Combined Effects of Bisphosphonates and TDF→TAF Switch in HIV+ Adults With Low BMD

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Introduction

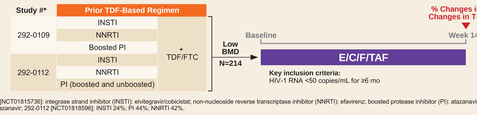
- Fracture risk is higher in people living with HIV and is, in part, due to low bone mineral density (BMD)[1]
- Use of tenofovir disoproxil fumarate (TDF) has been associated with low BMD
- BMD improves by 2–3% over a 2–3-y time frame in HIV-1–infected adults who switch from TDF to tenofovir alafenamide (TAF)[2,3]
- Bisphosphonates (BP) are the 1st-line treatment to prevent fractures in HIV-infected persons with low BMD or other risk factors for fracture and have been shown in this population to increase BMD by 8% at the lumbar spine and ~4% at the total hip at 2 years[4]
- Because of uncertainty about the safety of long-term use, a 3–5 year course of BPs is recommended with re-evaluation at that time
- For some individuals, a strategy of switching off of TDF in combination with BP initiation may be preferred, but it is unclear how changes in BMD with this combined strategy compare with changes with switching off of TDF alone

Objectives

- To evaluate % change in BMD, and changes in T-scores at the lumbar spine and total hip in BP vs non-BP users over 144 wk
- To evaluate the effect of BP use on bone outcomes independent of age, race, sex, baseline smoking status, body mass index (BMI), and BMD with linear regression and inverse probability of treatment weights (IPTW)

Methods

Study Design

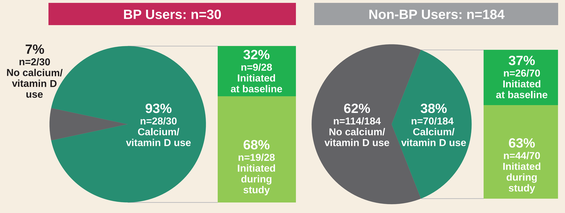


*292-0109 [NCT01815736]: integrase strand inhibitor (INSTI): elvitegravir/cobicistat; non-nucleoside reverse transcriptase inhibitor (NNRTI): efavirenz; boosted protease inhibitor (PI): atazanavir/cobicistat or ritonavir-boosted atazanavir; 292-0112 [NCT01818596]: INSTI 24%; PI 44%; NNRTI 42%.

- Data were pooled from 2 prospective, 144-wk, Phase 3 studies of virologically suppressed people living with HIV on TDF-based regimens who had clinically significant low BMD by dual-energy X-ray absorptiometry (T-score ≤-2.0 at lumbar spine, femoral neck, or total hip) and were switched to E/C/F/TAF

Results

Calcium/Vitamin D Use

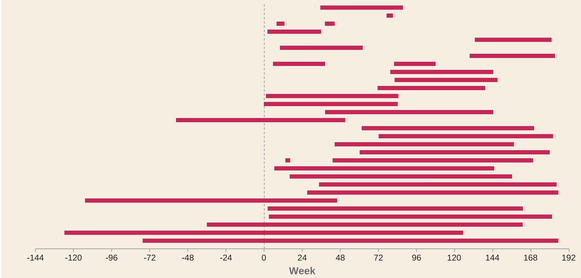


Baseline Characteristics*

		BP Users n=30†	Non-BP Users n=184	Total With Low BMD N=214
Age, y		50 (39, 58)	45 (37, 53)	46 (38, 54)
Female		10 (33)‡	22 (12)	32 (15)
Race	Black	2 (7)	31 (17)	33 (15)
	White	21 (70)	114 (62)	135 (63)
	Asian	1 (3)	26 (14)	27 (13)
BMI, kg/m²		24.0 (22.6, 25.9)	23.1 (20.8, 26.2)	23.2 (21.0, 26.1)
Clinical BMD status: osteoporosis§		14 (47)	57 (31)	71 (33)
Medical history	Smoking	12 (40)	42 (23)	54 (26)
	Consumes ≥3 alcoholic drinks/d	1 (3)	7 (4)	8 (4)
Hip	BMD, g/cm²	0.79 (0.74, 0.85)‡	0.84 (0.78, 0.90)	0.84 (0.78, 0.89)
	T-score	-1.71 (-2.29, -1.50)‡	-1.56 (-2.00, -1.19)	-1.62 (-2.02, -1.25)
Spine	BMD, g/cm²	0.84 (0.78, 0.89)‡	0.90 (0.83, 0.96)	0.88 (0.83, 0.96)
	T-score	-2.46 (-2.88, -2.03)‡	-2.21 (-2.59, -1.84)	-2.23 (-2.64, -1.88)
10-y probability of hip fracture (FRAX), %		2.19 (0.74, 3.53)‡	0.82 (0.36, 1.63)	0.89 (0.39, 1.95)
10-y probability of major osteoporotic fracture (FRAX), %		4.84 (2.53, 8.79)‡	2.99 (1.92, 5.29)	3.11 (2.01, 5.63)
CD4 count, cells/μL		750 (513, 916)	648 (484, 809)	651 (485, 823)
Previous PI use		17 (57)	91 (49)	108 (50)
Taking calcium/vitamin D		28 (93)‡	70 (38)	98 (46)

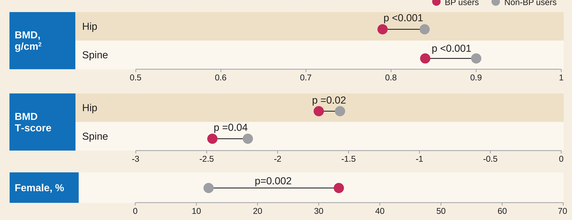
*Results presented as median (interquartile range [IQR]) or n (%); †6 participants used BP at baseline; median (quartile [Q] 1, Q3) use was 463 d (288, 728) prior to baseline visit; ‡Difference observed between BP vs non-BP users; §Defined as T-score ≤-2.5 based on lowest score from lumbar spine, femoral neck, and total hip. FRAX®, Fracture Risk Assessment Tool.

Duration of BP Use Over 144 Weeks



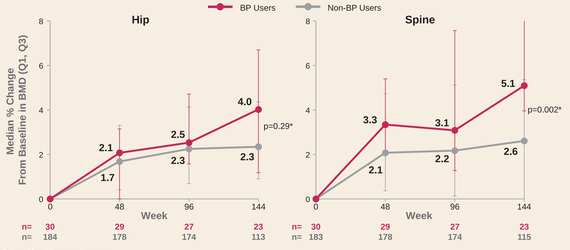
- There was no relationship of duration of BP use and change in % BMD or T-score at either site (Spearman's ρ=0.02–0.27; p=0.21–0.92)
- 30/214 participants (14%) used BPs with median (Q1, Q3) use of 742 d (369, 954)
  - 29 used alendronate sodium and 2 used zoledronic acid
  - Median start date for those starting after baseline: 245 d (IQR 50, 501)

Differences in Baseline Covariates



- At baseline, BP users were more likely to be women and have lower spine and hip BMD

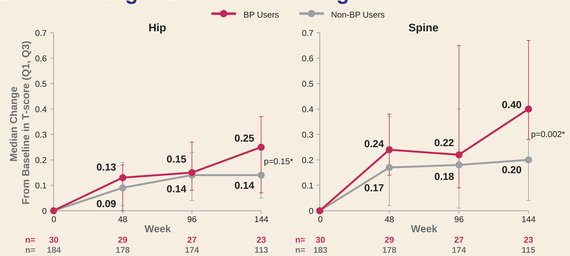
Median Changes in BMD Through Week 144



*Estimated from Wilcoxon rank-sum test.

- At 144 wk:
  - Both BP and non-BP users had significant increases from baseline in hip and spine BMD (p <0.001)
  - BP users had a more significant increase in spine BMD than non-BP users (p=0.002)

Median Changes in T-scores Through Week 144



*Estimated from Wilcoxon rank-sum test.

- Both BP and non-BP users had significant increases from baseline in hip and spine T-scores (p <0.001)
- BP users had a more significant increase in spine T-score than non-BP users (p=0.002)

Changes in BMD by BP Use

Mean % Change at Week 144 (95% CI)*	BP Users	Non-BP Users	p-Value
Hip BMD			
Unadjusted	4.2 (2.8, 5.6)	3.0 (2.2, 3.9)	0.29 (-0.5, 2.8)
Adjusted, linear	4.3 (2.2, 6.4)	4.2 (2.8, 5.5)	0.89 (-1.9, 2.2)
Adjusted, IPTW	4.4 (2.9, 5.6)	4.2 (2.8, 5.6)	0.79 (-1.1, 1.5)
Spine BMD			
Unadjusted	5.9 (4.2, 7.7)	2.8 (1.8, 3.9)	0.002 (1.1, 5.1)
Adjusted, linear	5.6 (2.7, 8.4)	3.0 (1.2, 4.9)	0.08 (-0.3, 5.4)
Adjusted, IPTW	5.7 (3.8, 7.6)	3.5 (1.7, 5.4)	0.02 (0.3, 4.0)

*95% confidence interval (CI) of difference between mean or least-squares mean of BP users vs non-BP users (ie, BP users – non-BP users); age, sex, race, and baseline smoking status, BMI, and BMD were adjusted in linear regression and IPTW models.

- There were statistically significant differences in % changes in spine BMD at Week 144 in BP vs non-BP users after controlling for age, sex, race, and baseline smoking status, BMI, and spine BMD

Changes in T-scores by BP Use

Mean Change at Week 144 (95% CI)*	BP Users	Non-BP Users	p-Value
Hip T-score			
Unadjusted	0.23 (0.15, 0.30)	0.17 (0.12, 0.21)	0.15 (-0.02, 0.15)
Adjusted, linear	0.25 (0.14, 0.36)	0.24 (0.17, 0.31)	0.81 (-0.10, 0.12)
Adjusted, IPTW	0.26 (0.19, 0.34)	0.24 (0.17, 0.32)	0.58 (-0.05, 0.09)
Spine T-score			
Unadjusted	0.44 (0.31, 0.56)	0.23 (0.14, 0.31)	0.002 (0.06, 0.36)
Adjusted, linear	0.43 (0.21, 0.64)	0.22 (0.08, 0.37)	0.06 (-0.01, 0.42)
Adjusted, IPTW	0.43 (0.30, 0.57)	0.25 (0.11, 0.38)	0.01 (0.05, 0.32)

*95% CI of difference between mean or least-squares mean of BP users vs non-BP users (ie, BP users – non-BP users); age, sex, race, and baseline smoking status, BMI, and BMD T-scores were adjusted in linear regression and IPTW models.

- There were statistically significant differences in changes in spine T-scores at Week 144 in BP vs non-BP users after controlling for age, sex, race, and baseline smoking status, BMI, and spine T-scores

Limitations

- Small sample size of BP users
- Nonrandomized exposure to BPs
- Variable duration of BP exposure, with some participants starting many months before baseline visit and some with very short exposure time after TDF→TAF switch
- Given large differences in calcium/vitamin D use in BP vs non-BP users, effect of calcium/vitamin D use on BMD change could not be adequately determined
- No data available on BP adherence

Conclusions

- Switching from TDF to TAF improved BMD over 144 weeks in people living with HIV with low BMD
- There were statistically significant differences in % changes and T-scores in spine BMD at Week 144 between BP and non-BP users after multivariable adjustment
- No differences were observed in % changes or T-scores in hip BMD between BP and non-BP users
- The effect of TDF switching + BP use on BMD over 144 weeks may not be additive, particularly at the hip
- Future controlled studies are required to confirm these findings and examine whether a sequential strategy of TDF switching followed by BP use would result in improved BMD gains compared with a combined strategy of concomitant TDF switching + BP use

References

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