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Low Bone Mineral Density in Older People Living with HIV: the Renal-Bone Axis and ART

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Background

- Low bone mineral density (BMD) in people living with HIV (PWH) and receiving antiretroviral treatment (ART) is estimated to be over 3 times higher than in HIV uninfected individuals[1,2].
- Most data on low BMD in PWH are derived from younger adults and little is known about how ART and alterations in the renal-bone axis relate to BMD loss in older PWH.
- We explored the relative contribution of ART and alterations in renal and bone biomarkers to lower BMD in older PWH.

Methods

- **Design:** Sub-analysis of the **GS-US-104-0423** study: a Phase 4 Cross-Sectional, multicentre study of BMD in PWH.
- **Population:** HIV-1 positive men > 50 years and postmenopausal women on stable ART.
- ART was stratified into 4 groups based on always or never treated with tenofovir disoproxil fumarate (TDF) and/or protease inhibitors (PI): non-TDF+non-PI; non-TDF+PI; TDF+non-PI; TDF+PI.
- **Assessments:**

Bone and Renal Function	Markers analysed
BMD by dual X-ray absorptiometry	• BMD at Lumbar Spine (LS-BMD) • BMD at Femoral Neck (FN-BMD)
Renal Tubular Markers (Stored Urine Samples)	• Retinol binding protein - expressed as ratio to urine creatinine (RBP/Cr) • Carbonic anhydrase III - expressed as ratio to urine creatinine (CA3/Cr) • Fractional excretion of phosphate ($FEPO_4$)
Bone Turnover Markers (BTM) (Stored Blood Samples)	• Bone formation: - osteocalcin (OC) - procollagen type 1 amino-terminal propeptide (P1NP) • Bone Resorption: - C-terminal cross-linking telopeptide of type 1 collagen (CTX-1)
Markers of Bone Regulation (Stored Blood Samples)	• Osteoprotegerin (OPG) • Surface-bound receptor activator of nuclear factor kappa-B ligand (sRANKL) • Phosphatonin (FGF-23) • 25(OH) vitamin D • Parathyroid hormone (PTH)

- Low BMD was defined as T-score <-1.

- **Statistical analysis:**

- Differences in renal and bone parameters according to ART: Kruskal-Wallis tests for continuous variables and Chi-squared tests for comparison of categorical variables.

- Impact of ART exposure on BMD: Step-wise multivariable logistic regression models. ART exposure was first adjusted by demographic factors, BMI and current smoking status. Additional adjustment for bone and renal biomarkers was based on significant associations of these biomarkers with BMD on univariate testing.

Results

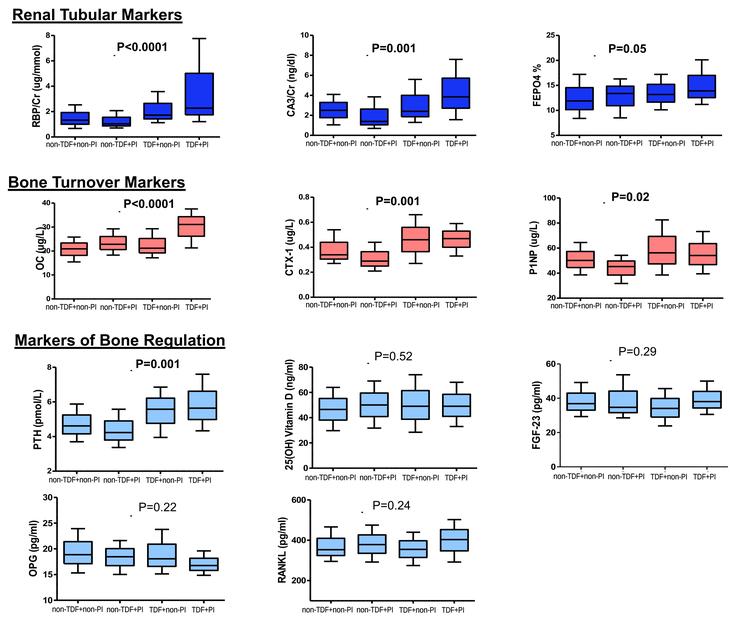
- Of 440 subjects recruited to the parent study, 247 individuals had available samples to contribute to this analysis.
- Median age 57 [IQR 53, 65] years, 47% female, 87% white, time on ART 10 [6, 16] years, CD4+ T-cell 643 [473, 811] cells/mm^3 and 98% with HIV RNA<200c/mL.
- Prevalence of low BMD at LS and FN was 55% and 60%, respectively (osteopenia: 38% and 50%, osteoporosis 17% and 10%).

Variables Median (IQR) unless stated	non-TDF+non-PI (N=79)	non-TDF+PI (N=50)	TDF+non-PI (N=64)	TDF+PI (N=54)
Age (years)	55 (53,65)	58 (54,65)	55 (52, 61)	53 (59, 63)
Female sex, N(%)*	43 (54)	14 (28)	37 (58)	21 (39)
Black ethnicity, N(%)	16 (20)	5 (10)	7 (11)	4 (7)
BMI (Kg/m^2)*	24.2 (22.0, 26.6)	24.2 (21.8, 26.1)	26.1 (23.3, 30.8)	26.4 (23.3, 28.4)
Current smoker, N(%)	16 (20)	16 (33)	16 (25)	19 (36)
CD4+ T- cell count (cells/mm^3)	667 (502, 818)	601 (444, 798)	643 (552, 854)	643 (406, 758)
HIV RNA <200 c/mL, N(%)	77 (97)	49 (98)	64 (100)	51 (96)
Time since HIV diagnosis (years)*	16.5 (13.5, 19.5)	16.5 (10, 23.5)	8.5 (6, 13.5)	7.5 (5.5, 11.5)
Time on ART (years)*	15 (12, 17)	13.5 (7, 18)	6 (5, 8.5)	6 (4, 8)
LS-BMD (g/cm^2)	1.03 (0.93, 1.15)	1.08 (0.95, 1.18)	1.01 (0.94, 1.11)	0.98 (0.88, 1.17)
T-score < -1 to -2.5 (%)	23 (29.9)	21 (47.7)	22 (37.3)	20 (41.7)
T-score < -2.5 (%)	10 (13)	8 (18.2)	14 (23.7)	8 (16.7)
FN-BMD (g/cm^2)	0.83 (0.73, 0.95)	0.86 (0.76, 0.98)	0.82 (0.73, 0.92)	0.83 (0.72, 0.94)
T-score < -1 to -2.5 (%)	32 (43.8)	24 (55.8)	23 (39.7)	31 (64.6)
T-score < -2.5 (%)	10 (14)	12 (24)	15 (23)	12 (22)

* Significant between-group differences

Renal and bone biomarkers stratified by ART group

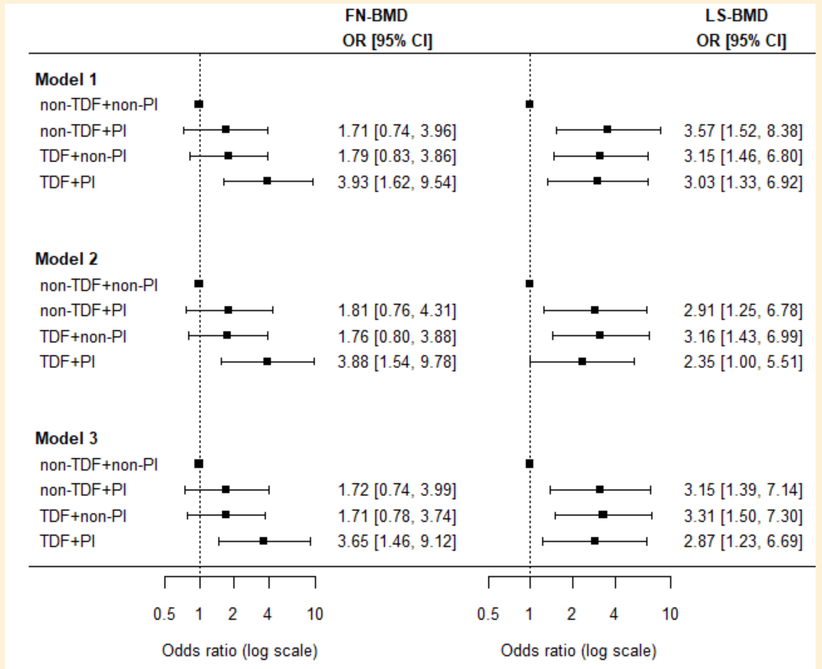
- Of the biomarkers examined, RBP/Cr, CA3/Cr, $FEPO_4$, OC, P1NP, CTX-1 and PTH differed significantly by ART group, with higher values in the TDF groups.



Comparison of renal and bone biomarkers stratified by ART group. Data are median (IQR)

Results

Impact of ART exposure on low BMD



Model 1: ART exposure adjusted by age, gender, ethnicity, BMI and current smoking; Model 2: Additional adjustment for OC, CTX-1 and PTH; Model 3: Additional adjustment for RBP/Cr

- Using non-TDF+non-PI as the ART reference group, exposure to TDF+PI was associated with 4 times greater risk of low FN-BMD and exposure to TDF and/or PI with 3 times greater risk of low LS-BMD, after adjustment for demographic factors, BMI and smoking (model 1). The observed association was not modified after correcting for time since HIV diagnosis and ART exposure.
- Of the biomarkers analysed, OC, CTX-1, PTH and RBP/Cr showed a negative correlation with BMD on univariate testing and were included in further models.
- The observed effect of ART on BMD was not modified after the inclusion of OC, CTX-1 and PTH in the model (model 2). Similarly, adjustment by RBP/Cr did not modify the observed association (model 3). None of these biomarkers remained associated with low BMD on the adjusted models.

Conclusions

- **Exposure to ART rather than levels of bone turnover or renal tubular markers best predicts low BMD in older PWH.**
- **Treatment with TDF/PI combined predicted low FN-BMD while TDF and/or PI predicted low LS-BMD.**
- **These data do not support routine measurement of biomarkers to predict low BMD in older PWH.**

References & Acknowledgments

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The authors gratefully acknowledge the investigators, study staff and all participant subjects. This study was funded by Gilead Sciences, Inc.