Bone Changes With TDF-containing and Non-TDF-containing Prep in U.S. Men and Women

Todd T Brown[1], Tim Wilkin[2], Kenneth H Mayer[3], Raphael J Landovitz[4], Ying Q Chen[5], Jing Wang[6] Alicia Young[6], Mark A Marzinke[1], Wairimu Chege[7], Marybeth McCauley[8], Roy M Gulick[2]

[1]Johns Hopkins University, Baltimore, MD, [2]Weill Cornell Medicine, New York, NY, [3]Fenway Health, Boston, MA, [4]UCLA Center for Clinical AIDS Research & Education, Los Angeles, CA, [5]Fred Hutchinson Cancer Research Center, Seattle, WA, [6]Statistical Center for HIV/AIDS Research and Prevention, Seattle, WA, [7]National Institute of Allergy and Infectious Diseases, Bethesda, MD, [8]FHI 360, Washington, DC

BACKGROUND

- Pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) is highly effective in reducing incident HIV infection in high risk populations.
- While generally well-tolerated, TDF-containing PrEP has been associated with decreases in bone mineral density (BMD) in men and women.
- The magnitude of the bone loss with TDF-containing PrEP is dependent on PrEP adherence.
- Due to long-term toxicities of TDF-containing PrEP regimens, the development of non-TDF PrEP alternatives is warranted. However, BMD effects of non-TDF-containing PrEP regimens have not been reported.
- HPTN 069/ACTG 5305 showed similar tolerability of four different daily PrEP regimens: (1) maraviroc 300 mg (MVC); 2) MVC 300 mg plus FTC 200 mg; (3) MVC 300 mg plus TDF 300 mg; or (4) TDF 300 mg plus FTC 200 mg.
- Here, we report the BMD results of HPTN 069/ACTG 5305 and explore factors that are associated with BMD loss in those randomized to TDF-containing PrEP.

METHODS

STUDY POPULATION

- HIV-uninfected men, transgender women (TGW) and cisgender women at 13 sites in the United States and Puerto Rico were enrolled. Dual-energy x-ray absorptiometry (DXA) scanning was offered to the first 200 men/TGW and all cisgender women.
- Two different study populations were assessed in this analysis:
  1. The modified intent to treat (mITT) population included participants who were randomized to treatment and had DXA results available at baseline and 48 weeks, regardless of whether the participant was receiving study medications through week 48.
  2. The Adherence Subset included those participants in the mITT population who had study drug levels measured and had detectable levels at 24 and 48 weeks.
- Study Arms were collapsed into TDF-containing and non-TDF-containing arms.

CLINICAL AND LABORATORY ASSESSMENTS

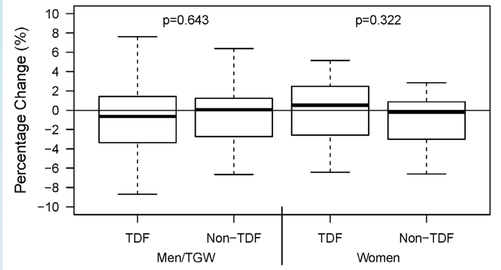
- Problem alcohol use was defined as an affirmative response to the question, “Have you ever tried and failed to control, cut down, or stop using alcohol? “.
- Popper and methamphetamine use were defined as any use in the previous 3 months.
- 25-OH vitamin D was assessed by local laboratories. Deficiency defined as < 20 ng/mL.
- Hypophosphatemia on study was defined as ≥ grade 2 (< 2.0 mg/dL) at week 24 or week 48.
- MVC, FTC, and tenofovir (TFV) were quantified via validated liquid-chromatographic-tandem mass spectrometric (LC-MS/MS) methods, with assay limits of quantitation of 0.5 ng/mL (MVC) and 0.3 ng/mL (FTC, TFV).
- BMD was measured at the lumbar spine and hip by dual-energy x-ray absorptiometry (DXA) and centrally read. Z-scores were calculated from the site-specific BMD measures using normative data matched for age, sex and race.

STATISTICAL ANALYSIS

- Wilcoxon signed rank tests were used to test the median difference of percentage BMD change between the two treatment groups, stratified by the sex.
- Linear regression was used to test associations between baseline and on treatment factors and percentage BMD change.

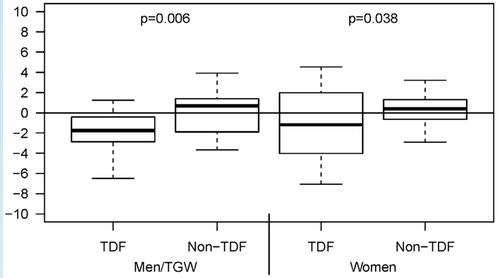
RESULTS

Figure 1. Changes in Spine BMD over 48 weeks with TDF and Non-TDF PrEP: Adherence Subset



- At the lumbar spine, median (Q1, Q3) of BMD change was -0.11% (-2.91%, 2.02%) in the TDF arm and was -0.15% (-2.74%, 1.22%) in the Non-TDF arm (between arm p=0.73).
- Results were similar in men and women (Figure 1).
- Results were similar in the mITT population (data not shown).

Figure 2. Changes in Hip BMD over 48 weeks with TDF and Non-TDF PrEP: Adherence Subset



- At the total hip, median (Q1,Q3) of BMD change was -1.46% (-3.28%, 0.52%) in the TDF arm and was 0.52% (-1.40%, 1.37%) in Non-TDF arm (between arm p=0.0006).
- Results were similar in men and women (Figure 2).
- Results were similar in the mITT population (data not shown).

RESULTS

Table 1: Baseline Characteristics of Study Population with DXA (N=307)

	Men/TGW		Total	Women		Total
	TDF	Non-TDF	Total	TDF	Non-TDF	Total
N	88	84	172	71	64	135
Age (years) Mean (SD)	34 (10.8)	32 (10.1)	33 (10.5)	39 (11.2)	37 (11.2)	38 (11.2)
Race: Black (%)	24%	30%	27%	66%	63%	64%
BMI Mean (SD)	27 (5.8)	27 (4.9)	27 (5.3)	32 (8.1)	31 (7.1)	31 (7.6)
Lumbar spine Z-score						
Median	-0.6	-0.4	-0.5	0.2	0.3	0.2
(Q1,Q3)	(-1.5, 0.4)	(-1.1, 0.6)	(-1.3, 0.4)	(-0.5, 1.3)	(-0.5, 1.1)	(-0.5, 1.2)
Total hip Z-score						
Median	-0.3	-0.4	-0.3	0.4	0.2	0.3
(Q1,Q3)	(-0.9, 0.4)	(-1.1, 0.2)	(-0.9, 0.3)	(-0.7, 1.2)	(-0.3, 1.1)	(-0.5, 1.1)
Femoral neck Z-score						
Median	-0.1	-0.4	-0.3	0.2	0.0	0.1
(Q1,Q3)	(-0.8, 0.5)	(-1.0, 0.5)	(-0.9, 0.5)	(-0.8, 1.0)	(-0.7, 0.8)	(-0.7, 0.9)

Table 2: Characteristics of Adherence Subset (N=135)

	TDF	Non-TDF	Total	p
N	71	64	135	
Baseline				
Age , years Median (Q1,Q3)	32 (27, 45)	33 (27, 44)	32 (27,44)	0.86
Men, %	49%	58%	53%	0.32
Race: % Black	47%	36%	42%	0.22
BMI, Median (Q1,Q3)	28 (24, 33)	27 (24,31)	28 (24,32)	0.75
Problem alcohol use	7%	10%	8%	0.64
Popper Use in last 3 months	21%	19%	20%	0.77
Methamphetamine Use	3%	13%	8%	0.045
25 OH Vitamin D < 20 ng/mL, %	38%	34%	36%	0.66
On Treatment				
Receiving MVC	45%	100%	71%	<.0001
Hypophosphatemia (< 2 mg/dL)	9%	8%	8%	0.89

Table 3. Univariate Associations with Percentage Change in BMD in TDF Adherence Subset

	Lumbar Spine		Total Hip	
	Est (%)	p	Est (%)	p
Age<25 y	-.50 [-3.1,2.10]	0.70	0.11 [-3.1,3.31]	0.95
Sex (Male)	-.74 [-2.5,1.00]	0.40	-.19 [-2.2,1.85]	0.85
Race (Black)	1.21 [-.52,2.94]	0.17	-1.4 [-3.4,0.64]	0.18
BMI≥25 kg/m²	-1.9 [-3.8,-.09]	0.04	0.96 [-1.2,3.16]	0.39
Problem Alcohol Use	0.14 [-3.3,3.55]	0.93	-1.9 [-5.9,2.05]	0.34
Popper Use	1.54 [-.61,3.68]	0.16	0.37 [-2.2,2.91]	0.77
Methamphetamine Use	1.09 [-4.1,6.30]	0.68	0.26 [-5.8,6.37]	0.93
25 OH Vit D < 20 ng/mL	-.60 [-2.4,1.20]	0.51	0.44 [-1.7,2.54]	0.68
Receiving MVC	-.74 [-2.5,1.01]	0.40	-.05 [-2.1,2.00]	0.96
Hypophosphataemia	-.19 [-3.3,2.92]	0.90	-2.0 [-5.6,1.63]	0.28

- Higher BMI (≥ 25 kg/m²) associated with greater BMD loss at lumbar spine
- No other baseline or on-treatment factors were associated with BMD loss at the lumbar spine or hip

CONCLUSIONS

- TDF-containing PrEP was associated with significantly greater bone loss at the hip, but not the lumbar spine, compared to non-TDF PrEP (MVC alone and MVC+FTC arms).
- No differences were observed between the effect of TDF on BMD in men and women, although baseline BMD was lower in men.
- Vitamin D deficiency at baseline or hypophosphatemia on treatment were not associated with bone changes in those randomized to TDF-containing PrEP.
- MVC±FTC PrEP may have better bone safety compared to TDF-containing PrEP.

2017 CROI Conference
Seattle, WA, USA

- **Women were older, more likely to be Black, and had a higher BMI than men.**
- **Men, but not women had a low BMD at baseline (Z-scores < 0).**

The HPTN is sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), the US National Institute of Mental Health, and the US National Institute on Drug Abuse, all components of the US National Institutes of Health. The ACTG is sponsored by NIAID. The authors would also like to recognize the participants, their partners and families, as well as the study team, the pharmaceutical sponsors who provided study drugs (ViiV HealthCare and Gilead) and the study staff at the following participating sites: Case Western Reserve, Cleveland, OH, ; Fenway/Harvard Medical School, Boston, MA,; George Washington University, Washington, DC; Johns Hopkins University, Baltimore, MD; New Jersey Medical School, Newark, NJ; University of California, Los Angeles, CA; University of North Carolina, Chapel Hill, NC; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburgh, PA; University of Puerto Rico, San Juan, PR; University of Washington, Seattle, WA; and Weill Cornell Medicine, New York, NY.

Poster Number: 981