

BACKGROUND

- ART is associated with renal and bone toxicity, but little is known about the potential cumulative effects of ARV exposure from early in life into adulthood
- The incidence of chronic kidney injury in HIV has declined due to ART, although specific ARVs, such as tenofovir, can cause renal toxicity
- Microalbuminuria persists in the HIV-infected population along with abnormalities in bone density and osteoporosis
- Tenofovir has also been shown to decrease bone mineral density (BMD) and increase the rate of bone turnover

METHODS

- Subjects: 65 subjects infected with HIV in early life and 21 matched controls
- All subjects were >18 years old at last follow up visit
- Each participant completed a detailed clinic assessment including laboratory tests, physical exam, anthropometrics, and body composition measurements
- Dual-energy X-Ray absorptiometry (DEXA) was used for bone mineral density (BMD)
- Lifetime ART history was compiled for each HIV infected subject
- A longitudinal analysis was performed on 33 HIV infected subjects with longitudinal follow up data (mean= 4.4 years of follow up)
- A cross sectional analysis was performed between controls and HIV-infected subjects at their last follow up visit with a DEXA scan

Table 1. Demographics and Clinical Characteristics

	HIV+ (n=65)	Control (n=21)	P-value
Age (y)	23 (20, 27)	25 (22,27)	0.11
Sex, male (n, %)	25 (39)	10 (48)	0.46
Race			
Caucasian	24 (37)	11 (52)	0.54
African-American	33 (51)	9 (43)	
Other	8 (12)	1 (5)	
Ethnicity, Hispanic (n, %)	9 (14)	4 (19)	0.56
BMI (kg/m ²)	24.5 (21.9, 28.4)	24.8 (22.5, 28.8)	0.44
Height (cm)	165 (159, 169)	165 (160, 173)	0.23
Smoker ever (n, %)	18 (28)	4 (19)	0.41
Total Cholesterol (mg/dL)	164 (136, 178)	174 (155, 196)	0.05
Triglycerides (mg/dL)	87 (63, 130)	66 (54, 86)	0.04
Vitamin D deficiency (n,%)	21(38)	9 (43)	0.71
CD4 count (cells/ μ L)	542 (281, 805)	810 (646, 973)	0.002
HIV+ (n = 65)			
Currently on ARVs (n, %)	55 (85)		
Years on ARVs *	15.8 (12.4, 19.5)		
Years on PIs	9.8 (5.9, 13.8)		
Years on NNRTIs	2.7 (0, 7.7)		
Years on tenofovir (TDF)	3.1 (0, 6.6)		
Years on stavudine (d4T)	3.5 (0, 6.8)		
Years on didanosine (ddl)	4.12 (0.74, 5.86)		
HIV RNA < 40 (copies/mL) (n,%)	37 (57)		
HIV Viral Load (copies/mL)	5038 (1332, 60452)		
Perinatal Transmission (n, %)	54 (83)		

*Values are expressed as median (IQR) unless otherwise indicated

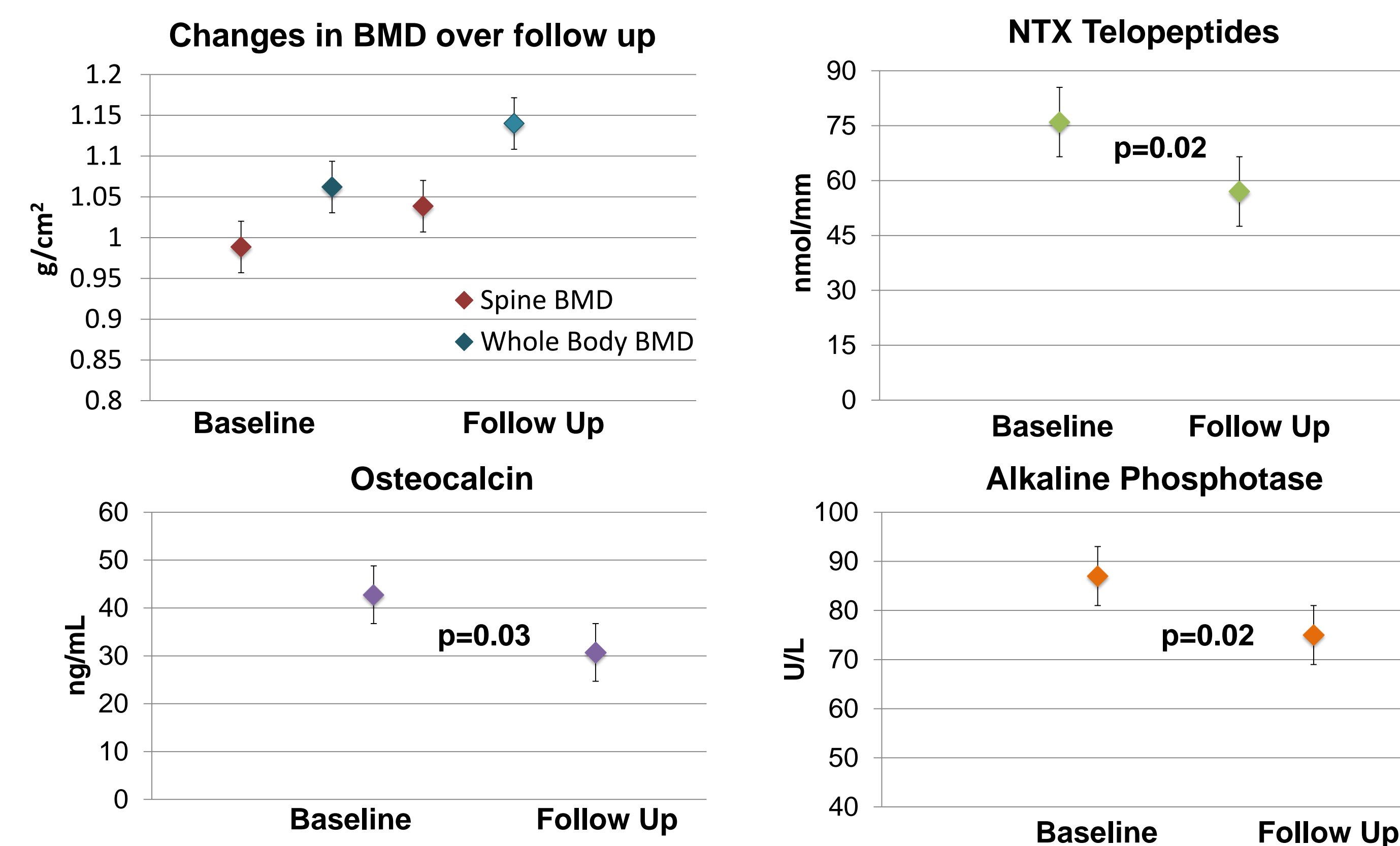
RESULTS

Longitudinal Results, HIV group only

Bone Density and Bone Parameters

- Whole Body BMD, Lumbar Spine BMD, and Whole body BMD Z-scores all increased from baseline to last follow up (p<0.0001, p=0.0001, p=0.001, respectively)
- Three subjects (9%) had a BMD Z-score < -2.0 at initial evaluation, but none had a Z-score < -2.0 at last follow-up
- NTX- telopeptides, osteocalcin, and alkaline phosphatase significantly decreased over time

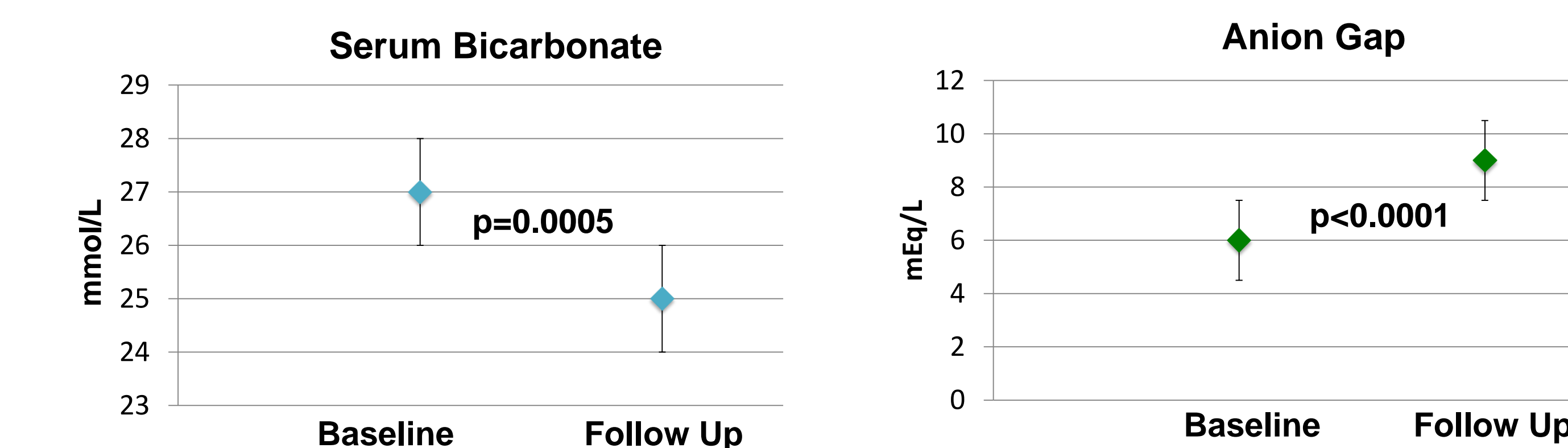
Figure 1. Changes in Bone Parameters



Renal Parameters

- eGFR, albumin/creatinine ratio, protein/creatinine ratio, and creatinine did not change
- Increasing years on TDF and increasing CD8 T cells correlated with decline in eGFR (r=-0.43, p=0.02 and r=-0.41, p=0.02, respectively)
- The anion gap increased significantly, and serum bicarbonate decreased significantly
- Increasing anion gap correlated with increasing protein/creatinine ratio (r=0.48, p=0.01) and increasing years of TDF exposure (r=0.37, p=0.04)

Figure 2. Changes in Renal Parameters



Cross Sectional Results at last follow up, HIV group vs. Control

- The HIV group had lower whole body BMD, and BMD Z-scores, but only one HIV infected subject had whole body BMD Z-score < -2
- Longer duration of ddl and d4T exposure correlated with lower whole body BMD (r=-0.28, p=0.03 and r=-0.28, p=0.03 respectively) and BMD Z-scores (r=-0.32, p=0.01 and r=-0.29, p=0.03, respectively)
- Duration of ddl exposure also correlated with lower lumbar spine BMD and Z-scores (r=-0.29, p=0.04 and r=-0.35, p=0.01, respectively)
- Within the HIV group, lower eGFR correlated with increased CD8 T cells (r=-0.26, p=0.04)
- Years on TDF correlated with higher anion gap (r=0.34, p=0.008), but did not correlate with any bone markers

Table 2. Cross Sectional Results

	HIV+ (n=65)	Control (n=21)	P-value
Bone Density			
Whole Body BMD (g/cm ²)	1.15 (1.08, 1.22)	1.21 (1.15, 1.28)	0.008
Whole Body BMD Z-Score	-0.1 (-1, 0.7)	0.4 (-0.2, 1.6)	0.01
Lumbar Spine BMD (g/cm ²)	1.03 (0.94, 1.14)	1.07 (0.97, 1.12)	0.41
Lumbar Spine Z-Score	-0.5 (-1.3, 0.4)	-0.3 (-0.9, 0.3)	0.57
Bone Parameters			
25-hydroxyvitamin D (ng/mL)	23 (16, 32)	21 (17, 34)	0.97
NTX-Telopeptides (nmol/mm)	52 (34, 70)	33 (21, 57)	0.03
Alkaline Phosphatase (U/L)	76 (62, 93)	67 (51, 82)	0.02
Osteocalcin (ng/mL)	30.1 (23.4, 39.6)	22.1 (16, 25.5)	0.007
Parathyroid Hormone (pg/mL)	40 (34.3, 53.4)	34.4 (29.6, 38.7)	0.02
Phosphorus, Inorganic (mg/dL)	3.3 (3, 3.7)	3.6 (3.2, 4)	0.08
Calcium (mmol/L)	2.27 (2.18, 2.35)	2.31 (2.28, 2.38)	0.04
Renal Parameters			
eGFR (mL/min/1.72m ²)	129 (116, 142)	118 (113, 128)	0.02
Proteinuria (n, %)	2 (3)	0 (0)	0.40
Microalbuminuria (n, %)	5 (9)	2 (10)	0.85
U. Albumin/Creatinine Ratio (mg/g)	6.9 (4.6, 15.3)	4.6 (2.9, 6.4)	0.006
U. Protein/Creatinine Ratio (mg/mg)	0.13 (0.11, 0.17)	0.09 (0.08, 0.14)	0.008
Creatinine (mg/dL)	0.71 (0.64, 0.84)	0.78 (0.72, 0.95)	0.03
Anion Gap (mEq/L)	10 (9, 13)	8 (7, 11)	0.004
Bicarbonate (mmol/L)	25 (23, 26)	27 (24, 29)	0.009
Glucosuria (n, %)	2 (3)	1 (5)	0.78

CONCLUSIONS

Bone

- Subjects with lifelong HIV and extensive ARV exposure had decreased bone density and evidence of dysfunctional bone formation associated with cumulative ddl and d4T exposure.
- There was a tendency for improvements in bone health over time. Longitudinal analyses suggested a normalization of bone density in the HIV group.

Renal

- Microalbuminuria, proteinuria and low eGFR were uncommon in both groups.
- Subclinical markers of renal dysfunction were increased in the HIV infected group and correlated with exposure to TDF.