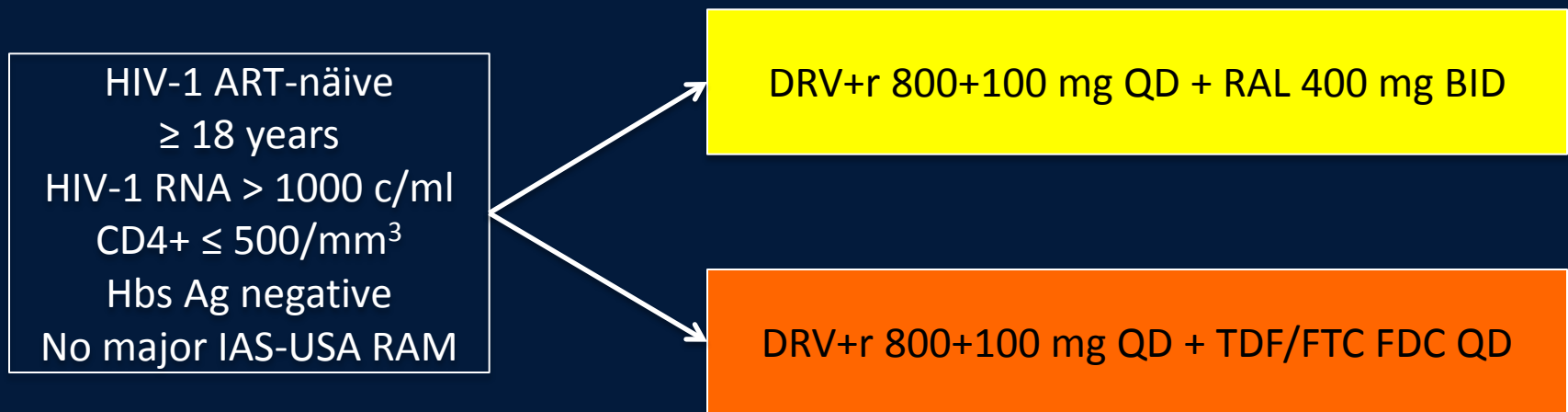
NEAT 001/ANRS 143. BMD sub-study

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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 substudy: patients randomised at same time main study
- Whole body dual-energy x-ray absorptiometry (DXA) scans assessed BMD (total hip, lumbar spine, femoral neck)
- Hologic and Lunar devices used. No central reading

BACKGROUND

- High prevalence of osteopenia/osteoporosis in HIV+ (15%/30%)
- Fragility fractures more frequent in HIV+
- RCT showed a decline in BMD by 2-6% regardless of ART regimen
- Tenofovir use is consistently associated with BMD loss
- No clinical trial of a nucleos(t)ide sparing regimen vs. a TDF containing regimen in naïve patients, has evaluated the impact of ART in BMD changes in total hip, femoral neck and lumbar spine

HYPOTHESIS

A nucleos(t)ide-sparing regimen would ameliorate bone mineral density loss associated with ARV therapy initiation

Objectives

- Compare changes in BMD between treatment arms
- Evaluate clinical factors associated with BMD loss

Primary endpoint:

Mean percentage change of BMD in lumbar spine and hip at 48w

Secondary:

- Mean % change at 96w
- Proportion with WHO criteria for osteoporosis/osteopenia
- Proportion with a Z score < -2
- Incidence of fractures

All analysis done using intent-to-treat exposed approach (ITT-e)

ART modifications and patients without DEXA scan ignored

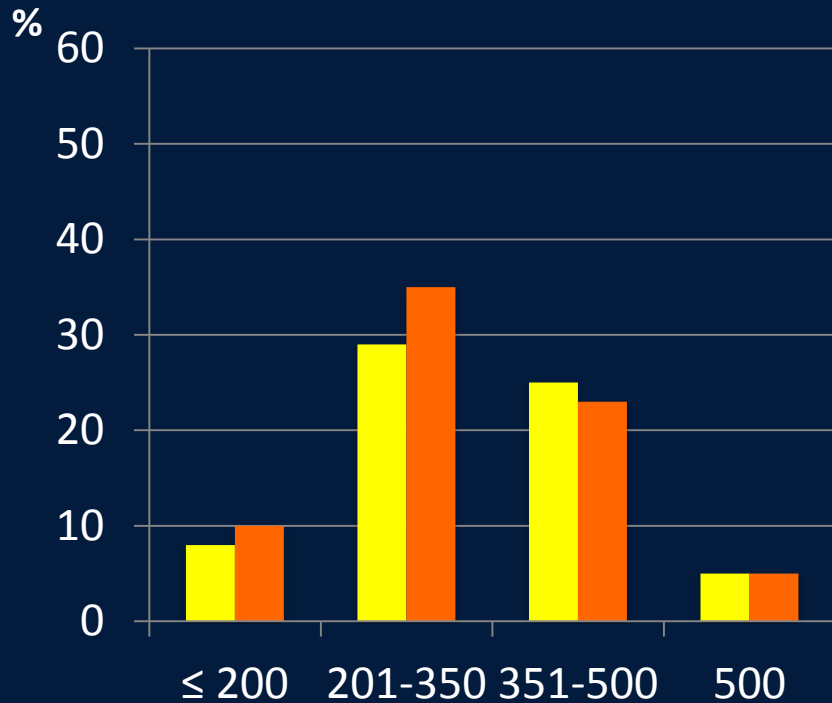
Baseline Characteristics

		DRV/r + RAL N = 70	DRV/r + TDF/FTC N = 76	Total N = 146
Gender	Male n (%)	62 (88.6%)	72 (94.7%)	134 (91.8%)
Age, years	Median (IQR)	39 (30-45)	40 (32-45)	40 (31-45)
Ethnic group	Caucasian n(%)	57 (81.4%)	63 (82.9%)	120 (82.2%)
	Other n(%)	13 (18.6%)	13 (17.1%)	26 (17.8%)
CDC stage	B/C n(%)	11 (15.7%)	13 (17.2%)	24 (16.4%)
HIV duration, years	Median (IQR)	1.8 (0.7-4.3)	1.8 (0.3-3.5)	1.8 (0.5-3.8)
Baseline HIV-1 RNA log ₁₀ copies/ml	Median (IQR)	4.8 (4.3-5.2)	4.7 (4.4-5.1)	4.7 (4.3-5.2)
Baseline CD4+, cells/mm ³	Median (IQR)	344 (280-401)	333 (277-412)	338 (279-410)
HCV serology +	n(%)	2 (2.9%)	1 (1.3%)	3 (2.1%)
Smoking	Current n(%)	26 (37%)	34 (44.7%)	60 (41%)
Alcohol use	Current n(%)	3 (4.3)	2 (2.6)	5 (3.4%)
BMI Kg/m ²	Median (IQR)	22.5 (21.4-26.1)	23.3 (21.7-26.3)	23 (21.6-26.2)

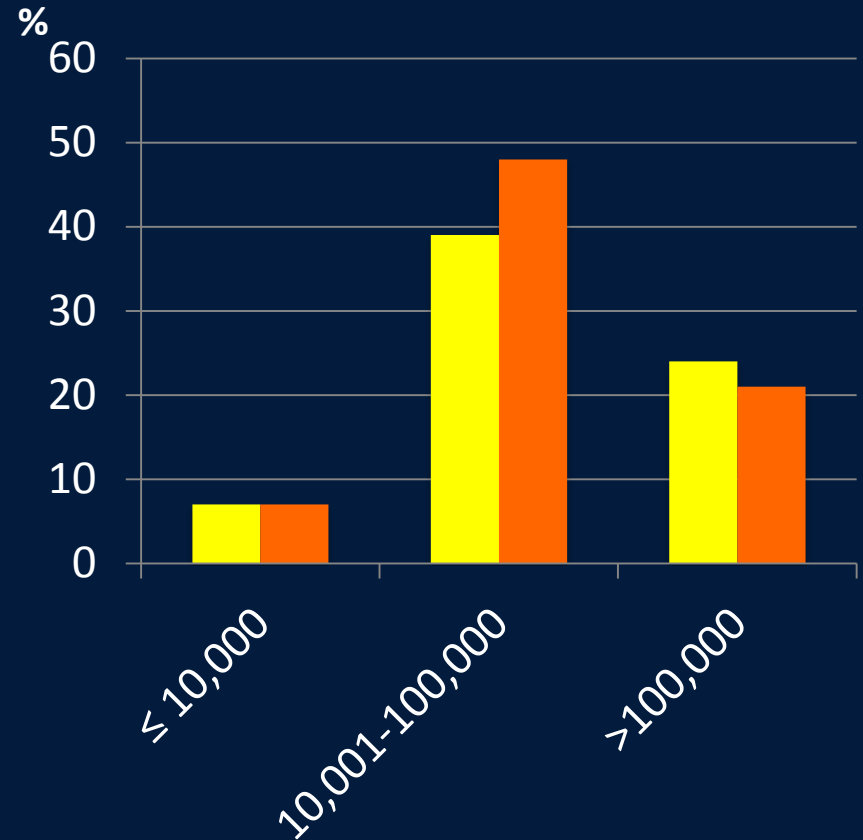
CD4 and viral load at randomisation

■ DRV r + RAL

■ DRV r + TDF/FTC



CD4+ cells /mm³ (p=0.89)



Viral load copies/mL (p=0.64)

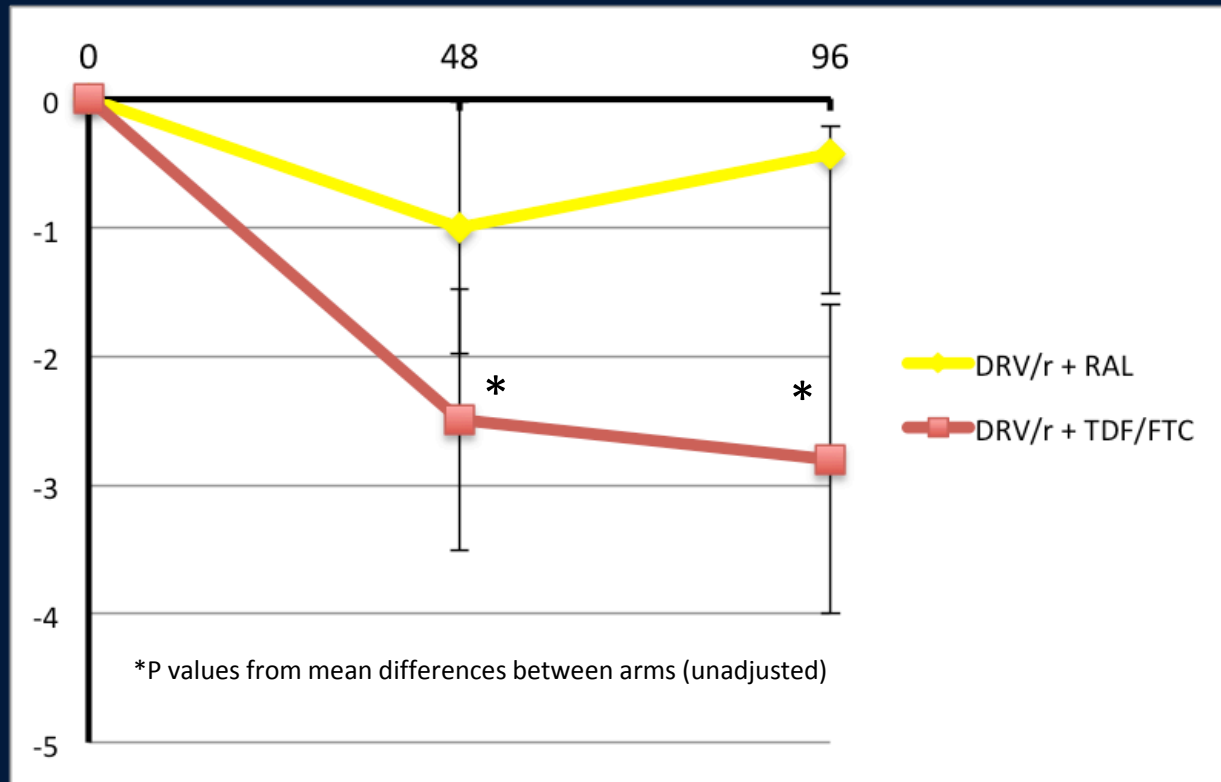
Bone parameters at randomisation

	DRV/r + RAL N = 70	DRV/r + TDF/FTC N = 76	P
Previous Fracture n(%)	8 (11.6%)	15 (20%)	0.17
Hrs walking/week median (IQR)	4 (2-6)	4(2-7)	0.2
Calcium/Vit D supplement n(%)	14 (20%)	10 (13.1%)	0.64
Bone disease ¹ n(%)	13 (18.6%)	16 (21%)	0.71
Family history Fx ² n(%)	9 (12.9%)	7 (9.2%)	0.48
BMD median (IQR) g/cm ²			
Lumbar spine	1.10 (1.00-1.22)	1.16 (1.02-1.23)	0.26
Femoral neck	0.93 (0.86-1.06)	0.98 (0.89-1.11)	0.13
Total hip	1.01 (0.93-1.11)	1.07 (0.97-1.16)	0.032

¹Includes AR, hypogonadism, hypothyroidism. ²Includes mother, father, sister or brother, and assumes no history where not reported; p-value from Kruskal-Wallis test for continuous variables and chi-squared test for categorical variables.

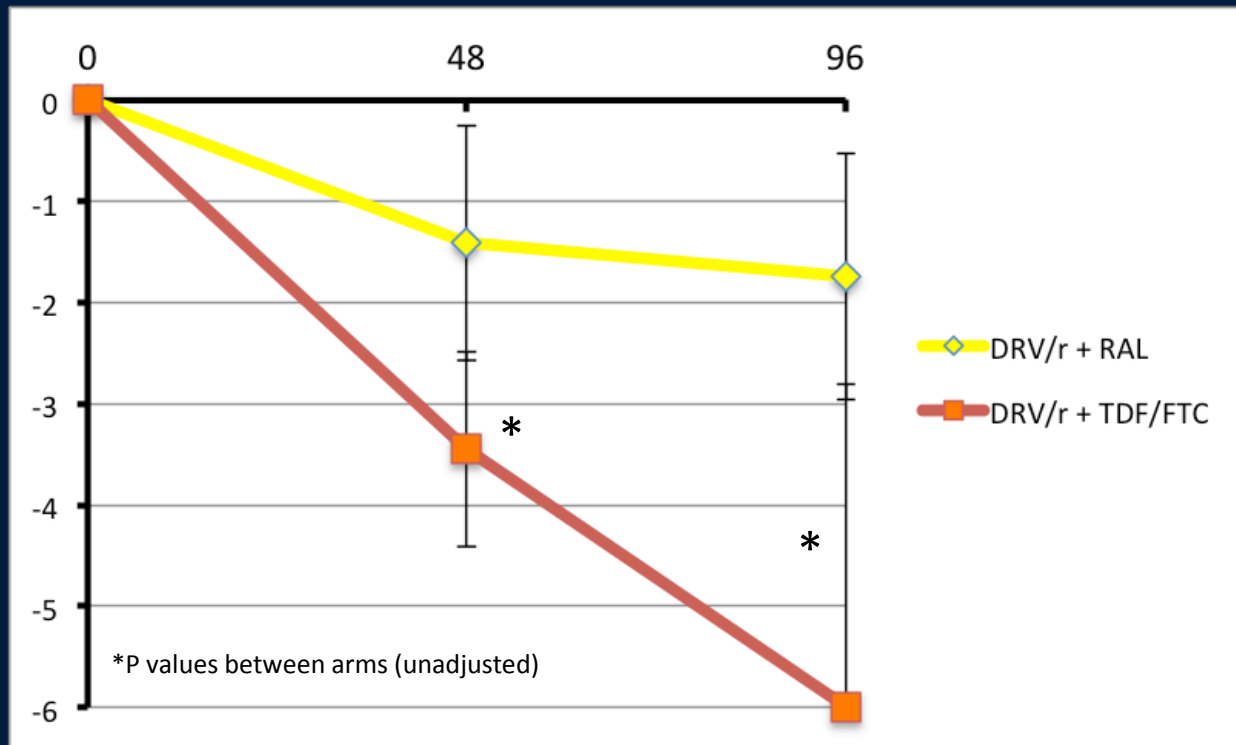
45 patients with Osteopenia/osteoporosis at baseline
 [24 in DRV/r + RAL and 21 in DRV/r + TDF/FTC]

Mean % Change in lumbar spine BMD



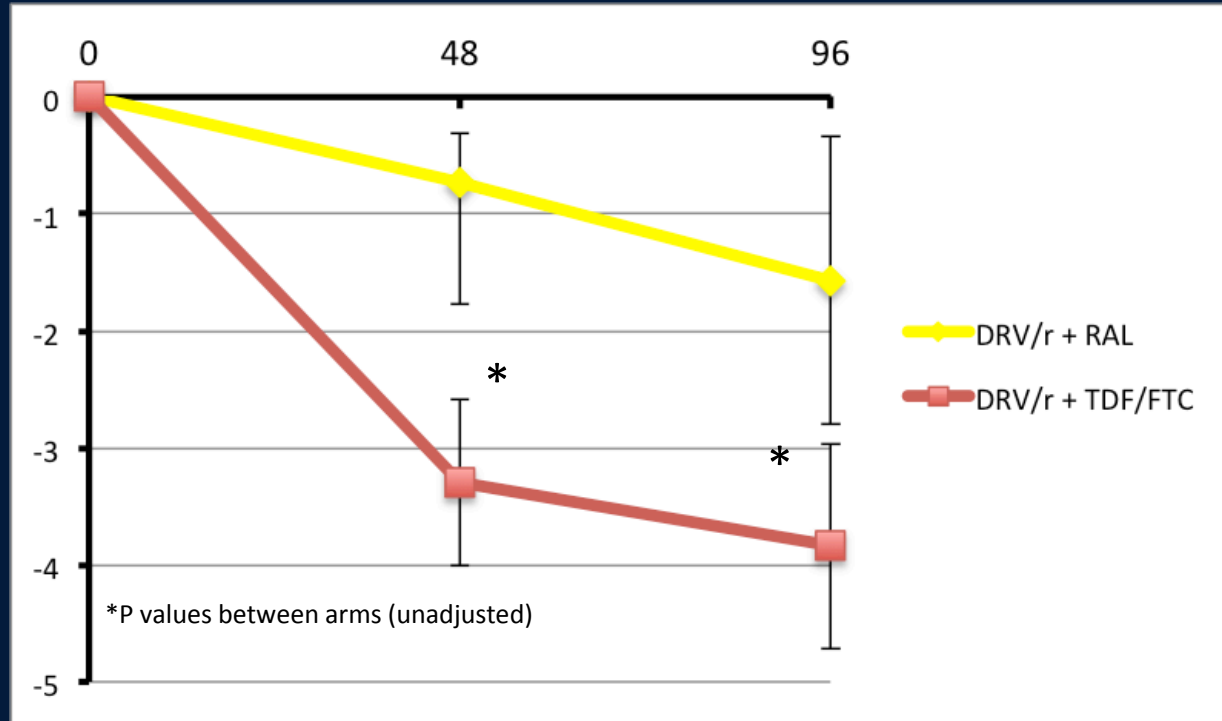
	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n = 70	51	-1.0 (-1.98, -0.02)	48	-0.43 (-1.51, 0.65)
DRV/r + TDF/FTC n = 76	63	-2.49 (-3.51, -1.47)	57	-2.8 (-4.0, -1.6)
Mean difference (95% CI); p	- 1.49 (-2.94, -0.04); p = 0.046*		-2.37 (-4.0, -0.74); p = 0.0054*	

Mean % Change in femoral neck BMD



	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n = 70	55	-1.41 (-2.57, -0.25)	49	-1.74 (-2.96, -0.52)
DRV/r + TDF/FTC n = 76	67	-3.45 (-4.41, -2.49)	59	-5.99 (-9.18, -2.80)
Mean difference (95% CI); p	- 2.04 (-3.53, -0.55); p = 0.0084*		-4.25 (-7.92, -0.58); p = 0.025*	

Mean % Change in total hip BMD



	48 weeks		96 weeks	
	N	Mean % change (95% CI)	N	Mean % change (95% CI)
DRV/r + RAL n = 70	55	-0.73 (-1.77, 0.31)	49	-1.57 (-2.8, -0.34)
DRV/r + TDF/FTC n = 76	67	-3.3 (-4.01, -2.59)	58	-3.86 (-4.74, -2.98)
Mean difference (95% CI); p	- 2.57 (-3.79, -1.35); p < 0.0001*		-2.29 (-3.78, -0.80); p = 0.0032*	

New cases of osteoporosis, osteopenia and Z-score <-2

	RAL + DRV/r			TDF/FTC + DRV/r			OR (95% CI) for osteopenia (TDF/FTC vs RAL)
Week 0-48	Osteoporosis	Osteopenia	Z < -2.0	Osteoporosis	Osteopenia	Z < -2.0	
Lumbar spine	0	4	1	1	7	2	1.42 (0.39-5.26)
Femoral neck	0	6	0	0	3	0	0.37 (0.087-1.57)
Total hip	1	2	1	0	5	0	2.03 (0.38-10.98)
Week 48-96							
Lumbar spine	0	4	1	2	4	2	0.81 (0.19-3.47)
Femoral neck	1	8	0	1	7	1	0.67 (0.22-2.04)
Total hip	1	2	1	0	2	0	0.79 (0.11-5.88)

There were **4 new fractures** (1 in RAL + DRV/r and 3 in TDF/FTC + DRV/r) at 48 weeks and **3 more** at 96 weeks (1 in RAL + DRV/r and 2 in TDF/FTC + DRV/r)

Factors associated with % change in BMD at 48 weeks

		Univariate			Multivariate		
		β	95% CI	p	β	95% CI	p
Lumbar spine							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-1.44	-2.94, -0.04	0.046	-1.39	-2.77, -0.01	0.051
VL at baseline	Per log ₁₀ c/ml higher	-1.99	-3.13, -0.85	0.0009	-1.94	-3.06, -0.82	0.001
Femoral neck							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-2.04	-3.53, -0.55	0.008	-2.01	-3.62, -0.4	0.015
Sports (hours)	Any vs. none	-2.01	-1.26, 0.24	0.082	-1.84	-4.02, 0.34	0.1
VL at baseline	Per log ₁₀ c/ml higher	-1.2	-2.42, 0.02	0.054	-1.29	-2.58, 0	0.053
Total Hip							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-2.57	-3.79, -1.35	<0.0001	-2.55	-3.75, -1.35	<0.0001
BMI	Per Kg/m ² higher	0.15	-0.02, 0.32	0.085	0.12	-0.04, 0.28	0.16
VL at baseline	Per log ₁₀ c/ml higher	-1.15	-2.19, -0.11	0.03	-1.02	-2.0, -0.04	0.042

Factors associated with % change in BMD at 96 weeks

		Univariate			Multivariate		
		β	95% CI	p	β	95% CI	p
Lumbar spine							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-2.37	-4.00, -0.74	0.005	-2.34	-3.96, -0.73	0.005
VL at baseline	Per log ₁₀ c/ml higher	-1.27	-2.56, 0.02	0.055	-1.24	-2.49, 0.01	0.054
Femoral neck							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-4.25	-7.92, -0.58	0.025	-3.48	-7.44, 0.48	0.088
Stage	B/C vs. A	-4.95	-10.28, 0.38	0.071	-4.01	-9.44, 1.42	0.15
Prior history of Bone fracture	Any vs. none	-6.04	-11.18, -0.9	0.023	-4.81	-10.12, 0.50	0.079
Sports (hours)	Any vs. none	-6.36	-11.65, -1.07	0.021	-5.50	-10.65, -0.35	0.039
Total Hip							
Treatment arm	TDF/FTC + DRV/r vs RAL + DRV/r	-2.32	-3.79, -0.85	0.002	-2.32	-3.79, -0.85	0.002

CONCLUSIONS

- Use of the nucleos(t)ide sparing regimen DRV/r + RAL was associated with significantly less bone mineral density (hip ,lumbar spine) loss at W48 and W96 weeks than a regimen of TDF/FTC + DRV/r in first line ART.
- During 96 weeks no difference in osteopenia/osteoporosis nor fractures was found.
- At 48 weeks treatment arm and viral load at baseline were associated with percentage change in lumbar spine and total hip bone mineral density

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