Poster 683

Switching from TDF To TAF in HIV-Infected Adults With Low BMD: A Pooled Analysis

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Background

- Studies have demonstrated that some antiretroviral therapies (ART) may contribute to osteoporosis and fracture risk in HIV-infected individuals
- With ART initiation, use of tenofovir disoproxil fumarate (TDF) compared to non-TDF regimens leads to greater bone mineral density (BMD) decline associated with a marked increase in bone turnover[1,2]
- The mechanisms underlying TDF-related BMD loss are not clear, but may include the effects of renal phosphate wasting
- Switching off of TDF to abacavir or raltegravir may improve BMD in those with low BMD, but data are limited[3,4]
- Switching from TDF to tenofovir alafenamide (TAF) has also been associated with improvement in BMD, but this strategy has not been investigated specifically in those with low BMD

Objectives

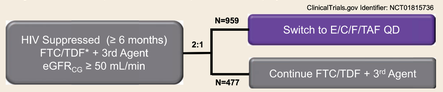
- To determine the percentage BMD change and absolute T-score change at the lumbar spine and total hip over 96 weeks in HIV-infected individuals with low BMD switching from TDF to TAF
- To determine baseline (pre-switch) factors associated with a clinically significant change (≥ 5% increase) in lumbar spine and total hip over 96 weeks[5] after switching from TDF to TAF in participants with low BMD

Methods

- This analysis consisted of pooled data from two prospective Phase 3 studies (Studies 109 and 112) of HIV suppressed adults who met two key criteria at study entry (Figure 1)
  - On a TDF-containing regimen and switched to elvitegravir, cobicistat, and emtricitabine co-formulated with TAF (E/C/F/TAF)
  - Presence of clinically significant low BMD (as defined by a T-score ≤ -2.0 at either the lumbar spine, total hip or femoral neck)

Figure 1. Study Design

Study 109: Phase 3, multi-centered, randomized, open label



In Study 109, 959 participants switched from a TDF-containing regimen to E/C/F/TAF

*At study entry, participants had been on a TDF-containing regimen for at least 96 weeks

Study 112: Phase 3, multi-centered, single-arm, open label

In Study 112, 158 participants switched from a TDF-containing regimen to E/C/F/TAF

*At study entry, participants on a TDF-containing regimen had been on it for at least 24 weeks

Studies 109 and 112 Pooled:
1117 participants switched from a TDF-containing regimen to E/C/F/TAF

Methods (cont'd)

- Bone mineral density were assessed by Dual Energy X-ray Absorptiometry (Lunar and Hologic)
- DEXA results (baseline, Week 48, and Week 96) were analyzed centrally by BioClinica, Newton, PA
- T-score adult reference population: NHANES (1998)
  - Normal (T-score ≥ -1.0), osteopenia (T-score > -2.5 to < -1.0), or osteoporosis (T-score ≤ -2.5)
  - Clinically significant low BMD at baseline was defined as T-score ≤ -2.0 at the lumbar spine, total hip or femoral neck
  - BMD clinical status at each visit was defined by the lowest T-score at the lumbar spine, total hip, and femoral neck for each participant
- Week 96 BMD endpoints
  - Percentage BMD change and absolute T-score change at the lumbar spine and total hip (Wilcoxon Signed Rank Tests)
  - Change in BMD clinical status (normal, osteopenia, or osteoporosis)
- Other baseline assessments
  - Body mass index (weight (kg)/height (m^2))
  - Estimated glomerular filtration rate by Cockcroft-Gault equation
  - CD4 cell count
  - Fractional excretion of phosphate (FEO_4) was measured by concurrent collection of urine (U) and serum (S) phosphate (PO_4) and creatinine (Cr)

$$FEPO_4 = \frac{SCr\ (mg/dL) \times UPO4\ (mg/dL)}{SPO_4\ (mg/dL) \times UCr\ (mg/dL)} \times 100\%$$

- Bone turnover markers assessed included Procollagen 1 Intact N-terminal Propeptide (P1NP) and C-terminal telopeptide (CTX)
- Proteinuria was measured by urine dipstick
  - On urine dipstick, none or trace protein is grade 0, 1+ is grade 1, 2-3+ is grade 2, 4+ is grade 3 proteinuria
- Multivariate logistic regression models were used to determine baseline predictors of a clinically significant improvement (outcome: ≥ 5% increase at Week 96) in lumbar spine and total hip BMD
- Models were adjusted for age (stratified by 10-year intervals), race (Black vs. Non-Black), sex, BMI, and spine or hip BMD (g/cm^2 as continuous variable) plus the following covariates that were independently associated with the outcome (based on P < 0.10)
  - $eGFR_{CG}$ < 60 vs. ≥60 mL/min*
  - Proteinuria Grade 1-3 vs Grade 0
  - $FEPO_4$ <10%, 10-20%, and > 20%
  - PINP levels (log-transformed and stratified based on tertiles)
  - CTX levels (log-transformed and stratified based on tertiles)***
  - Current smoker**
  - Consume ≥3 alcoholic drinks per day***
  - Baseline CD4 cell count (<350, 350 to <500, ≥500 cells/μL)***
  - Protease inhibitor use***
- Analyses were done using SAS® (SAS Institute Inc., Cary, NC, USA)

Covariates with P > 0.10

*Excluded from the lumbar spine final models

**Excluded from the total hip final models

***Excluded from lumbar spine and total hip final models

Results

- 1117 participants suppressed on a TDF-containing regimen from Studies 109 and 112 switched to E/C/F/TAF at study entry
- At baseline, 214 (19%) participants suppressed on a TDF-containing regimen had clinically significant low BMD
- Baseline demographics and disease characteristics (Table 1)
  - Baseline median (Q1,Q3) T-score from the lowest T-score at lumbar spine, total hip, and femoral neck: -2.40 (-2.82, -2.18)

Results (con't)

Table 1. Baseline Characteristics of Participants with Low BMD

	Total N =214
Age, Median (Range) Years	46 (22-77)
<30	12%
≥30 to <40	21%
≥40 to <50	30%
≥50 to <60	26%
≥60	11%
Black Race	15%
Non-Black Race	84%
Sex (female)	15%
Body Mass Index, kg/m²	
<25 (Normal)	66%
25 to <30 (Overweight)	24%
≥30 (Obese)	9%
Current Smoker	26%
Protease Inhibitor Use	50%
Consume ≥3 Alcoholic Drinks/Day	4%
CD4 Cell Count < 350 Cells/μL	10%

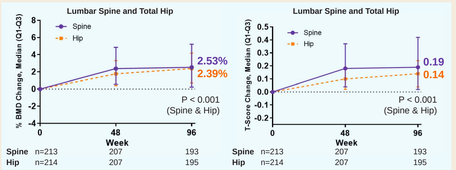
Lumbar Spine	
Median (Q1, Q3) BMD, g/cm^2	0.882 (0.827, 0.957)
Median (Q1, Q3) T-score	-2.23 (-2.64, -1.88)
Total Hip	
Median (Q1, Q3) BMD, g/cm^2	0.837 (0.776, 0.888)
Median (Q1, Q3) T-score	-1.62 (-2.02, -1.25)
Femoral Neck	
Median (Q1, Q3) BMD, g/cm^2	0.741 (0.653, 0.807)
Median (Q1, Q3) T-score	-2.05 (-2.35, -1.47)
CTX (log_{10} ng/mL)	0.58 (0.49, 0.67)
P1NP (log_{10} ng/mL	1.80 (1.67, 1.89)
$eGFR_{CG}$ <60 mL/min	18%
Dipstick Proteinuria (Grade 1-3)	18%
$FEPO_4$	
<10%	32%
10% to 20%	50%
>20%	18%

2.8% (N=6) of participants were on a bisphosphonate at baseline

- Proportion with osteoporosis at baseline (T-score ≤ -2.5 based on the lowest T-score at lumbar spine, total hip, or femoral neck): 43% (93/214)

Figure 2. Changes in BMD (%) and in T-Score Through Week 96

A. Changes in BMD **B. Changes in T-Score**



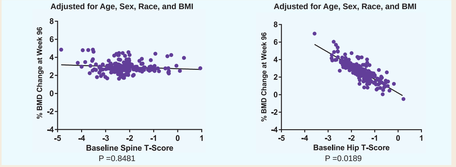
Spine	n=213	207	193
Hip	n=214	207	195

P value for the change from baseline in BMD (%) or T-score at Week 96 (Wilcoxon Signed Ranked Test).

- After adjustment for age, race, sex, and BMI
  - There was no significant association between the % BMD increase at Week 96 and baseline T-score at the lumbar spine (Figure 3A)
  - Greater % BMD increase at Week 96 was significantly associated with lower baseline (study entry) T-score at the total hip (Figure 3B)

Figure 3. Change in % BMD at Week 96 vs. Baseline T-Score

A. Lumbar Spine BMD **B. Total Hip BMD**



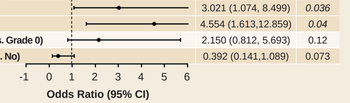
P values assess the association between baseline T-score and % BMD change at Week 96, after adjusting for age, sex, race, and BMI.

Proportion of participants with ≥5% increase in BMD at Week 96
- Lumbar Spine: 27% (52/193)
- Total Hip: 16% (32/195)

Figure 4. Multivariate Logistic Regression Models For ≥5% Increase in Bone Mineral Density at Week 96

A. Lumbar Spine BMD

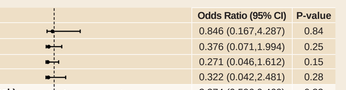
	Odds Ratio (95% CI)	P-value
Age (vs. <30 years)		
30 to <40	0.517 (0.132, 2.033)	0.35
40 to <50	0.536 (0.144, 1.989)	0.35
50 to <60	0.479 (0.108, 2.132)	0.33
≥60	1.093 (0.226, 5.272)	0.91
Race (Black vs. non-Black)	0.778 (0.224, 2.705)	0.69
Sex (Female vs. Male)	0.525 (0.166,1.666)	0.27
Body Mass Index (vs. <25 kg/m²)		
25 to <30	1.320 (0.557, 3.129)	0.53
≥30	5.359 (1.587, 18.098)	*0.007*
Lumbar Spine BMD (g/cm²)	1.940 (0.061, 61.827)	*0.71*
$FEPO_4$ (vs. <10%)		
10% to 20%	1.188 (0.487, 2.900)	0.70
>20%	2.167 (0.691, 6.800)	0.18
P1NP level (vs. ≤1.72 log_{10} ng/mL)		
>1.72 to 1.85	3.021 (1.074, 8.499)	*0.036*
>1.85	4.554 (1.613,12.859)	*0.04*
Proteinuria (Grade 1-3 vs. Grade 0)	2.150 (0.812, 5.693)	0.12
***Current Smoker (Yes vs. No)**	0.392 (0.141,1.089)	0.073



*Current smokers tended to be less likely to have a ≥5% increase in lumbar spine BMD since P >0.05.

B. Total Hip BMD

	Odds Ratio (95% CI)	P-value
Age (vs. <30 years)		
30 to <40	0.846 (0.167,4.287)	0.84
40 to <50	0.376 (0.071,1.994)	0.25
50 to <60	0.271 (0.046,1.612)	0.15
≥60	0.322 (0.042,2.481)	0.28
Race (Black vs. non-Black)	2.374 (0.596,9.460)	0.22
Sex (Female vs. Male)	1.683 (0.484,5.854)	0.41
Body Mass Index (vs. <25 kg/m²)		
25 to <30	0.540 (0.170,1.714)	0.30
≥30	2.547 (0.521,12.451)	0.25
Total Hip BMD (g/cm²)	0.006 (0.000,1.663)	0.075
$FEPO_4$ (vs. <10%)		
10% to 20%	4.151 (1.145,15.050)	*0.030*
>20%	14.541 (3.044,69.463)	*<0.001*
P1NP level (vs. ≤1.72 log_{10} ng/mL)		
>1.72 to 1.85	1.703 (0.490,5.922)	0.40
>1.85	1.986 (0.600,6.568)	0.26
Proteinuria (Grade 1-3 vs. Grade 0)	1.848 (0.577,5.917)	0.30
$eGFR_{CG}$ (<60 vs. ≥60 mL/min)	1.210 (0.298,4.908)	0.79



92% (86/93) of participants with osteoporosis (T-score ≤ -2.5) at baseline had BMD data at Week 96:
- 77% (66/86) maintained the osteoporosis clinical status
- 23% (20/86) no longer met criteria for osteoporosis (all had osteopenia)
  - The result remained the same when the analysis was restricted to participants who did not use a bisphosphonate during the study period

- Covariates independently associated (P < 0.10) with ≥ 5% BMD increase at Week 96 (after adjustment for age, race, sex, and BMI)
  - At the lumbar spine and total hip
    - Higher $FEPO_4$, higher P1NP levels, proteinuria (grade 1-3)
  - Only at the lumbar spine or total hip
    - Lumbar spine: Not a current smoker
    - Total hip: $eGFR_{CG}$ < 60 mL/min
- In multivariate logistic regression analyses (Figure 4)
  - Higher BMI (≥30 kg/m^2) and P1NP levels (>1.72 log_{10} ng/mL) levels were associated with ≥ 5% BMD increase at the lumbar spine (Figure 4A)
  - Higher $FEPO_4$ (≥ 10%) was associated with ≥ 5% BMD increase at the total hip (Figure 4B)

Conclusions

- HIV-infected individuals with clinically significant low BMD on a TDF-containing regimen who switched to E/C/F/TAF experience
  - ~2.5% lumbar spine and/or total hip BMD increase over 96 weeks
  - ≥5% BMD increases in some individuals (27% lumbar spine; 16% total hip)
  - a reversion from osteoporosis in approximately 1/4th of patients
- Switching from TDF to TAF may be an important treatment strategy to increase bone mineral density in those at the highest fracture risk
- Baseline urinary phosphate wasting or high bone turnover may identify TDF-treated HIV-infected patients with low BMD who may benefit the most from a switch to TAF

References

1. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224 s, a substudy of ACTG A5202. J Infect Dis 2011; 203:1791–1801
2. Moyle GJ, Stellbrink HJ, Compston J, Orkin C, Arribas JR, Domingo P, et al. 96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study. Antivir Ther. 2013;18(7):905-13.
3. Negredo E, Domingo P, Perez-Alvarez N, Gutierrez M, Mateo G, Puig J, et al. Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: two-centre randomized pilot study (Osteo?DF study). J Antimicrob Chemother 2014; 69:3368–3371.
4. Bloch M, Tong WW, Hoy J, Baker D, Lee FJ, Richardson R, et al. Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks. HIV Med 2014; 15:373–380.
5. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res 2000;15:1965-73.

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