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ARV naive HIV-infected adults had lower bone formation markers than HIV-uninfection

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INTRODUCTION

- Low bone mineral density (BMD) has been widely documented in HIV-infected patients, mostly from the western countries.
- Low BMD, osteoporosis, fracture risk and vitamin D deficiency were higher in HIV positive than HIV negative [1-8].
- Mechanisms of reduced BMD in HIV-infected patients remain unclear, but multifactorial plays a role: traditional risks, HIV-related chronic immune activation, HIV treatment (tenofovir disoproxil fumarate (TDF), and vitamin D deficiency [1-8]
- Although the international guidelines recommend to screen BMD in postmenopausal women, men aged >50 years, person with a history of low trauma fracture/ at high risk for falls, those with clinical hypogonadism, or taking oral glucocorticoids. However, this recommendation has not been widely applied in many resource limited settings.
- There are limited studies regarding bone health among HIV-infected patients from Asian countries, especially in females.

OBJECTIVE

To determine the prevalence and predictive factors of low BMD and vitamin D status in HIV-infected Thais who were not yet treated with ART, compared to HIV-uninfected control

METHODS

- The TNT-HIV 003 cohort was established in 2012 to evaluate the morbidity and mortality among HIV-infected patients from 3 sites in Thailand.
- Healthy subjects (free of diabetes, hypertension, active OI) aged ≥30 years, with and without HIV infection were enrolled.
- BMD at the lumbar spine (L1 to L4), femoral neck, and total hip as well as percentage of body fat were measured using Hologic DXA at the baseline and at 5 years.
- For this analysis, the data of BMD, serum 25-hydroxyvitamin D (25(OH)D) levels, and bone turnover markers (serum procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (OC) and C-terminal cross-linking telopeptide of type I collagen (CTX) at the patients' baseline visit were included.

RESULTS

- Data from a total of 571 participants were analyzed. Demographic and clinical characteristics of study population stratified by sex is presented in table1. None of them had fragile fracture, HCV infection, IVDU.
- HIV-infected patients were 1.5 years younger (men: 39.7±6 vs. 41.3±6 yr; women: 39.5±4 vs. 41.2±5 yr) and had lower BMI.
- Laboratory findings of the BMD substudy (N=296) is presented in Tables 2 and 3
  - Compared to HIV-uninfected controls, HIV-infected patients had higher mean serum 25-hydroxyvitamin D level but this was not correlated with BMD.
  - There were no differences in the actual BMD between subjects with and without HIV.
  - **The markers for bone formation, serum P1NP and osteocalcin were significantly lower in HIV-infected patients, particularly those with low CD4 count.**
- Only few participants were classified as having low bone mass
- Table 4: After adjusting for age and BMI, BMD continued to yield no differences between HIV-infected and HIV-uninfected women. On the other hand,age- and BMI-adjusted BMD became higher at the total hip and femoral neck in HIV-infected men compared to their control

Table 1. Demographic and clinical characteristics of study population stratified by sex

Characteristics	Male				Female			
	HIV- (n=127)	HIV+ CD4≥350 (n=85)	HIV+ CD4<350 (n=85)	P-value	HIV- (n=142)	HIV+ CD4≥350 (n=71)	HIV+ CD4<350 (n=61)	P-value
Age (years)	41.3(5.9)	40.1(6.3)	39.4(6.0)	0.07	41.2(5.0)	39.1(4.20)	40.0(4.1)	0.005
Weight (kg)	68.9(10.7)	64.3(8.7)	64.4(8.7)	<0.001	57.0(9.6)	56.8(9.8)	53.7(8.9)	0.07
BMI (kg/m^2)	24.1(3.4)	22.5(2.7)	22.5(2.7)	<0.001	23.3(3.9)	22.7(3.8)	22.3(3.6)	0.23
Body fat (%)	23.9(5.7)	20.7(5.7)	20.7(5.6)	<0.001	34.4(4.7)	31.3(5.3)	31.3(5.3)	0.003
Current location (% Bangkok)	60.0	60.5	36.5	-	62.7	34.0	27.6	-
Time of sun exposure (hours/week)	15 (10.5-23)	10.5 (6.3-17.5)	8.5 (3.5-12.5)	<0.001	5.5 (3.5-10.5)	8.5 (3.5-10.5)	5.5 (3.5-10.5)	0.65
Current smoker (%)	31(24.4)	21(24.7)	15(17.7)	-	9(6.3)	3(4.2)	4(6.6)	-
Alcohol (>1 drink /day)	27(21.3)	16(18.8)	14(16.5)	-	7(4.9)	5(7.0)	4(6.6)	-
Opioid or cocaine use ever	0(0)	0(0)	2(1.1)	-	0(0)	0(0)	1(1.6)	-
Calcium supplement	6(4.7)	0(0)	3(3.5)	-	4(2.8)	1(1.4)	2(3.3)	-
Multivitamins	19(15.0)	11(12.9)	11(12.9)	0.51	17(12.0)	5(7.0)	7(11.0)	0.53
HIV characteristics								
Years since HIV diagnosis (years)	-	5.1 (3.4-7.2)	4.0 (2.2-6.4)	0.16	-	5.9 (3.0-9.0)	6.1 (3.1-10.1)	0.68
CD4 at baseline (cells/mm^3)	-	488 (389-603)	210 (148-293)	<0.001	-	479 (429-557)	240 (156-293)	<0.001
HIV-1 RNA (log_{10}copies/ mL)	-	4.22(1.1)	4.80(0.9)	<0.001	-	4.01 (3.55-4.53)	4.94 (4.47-5.36)	<0.001

Data are reported as median (IQR), mean (SD), or number (percentage). Difference between the HIV-uninfected, HIV-infected (high CD4) and HIV-infected (low CD4) subjects were formally compared using ANOVA, Kruskal-Wallis, Chi-square test or Fisher's Exact test, as appropriate. HIV-, HIV-uninfected; HIV+, HIV-infected; BMI, body mass index

Table 2. Laboratory findings of the 296 patients in the substudy

Laboratory Results	Male				Female			
	HIV- (n=60)	HIV+ CD4≥350 (n=38)	HIV+ CD4<350 (n=52)	P-value	HIV- (n=67)	HIV+ CD4≥350 (n=29)	HIV+ CD4<350 (n=50)	P-value
Calcium (mg/dL)	9.76(0.3)	9.57(0.42)	9.48(0.48)	0.02	9.4(0.27)	9.4(0.39)	9.35(0.41)	0.60
iPTH (pg/mL)	50.4(21.3)	31.1(12.0)	36.4(14.4)	<0.001	41.9(17.5)	38.9(22.2)	33.9(16.0)	0.17
25(OH)D (ng/mL)	26.1(9.8)	32.1(12.8)	32.2(8.3)	0.003	20.7(6.2)	27.2(9.9)	31.9 (8.2)	<0.001
< 20, n (%)	14(23.3)	4(10.5)	2(3.85)	<0.001	34(50.8)	7(24.1)	2(4.0)	<0.001
20-30, n (%)	32(53.3)	13(34.2)	18(34.62)		26(38.8)	12(41.4)	18(36.0)	
>30, n (%)	14(23.3)	19(50)	27(51.92)		6(9.0)	10(34.5)	24(48.0)	
P1NP (ng/mL)	51.3(14.5)	48.2(16.2)	43.1(16.9)	<0.001	43.1(14.7)	36.0(11.0)	29.1(11.4)	<0.001
OC (pg/mL)	18.8(5.5)	15.5(5.7)	14.7(5.6)	<0.001	15.5(5.1)	12.4(3.6)	10.3(4.2)	<0.001
CTX (ng/mL)	0.38(0.14)	0.37(0.2)	0.31(0.13)	0.049	0.23(0.1)	0.24(0.11)	0.19(0.1)	0.09
Free androgen index (%)	61(18)	57(21)	57(18)	0.52	-	-	-	-

Data are reported as mean (SD) or number (percentage). Difference between the HIV-uninfected and the HIV-infected population was compared using ANOVA, Mann-Whitney two-sample statistic, where appropriate. Missing data for 25(OH)D levels: HIV-infected men, n=9; HIV-infected women n=6; HIV-uninfected women, n=1. HIV-, HIV-uninfected; HIV+, HIV-infected; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; P1NP, procollagen type 1 N-terminal propeptide ; OC; Osteocalcin; CTX, C-terminal cross-linking telopeptide of type I collagen

Table 3. Bone mineral density and classification according to the Z-score

Characteristics	Male				Female			
	HIV- (n=127)	HIV+ CD4≥350 (n=85)	HIV+ CD4<350 (n=85)	P-value	HIV- (n=142)	HIV+ CD4≥350 (n=71)	HIV+ CD4<350 (n=61)	P-value
Lumbar spine								
BMD (g/cm^2)	0.98(0.11)	0.97(0.13)	1(0.12)	0.10	1.00(0.11)	0.99(0.12)	1(0.11)	0.74
Z score								
Mean (SD)	-0.13(0.82)	-0.26(0.9)	0.26(0.92)	0.11	0.08(0.93)	-0.05(1.05)	0.08(0.93)	0.61
<-2SD	1(0.8)	2(2.4)	1(1.2)	0.11	2(1.4)	0(0.8)	1(1.64)	0.24
-2SD to -1SD	17(13.4)	16(18.8)	11(12.9)		16(11.3)	15(21.13)	7(11.48)	
Femoral neck								
BMD (g/cm^2)	0.80(0.11)	0.80(0.13)	0.83(0.13)	0.10	0.77(0.1)	0.77(0.1)	0.78(0.13)	0.85
Z score								
Mean (SD)	0.04(0.93)	0.02(1.04)	0.3(1.04)	0.10	0.08(0.89)	0.03(0.91)	0.14(1.06)	0.82
<-2SD	0(0.0)	1(1.18)	0	0.82	1(0.7)	0	1(1.64)	0.93
-2SD to -1SD	21(16.5)	13(15.3)	15(17.7)		18(12.7)	9(12.68)	8(13.11)	
>-1SD	106(83.5)	71(83.5)	70(82.4)		123(86.6)	62(87.32)	52(85.25)	

Table 4. Multivariate analysis for factors related to BMD

Site	HIV status	Absolute BMD (g/cm^2)	Adjusted [i] Mean difference	95% CI	P-value [i]
Men (n=305)					
Lumbar spine	uninfected	0.979(0.11)	ref	-	
	infected	0.987(0.13)	0.023	-0.004 to 0.051	0.09
Total hip	uninfected	0.924(0.12)	ref	-	
	infected	0.930(0.13)	0.031	0.003 to 0.059	0.03
Femoral neck	uninfected	0.797(0.11)	ref	-	
	infected	0.819(0.13)	0.038	0.009 to 0.066	0.009
Women (n=276)					
Lumbar spine	uninfected	1.000(0.11)	ref	-	
	infected	0.994(0.12)	-0.00001	-0.026 to 0.026	>0.99
Total hip	uninfected	0.900(0.10)	ref	-	
	infected	0.902(0.12)	0.013	-0.010 to 0.037	0.27
Femoral neck	uninfected	0.769(0.09)	ref	-	
	infected	0.771(0.11)	0.009	-0.014 to 0.032	0.43

[i] Adjusted for age and BMI, [i] P-value were estimated by linear regression

CONCLUSION

Middle-aged Thai patients with HIV infection, who were not yet on ART, did not have lower BMD or lower vitamin D levels, however, they had lower bone formation markers compared to the HIV-uninfected controls.

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