# 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

HIV-1 ART-näive
≥ 18 years
HIV-1 RNA > 1000 c/ml
CD4+ ≤ 500/mm$^3$
Hbs Ag negative
No major IAS-USA RAM

→ DRV+r 800+100 mg QD + RAL 400 mg BID

→ DRV+r 800+100 mg QD + TDF/FTC FDC QD

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

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# 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

AIDS research hum retro viruses 2013;29: 256-265 *AIDS.* 2006; 20:2165-2174. *Clin Infect Dis.* 2010; 51:937-46. *Clin Infect Dis*. 2010; 51(8):963-72 . Curr Opin HIV AIDS 2014; 9: 428-435

# 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:

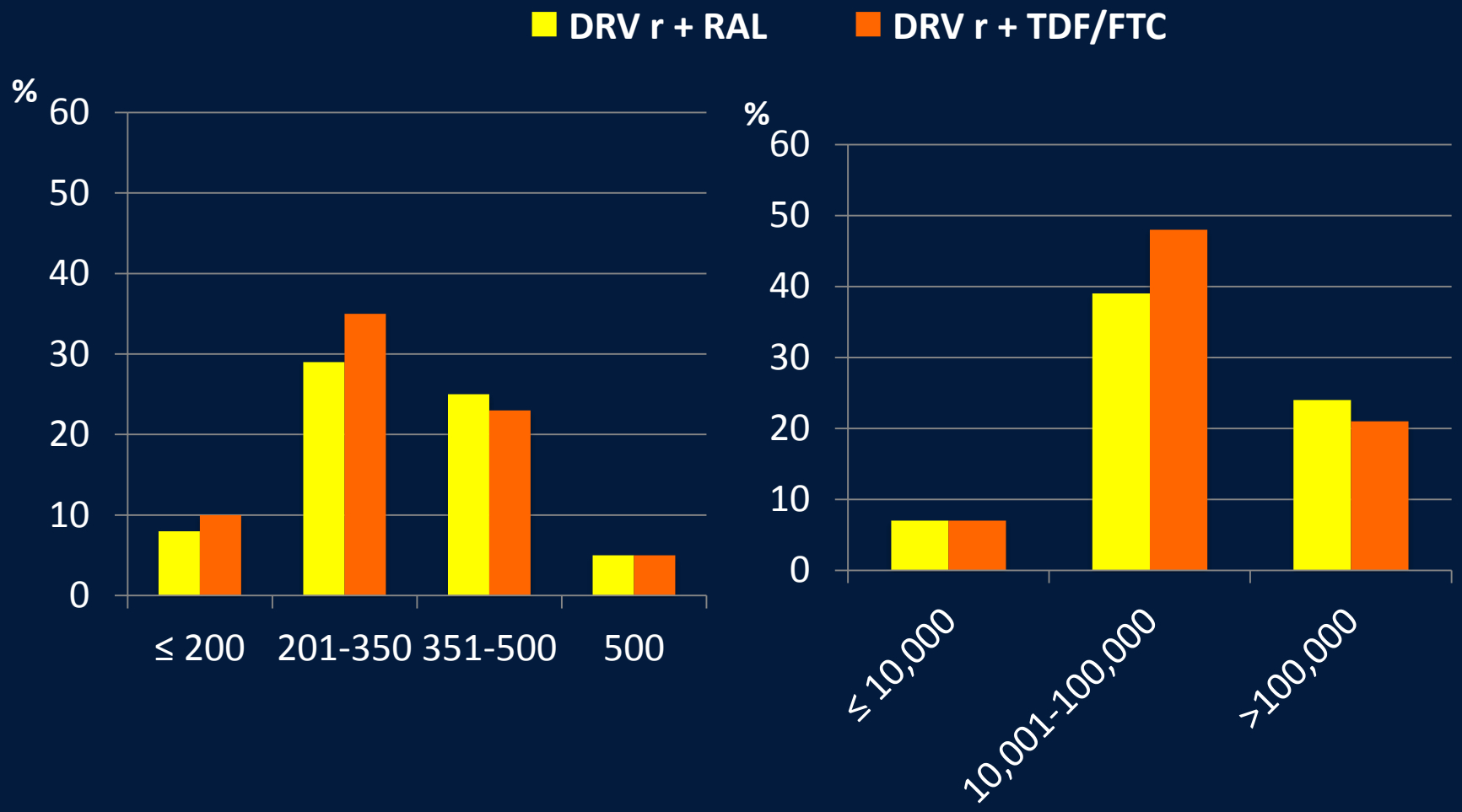
- Mean % change at 96w
- Proportion with WHO criteria for osteoporosis/osteopenia
- Proportion with a Z score < -2
- Incidence of fractures

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




CD4+ cells /mm³ (p=0.89)

Viral load copies/mL (p=0.64)

# Bone parameters at randomisation

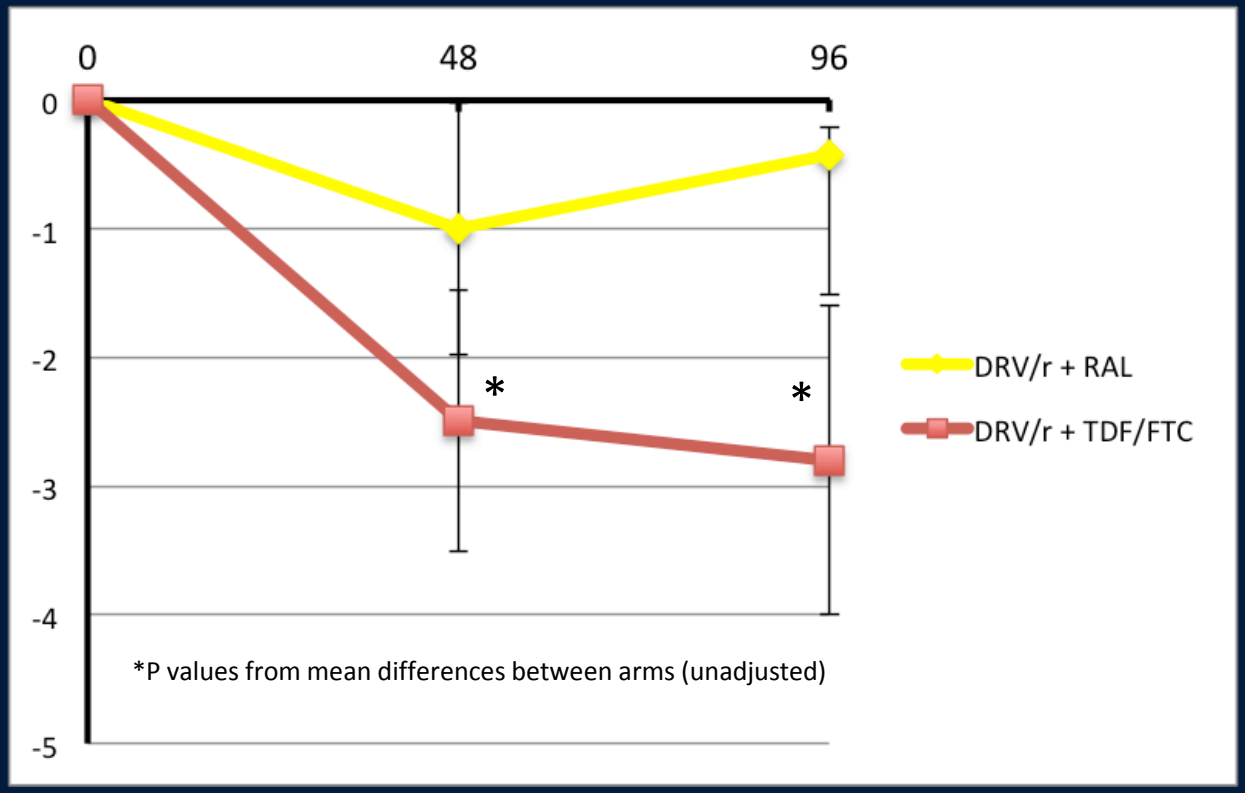
| | | DRV/r + RAL N = 70 | DRV/r + TDF/FTC N = 76 | P |
|---|---|---|---|---|
| Previous Fracture n(%) | | 8 (11.6%) | 15 (20%) | 0.17 |
| Hrs walking/week median (IQR) | | 4 (2-6) | 4(2-7) | 0.2 |
| Calcium/Vit D supplement n(%) | | 14 (20%) | 10 (13.1%) | 0.64 |
| Bone disease[1] n(%) | | 13 (18.6%) | 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 |

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

**45 patients with Osteopenia/osteoporosis at baseline**

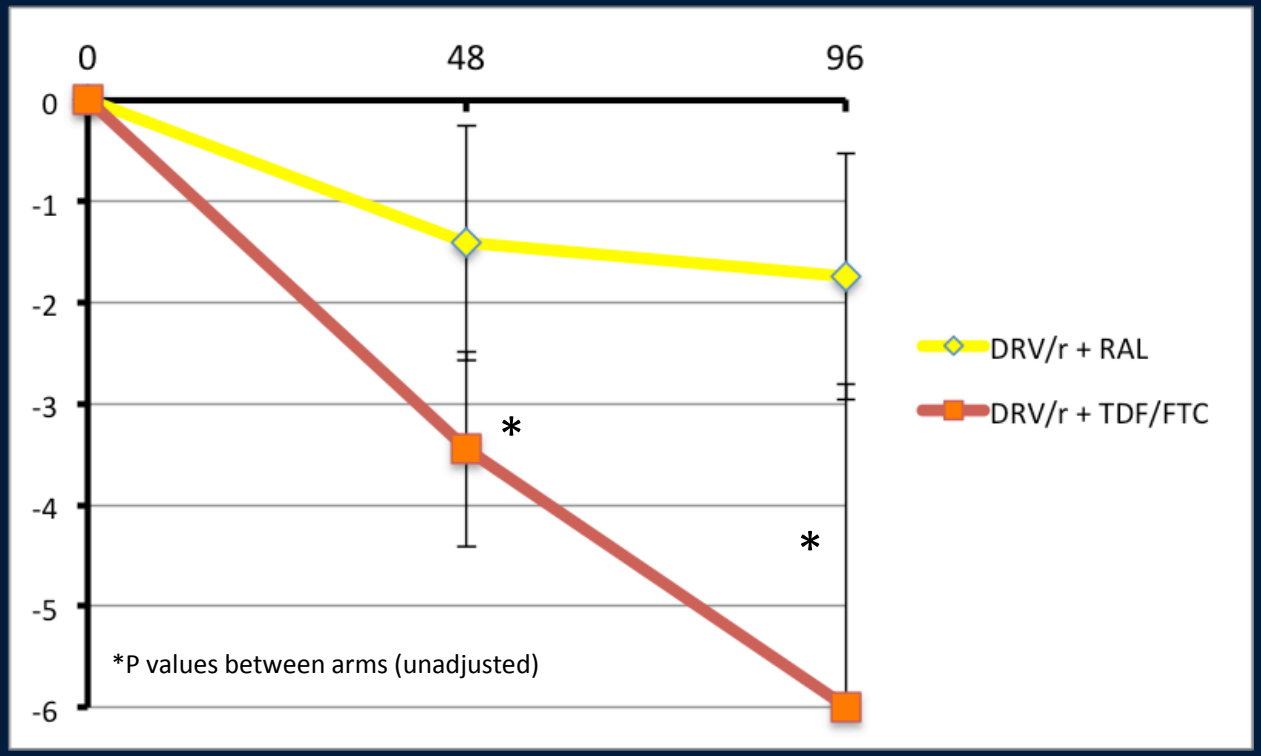
[24 in DRV/r + RAL and 21 in DRV/r + TDF/FTC]

# Mean % Change in lumbar spine BMD



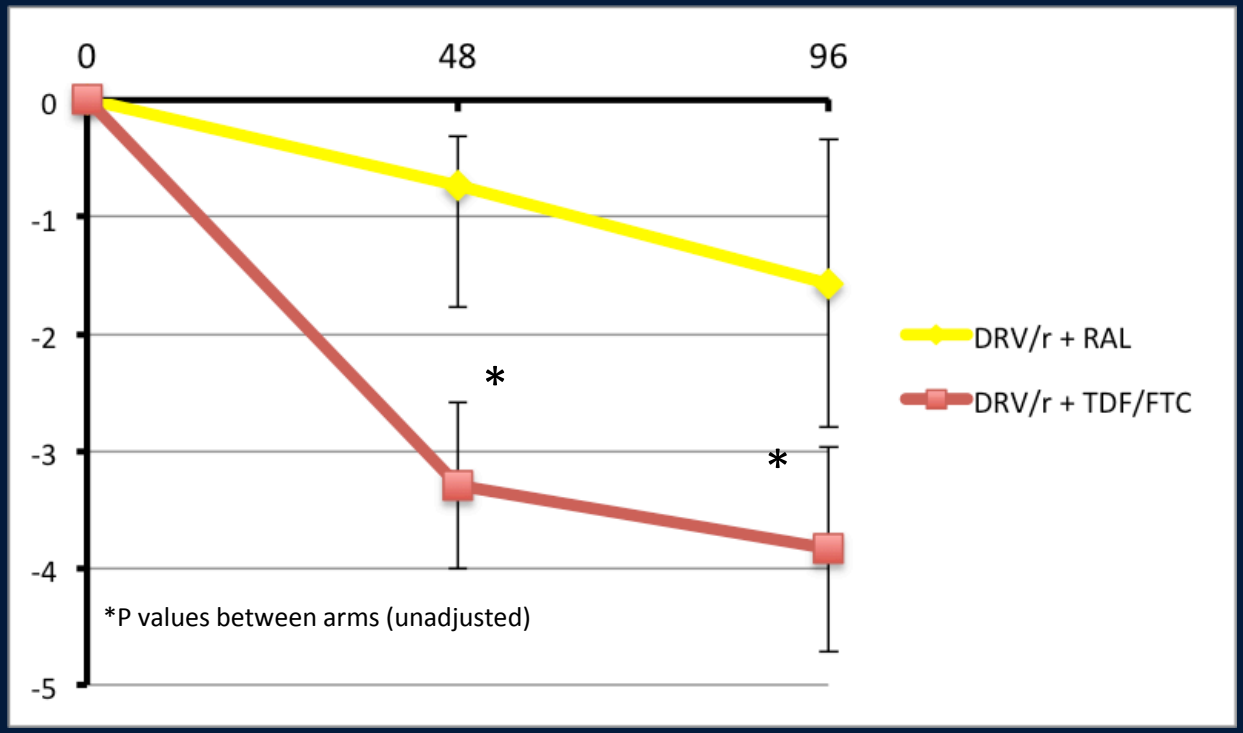

| | 48 weeks | | 96 weeks | |
|---|---|---|---|---|
| | N | Mean % change (95% CI) | N | Mean % change (95% CI) |
| DRV/r + RAL n =70 | 51 | -1.0 (-1.98, -0.02) | 48 | -0.43 (-1.51, 0.65) |
| DRV/r + TDF/FTC n = 76 | 63 | -2.49 (-3.51, -1.47) | 57 | -2.8 (-4.0, -1.6) |
| **Mean difference (95% CI); p** | **- 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 | Osteo porosis | Osteo penia | Z < -2.0 | Osteo porosis | Osteo penia | 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 | | |
|---|---|---|---|---|---|---|---|
| **Lumbar spine** | | β | 95% CI | p | β | 95% CI | p |
| 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 | | |
|---|---|---|---|---|---|---|---|
| **Lumbar spine** | | β | 95% CI | p | β | 95% CI | p |
| 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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