PETRAM RESULTS: BONE TURNOVER CHANGES ON 18F-NaF PET/CT AFTER A RANDOMISED SWITCH TO TAF

CROI ID 00609

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BACKGROUND

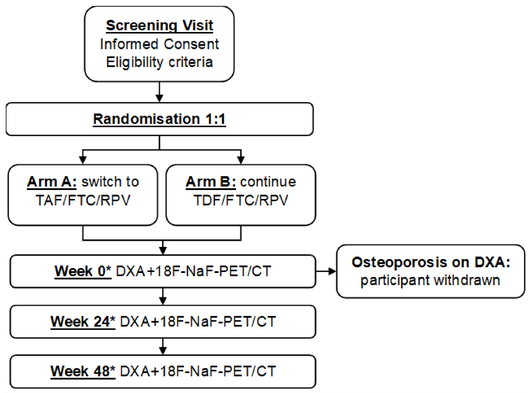
- The mechanism of bone loss in people living with HIV on antiretroviral therapy is poorly understood.
- Plasma bone turnover markers (BTMs) suggest uncoupling of bone resorption and formation by a treatment effect on bone cells [1].
- Switching away from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide fumarate (TAF)-containing regimens has been associated with bone mineral density (BMD) gains measured by dual-energy X-ray absorptiometry (DXA) [2]. One possible explanation is reversal of ongoing subclinical bone loss in the TDF to TAF switchers.
- Positron emission tomography (PET)/computed tomography (CT) with radiolabelled sodium fluoride (18F-NaF-PET/CT) imaging assesses regional bone formation to help differentiate between increased or decreased bone turnover at skeletal sites [3].

METHOD

- Open-label randomised 48-week trial, exploring regional bone formation at the hip and lumbar spine, as measured by 18F-NaF-PET/CT in patients switching to TAF-based ART regimen compared with those continuing a TDF-based regimen.
- Conducted at a single site in London, UK between 2019 and 2021

Primary Outcome: change in regional bone formation on 18F-NaF-PET/CT at the hip and lumbar spine between baseline and last study scan in those switching to TAF vs. continuing TDF.

Figure 1: PETRAM trial design



*Due to COVID-19, some scans were delayed. As such, scans were re-classified as 'baseline', 'mid-study', and 'last-study' scan.

PETRAM Study population

Key inclusion: HIV-1-positive cisgender males; Age 40-65yrs old; No known history of osteoporosis; On the fixed dose combination of TDF/emtricitabine(FTC)/rilpivirine (RPV) >24 weeks

Key exclusion: Current/previous treatment (within prior 12 months) that can affect bone metabolism

Radiological methodology

- 20-minute static 18F-NaF-PET/CT scan of the lumbar spine and hip was performed 1 hour after injection of 90 MBq of radiolabelled sodium fluoride (18F-NaF)
- A pre-PET CT scan provided attenuation correction of the PET images, and defined placement of the regions of interest for the PET scan analysis.
- A DXA scan measuring BMD at the lumbar spine, non-dominant hip and whole body was performed at the same 3 timepoints as the 18F-NaF-PET/CT.
- All 18F-NaF-PET/CT were performed on the same scanner at King's College London and Guy's and St. Thomas' PET Centre, all DXA performed on the same DXA scanner at the Osteoporosis unit at Guy's and St Thomas' NHS Foundation Trust.
- All scans were analysed by the same 2 experienced PET scientists blinded to the arm of randomisation of the participants.

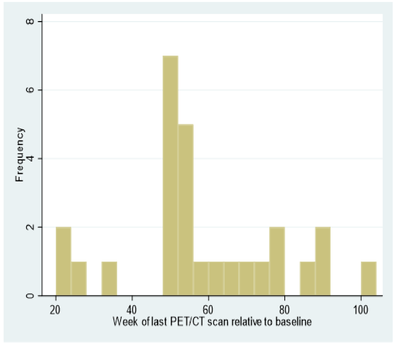
Bone biomarkers (exploratory end-point)

- Drawn at 3 study timepoints, batched and run at the Bioanalytical Facility, University of East Anglia for procollagen Type I N terminal propeptide (PINP) and cross-linked C telopeptides of Type I collagen (CTX).

COVID-19 mitigation

- The trial was severely affected by the SARS-CoV-2 pandemic, with delays in some baseline, week 24 and 48 scans, resulting in some 'week 24' scans being done when participants had been on study drug for 48 weeks (**Figure 2**)
- A protocol amendment in May 2021 therefore amended the primary outcome from the originally planned change in regional bone formation as measured by 18F-NaF-PET/CT at week 24, to change in regional bone formation between baseline and last scan.

Figure 2: Histogram showing the occurrence of the last scan for each participant relative to baseline



Sample size and statistical analysis

- Analysis of covariance (ANCOVA) adjusted for baseline value, study arm, and interval between baseline and last scan
- A sample of 30 (15 per arm) was estimated to provide 90% power to detect a mean change of 25% with SD of 20% in SUV between the arms.
- Change in bone biomarkers (CTX+PINP) is an exploratory outcome also analysed using ANCOVA.

RESULTS.

Table 1: PETRAM baseline characteristics

Characteristic		TAF (n=16)	TDF (n=13)	Total (n=29)
White ethnicity	n (%)	12 (75)	10 (77)	22 (76)
Age (years)	Mean (SD)	49.6 (5.3)	52.7 (4.8)	51.0 (5.2)
Years since HIV diagnosis	Mean (SD)	12.7 (5.8)	17.5 (7.8)	14.9 (7.1)
CD4+ T-cell count (cells/μL)	Mean (SD)	525 (162)	534 (152)	529 (155)
Duration of TDF/FTC/RPV use (months)	Mean (SD)	45 (22)	54 (16)	49 (20)
Weight (kg)	Mean (SD)	84.3 (12.9)	82.6 (6.2)	83.5 (10.3)
BMI (kg/m^2)	Mean (SD)	25.8 (3.2)	25.1 (2.7)	25.5 (2.9)
FRAX score	Mean (SD)	3.4 (1.4)	3.1 (0.6)	3.3 (1.1)
T-score Femoral Neck	Mean (SD)	-0.8 (1.2)	-0.7 (0.8)	-0.8 (1.0)
Vitamin D				
Sufficient (>50 nmol/L)	n (%)	8 (50)	8 (61)	16 (55)
Insufficient (25-50 nmol/L)	n (%)	7 (44)	4 (31)	11 (38)
Deficient (<25 nmol/L)	n (%)	1 (6)	1 (8)	2 (7)

n=2 of vitamin D deficient and n=7 of insufficient started vitamin D supplementation

- The time between baseline and final scans ranged between 23-103 weeks (median 55).
- There ***was no significant difference in change of SUV*** at the lumbar spine or hip between arms (Figure 3a+b, Table 2)
- There was a ***trend towards improved spine BMD*** **in the TAF arm** (+2.0%, 0-4.0, p=0.06), but not total hip, (Figure 3c+d, Table 2)
- Exploratory ***analysis of bone biomarkers showed large reductions in the TAF arm*** compared to TDF, for CTX [-28.2% (-43.5, -13.0, p=0.006)] more-so than PINP [-10.6 (-29.3, 8.1, p=0.31)] (Figure 4a+b, Table 3).

Figure 3a-d: Baseline vs. last scan lumbar SUV (a), total hip SUV (b), total spine BMD (c), and total hip BMD (d)

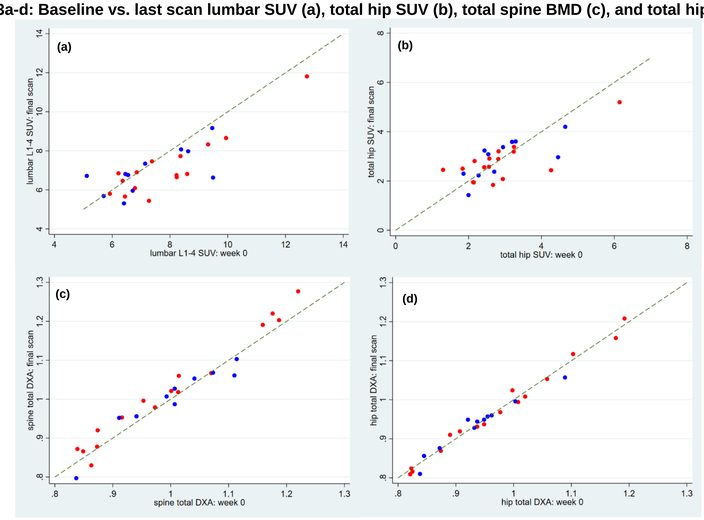


Table 2: Primary analysis of covariance of last-study 18F-NaF-PET/CT and DXA scans adjusted for delays in scans due to COVID-19. All participants with delayed scans remained on allocated treatment

Parameter	Baseline mean (SD)		Predicted relative change (%) at 48 weeks (95 % CI)		Relative % difference: TAF vs. TDF (95% CI)	P-value
	TAF	TDF	TAF	TDF		
Spine - SUV	7.8 (1.8)	7.3 (1.5)	-7.9 (-14.4, -1.5)	-5.3 (-12.1, 1.5)	-2.8 (-12.0, 6.5)	0.57
Hip - SUV	2.8 (1.1)	2.9 (0.9)	+0.3 (-12.2, 12.8)	+2.9 (-11.1, 16.9)	-2.6 (-19.4, 14.3)	0.77
Spine BMD	1.0 (0.1)	1.0 (0.1)	+1.7 (0.3, 3.1)	-0.3 (-1.8, 1.2)	+2.0 (0.0, 4.0)	0.06
Hip BMD	0.97 (0.12)	0.94 (0.07)	-0.2 (-1.1, 0.7)	-0.2 (-1.2, 0.8)	0.0 (-1.2, 1.4)	0.94

Figure 4a and b: Changes in bone biomarkers CTX (a) and PINP (b) by arm of randomisation

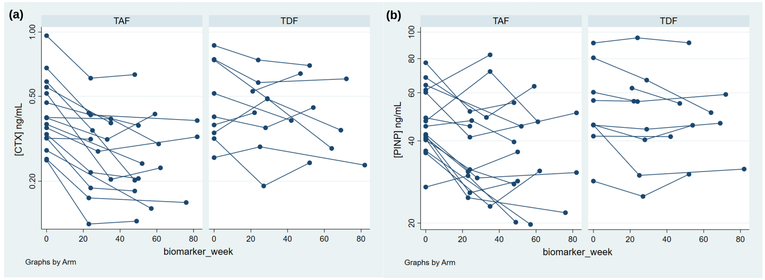


Table 3: Exploratory analysis of covariance of bone biomarkers CTX and PINP by arm of randomisation

Parameter	Baseline mean (SD)		Predicted relative change (%) at 24 weeks (95 % CI)		Relative % difference: TAF vs. TDF (95% CI)	P-value
	TAF	TDF	TAF	TDF		
CTX	0.44 (0.19)	0.51 (0.21)	-33.0 (-43.0, -23.1)	-6.7 (-23.2, 9.0)	-28.2 (-43.5, -13.0)	**0.006**
PINP	48.6 (13.6)	55.8 (18.8)	-18.6 (-30.5, -6.7)	-9.0 (-24.9, 6.8)	-10.6 (-29.3, 8.1)	0.31

CONCLUSIONS

- The reduction in bone biomarkers in the TAF arm, particularly CTX, ***suggests participants are moving from a high bone turnover state after switch.***
- This is supported by a decrease in SUV, which reflects a decreased rate of bone formation, and the trend towards increased spine BMD as bone lost during the high remodeling period is restored.
- The response is less in the hip than the spine, since this effect predominantly occurs in trabecular bone
- Overall, ***this pattern is similar to an individual with osteoporosis starting bisphosphonates***
- The lack of significant change in SUV may be from a lack of power.

References:

1. Oster et al. Bone Reports. 2020. https://doi.org/10.1016/j.bonr.2020.100727.
2. Maggiolo et al. Lancet HIV. 2019. https://doi.org/10.1016/S2352-3018(19)30195-X
3. Frost et al. J Clin Densitom. 2007. https://doi.org/10.1016/j.jocd.2006.10.006

Acknowledgements: Our grateful thanks to all the PETRAM participants, and all PETRAM Co-Investigators at Mortimer Market Centre, and colleagues at the PET Centre and Osteoporosis Unit at Guy's and St Thomas' NHS Foundation Trust

Financial declaration: PETRAM (NCT #: 03405012) is funded by an independent academic grant in support of investigator initiated research from Gilead Sciences. Pett and Dunn receive funding in support of their salary from the Medical Research Council, United Kingdom (grant MC_UU_00004/03 and MC_UU_00004/04)

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