

Changes in Bone Turnover, OPG/RANKL, and Inflammation with ART Initiation: A Comparison of Tenofovir- and Non-Tenofovir-Containing Regimens

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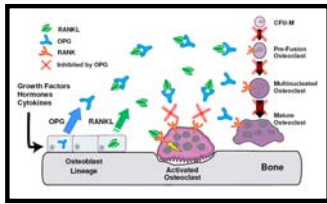
Background:

Bone mineral density decreases with antiretroviral therapy (ART) initiation, although the pathogenesis, including the role of tenofovir (TDF), is unclear.

Bone resorption and formation are normally coupled, and regulated through the interaction of osteoprotegerin (OPG), receptor activator for nuclear factor kappa B (RANK) and RANK ligand (RANKL). OPG and RANKL expression is influenced by inflammatory cytokines, hormones, and other factors (Figure 1).

The role of OPG/RANKL in ART-associated bone loss is not known.

Figure 1. OPG/RANKL in Bone Remodeling



Purpose:

cf. Ott, Endo Reviews, 2007

- To determine whether changes in bone turnover markers, OPG, and soluble RANKL differ in those initiating ART with TDF-containing regimens compared to those receiving other NRTIs

- To determine whether bone turnover is associated with OPG/RANKL or systemic inflammation.

Methods:

Study Population:

- HIV-infected Adults, ages 18-50 years
- ART-initiated while enrolled in the Case Western University CFAR cohort
- 50% initiated TDF-containing regimens.
- Subjects with concurrent treatment with bisphosphonates excluded

Biomarkers

- Assessed at 2 timepoints (prior to and 6-12 months after ART initiation)

Bone Turnover Markers:

- CTx: breakdown product of collagen (bone resorption marker)
- Osteocalcin (OC): bone matrix protein secreted by osteoblasts (bone formation marker)

Biomarkers

- OPG, sRANKL, calculated ratio of OPG/sRANKL
- Inflammatory Markers: soluble receptor TNF α I & II (sTNFR-I & sTNFR-II), IL-6

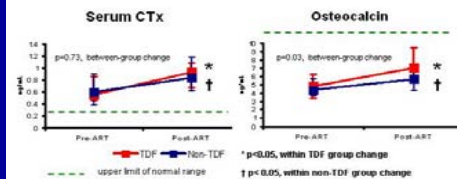
Statistical Analysis:

- Baseline characteristics compared by Mann-Whitney U or Chi-square Testing
- Change in biomarkers from pre-ART concentration by Wilcoxon testing
- Biomarkers log-transformed prior to multivariable regression analyses

Table 1: Subject Characteristics

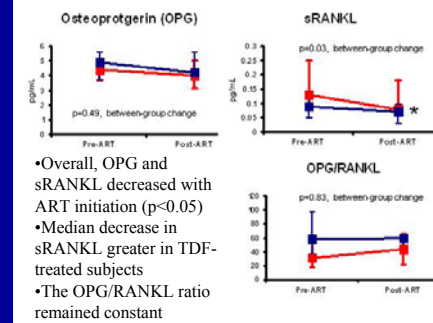
	TDF-Treated	Non-TDF Treated	p
n	44	43	
Age (years)	34 (30, 41)	37 (30, 44)	0.14
Race (% white)	41% (18)	33% (14)	0.42
% Male	75% (33)	77% (33)	0.85
Baseline Weight (kg)	74.4 (65.9, 81.1)	74.8 (66.1, 88.6)	0.55
% Smoking	71% (31)	56% (24)	0.16
% Current Etoh (> 2 units/day)	7% (3)	12% (5)	0.46
25 OH Vit.D (ng/mL)	22.6 (12.3, 31.5)	20.7 (13.4, 26.8)	0.50
Nadir CD4 (cells/mm ³)	91 (20, 232)	236 (148, 334)	0.0001
Post-ART CD4	331 (171, 474)	458 (262, 630)	0.003
Baseline Viral Load (copies/mL)	86400 (45316, 147500)	72759 (21575, 112381)	0.28
Post-ART VL < 400 copies/mL (n)	98% (43)	95% (41)	0.54
HIV Duration (months)	17.5 (3, 66)	12 (5, 36)	0.65
% PI	48% (21)	26% (11)	0.03
% LPV/r	2% (1)	9% (4)	0.16
% ATV	45% (20)	14% (6)	0.001
% FPV	0%	2% (1)	0.31
% AZT	0%	91% (39)	-
% ABC	0%	40% (17)	-
ART Duration prior to 2 nd Sample (days)	256 (214, 302)	238 (192, 260)	0.07

Figure 2: Bone Turnover Markers Before and After ART initiation with TDF and non-TDF Regimens (Median, Interquartile Range)



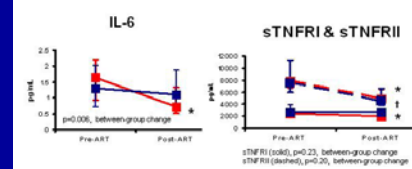
- Prior to ART initiation, 94% had CTx values and 1% had OC values above the normal range
- For the entire cohort, CTx increased by 41% (IQR: 5%, 87%) and OC increased by 33% (IQR: 8%, 88%).
- The median increase in OC was greater in TDF-treated subjects

Figure 3: OPG, sRANKL, and OPG/sRANKL Ratio with ART initiation



- Overall, OPG and sRANKL decreased with ART initiation (p<0.05)
- Median decrease in sRANKL greater in TDF-treated subjects
- The OPG/RANKL ratio remained constant

Figure 4: Inflammatory Markers with ART Initiation



- Median decrease in IL-6 greater in TDF-treated group, compared to non-TDF group
- sTNFR I decreased significantly in TDF-treated group, but not in the non-TDF group (Between-group difference not significant)
- sTNFR II decreased markedly and similarly in both groups

Table 2: The Relationship between OPG/RANKL, Inflammatory Markers and Bone Turnover

	% Change in CTx		% Change in OC	
	rho	p	rho	p
OPG	-0.08	0.47	-0.04	0.69
sRANKL	0.005	0.96	0.10	0.34
OPG/RANKL	-0.02	0.85	-0.11	0.32
Δ OPG	0.06	0.62	-0.13	0.24
Δ sRANKL	-0.17	0.11	-0.13	0.22
Δ OPG/RANKL	0.15	0.15	0.06	0.59
IL-6	0.08	0.45	0.32	0.003
sTNFR I	0.10	0.37	0.21	0.05
sTNFR II	0.02	0.87	0.27	0.01
Δ IL-6	-0.004	0.97	-0.07	0.52
Δ sTNFR I	-0.01	0.92	-0.18	0.09
Δ sTNFR II	-0.003	0.98	-0.17	0.12

- OPG, sRANKL, inflammatory cytokines at baseline or the changes in these markers were not related to the change in CTx
- only baseline inflammatory cytokines were related to change in OC

Table 3: Factors Associated with the Change in Bone Turnover Markers with ART Initiation*

3a. Factors Associated with Percent Change in CTx

	β	SE	p
Baseline CD4 < 50 cells/mm ³	41	18	0.03
Baseline CTx (per log difference)	-126	16	<0.001

3b. Factors Associated with Percent Change in OC

	β	SE	p
Age (per year difference)	-1.8	0.8	0.02
TDF (v. no TDF use)	34	14	0.02
PI (v. no PI use)	31	14	0.03
Baseline sTNFR I (per log difference)	54	16	0.001
Baseline OC (per log difference)	-117	16	<0.001

- Advanced HIV prior to ART initiation was associated with increases in CTx
- Younger age, TDF use, PI use, and higher baseline sTNFR I were associated with increases in OC

*all models adjusted for age, race, sex, pre-ART CD4 cell count, baseline weight, duration of ART prior to the second sample, TDF use, PI use, and baseline value of the bone turnover marker

Conclusions:

- Prior to ART initiation, bone resorption activity was high among young, untreated HIV-infected patients
- After 6-12 months of ART initiation, bone turnover increased markedly
- Changes in bone turnover were not associated with systemic concentrations of OPG or RANKL or changes in these markers
- Advanced HIV disease was associated with greater increases in bone resorption with ART initiation
- Tenofovir use, PI use, and higher baseline TNF α activity are independently associated with increases in osteocalcin with ART initiation.
- An acceleration of bone turnover with high levels of bone resorption may account for the decreases in bone mineral density with ART initiation observed in previous studies

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