Sheffield Infection Group

FRAX® is a good predictor of bone mineral density in people living with HIV of black ethnicity and/or low fracture risk

Ben Stone[1,2], David Dockrell[1,2] and Eugene McCloskey[3]

[1]Department of Infection and Tropical Medicine, Sheffield Teaching Hospitals NHS Foundation Trust

[2]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield

[3]Mellanby Bone Research Centre, Department of Oncology and Metabolism, University of Sheffield

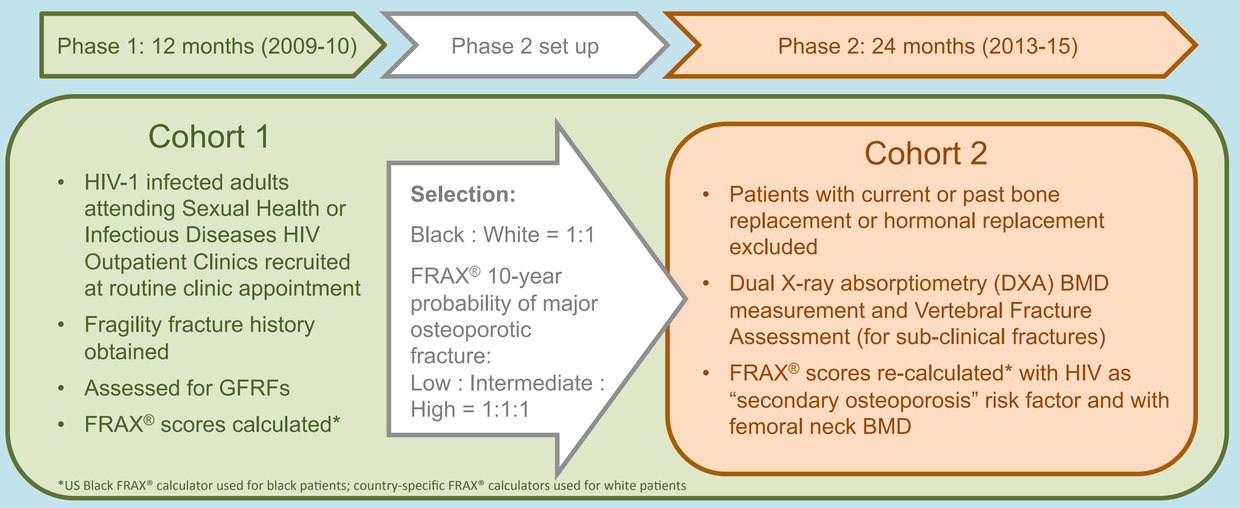
Background

- People living with HIV (PLWH) are at higher risk of reduced bone mineral density (BMD) and fragility fracture compared to age- and gender-matched HIV-negative controls[1-3]
- The reason for this is likely to be multifactorial, encompassing: (1) an increased prevalence of general fracture risk factors (GFRFs) in PLWH; (2) a direct effect of HIV; and (3) a contributory role of antiretroviral therapy (ART)[2]
- HIV guidelines recommend use of the FRAX® tool (www.sheffield.ac.uk/FRAX) for calculating 10-year fragility fracture risk in PLWH[4,5]; based on FRAX®-calculated 10-year fracture probability of fragility fracture (FRAX® scores), patients can be classified into low risk (offer lifestyle advice, reassure), intermediate risk (measure BMD and re-calculate FRAX® with femoral neck BMD measurement to determine low or high risk) or high risk (offer bone replacement therapy)
- FRAX® incorporates GFRFs but not HIV disease-specific factors, however
- Some guidelines recommend incorporating HIV into FRAX® as a "secondary osteoporosis" risk factor, therefore[5]
- Direct measurement of BMD without initial FRAX® calculation is also recommended in PLWH with specific GFRFs, including all post-menopausal women and all men aged ≥ 50 years[5]

Hypotheses

1. Both HIV disease-specific factors and GFRFs contribute to reduced BMD and fracture risk in PLWH
2. FRAX® correlates poorly with BMD in PLWH

Methods



Results

Table 1. Baseline demographics of Cohort 2 (n = 114)

	Black (n = 52)		White (n = 62)	
	Male (n=15)	Female (n=37)	Male (n = 52)	Female (n = 10)
Mean age (years) ± sd	49.3 ± 9.9	44.8 ± 8.5	49.9 ± 12.1	46.6 ± 11.6
Mean weight (kg) ± sd	79.7 ± 15.4	83.5 ± 16.3	78.9 ± 12.0	69.6 ± 13.3
Mean body mass index (kg m^{-2}) ± sd	26.3 ± 4.53	31.7 ± 5.65	25.1 ± 3.3	27.3 ± 6.2

Table 2. Significant determinants (*P* <0.05) of BMD on multivariate analysis in Cohort 2 (n = 114)

Covariate / factor	BMD measurement site / *P*-value			
	Lumbar spine	Total hip	Femoral neck	Total body
Body mass index	<.001	<.001	<.001	.030
Prior fragility fracture	.005	.038	-	.018
Rheumatoid arthritis	-	.030	-	-
Current or past other disorder*	-	.014	.014	.012
Significant steroid exposure	-	-	-	.002
Cumulative number of months ever on a protease inhibitor	-	.004	.007	-

*Presence of one or more other disorder associated with osteoporosis, i.e. hypogonadism, chronic diarrhoea, malabsorption, inflammatory bowel disease, organ transplant recipient, untreated longstanding hyperthyroidism, type 1 diabetes mellitus, chronic obstructive pulmonary disease, prolonged immobility, liver cirrhosis

The significant determinants of BMD within Cohort 2 following multivariate analysis were almost all FRAX®-incorporated GFRFs (Table 2). 25-hydroxyvitamin D and other GFRFs not incorporated into FRAX®, including recreational use, were not significant independent determinants of BMD in this cohort. Of HV-disease specific factors, including CD4 cell count, CD4 nadir, HIV viral load suppression and current and cumulative ART exposure, only cumulative number of months ever on a protease inhibitor was a significant independent predictor of BMD and only for total hip and femoral neck BMD.

Table 3. Relationship between FRAX® 10-year probability of major osteoporotic fracture ("FRAX® major") and hip fracture ("FRAX® hip") with lumbar spine (LS), total hip (TH), femoral neck (FN) and total body (TB) BMD in Cohort 2 patients with either low, intermediate or high "FRAX® major" or "FRAX® hip"

BMD site	Low FRAX® probability				Intermediate FRAX® probability				High FRAX® probability			
	FRAX® major (n = 39)		FRAX® hip (n = 51)		FRAX® major (n = 39)		FRAX® hip (n = 52)		FRAX® major (n = 36)		FRAX® hip (n = 31)	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
LS	-.446	**.004**	-	-	-.076	.664	-	-	-.167	.330	-	-
TH	-.294	.069	-.379	**.006**	-.382	**.017**	-.187	.305	-.281	.097	-.205	.157
FN	-.355	**.027**	-.498	**.001**	-.393	**.013**	-.119	.516	-.301	.074	-.193	.399
TB	-.196	.231	-	-	-.223	.172	-	-	-.147	.394	-	-

FRAX® correlated well with BMD in PLWH with low FRAX® scores and less well in those with high FRAX® scores.

Table 4. Relationship between FRAX® 10-year probability of major osteoporotic fracture ("FRAX® major") and hip fracture ("FRAX® hip") with lumbar spine (LS), total hip (TH), femoral neck (FN) and total body (TB) BMD in all (n = 114), black (n = 52) and white (n = 62) Cohort 2 patients

BMD site	All patients (n = 114)				Black patients (n = 52)				White patients (n = 62)			
	FRAX® major		FRAX® hip		FRAX® major		FRAX® hip		FRAX® major		FRAX® hip	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
LS	-.243	**.009**	-	-	-.405	**.003**	-	-	-.120	.354	-	-
TH	-.324	**.001**	-.384	**.001**	-.295	**.034**	-.410	**.003**	-.245	.055	-.275	**.030**
FN	-.408	**.001**	-.462	**.001**	-.434	**.001**	-.545	**.001**	-.211	.100	-.233	.068
TB	-.288	**.002**	-	-	-.370	**.007**	-	-	-.203	.114	-	-

There was a significant negative correlation between FRAX® and BMD at all sites in PLWH of black race and between "FRAX® hip" and total hip BMD in PLWH of white race (Table 4).

Table 5. Relationship between FRAX® 10-year probability of major osteoporotic fracture ("FRAX® major") and hip fracture ("FRAX® hip") calculated with HIV as a "secondary osteoporosis" risk factor ("HIV as 2y RF") with lumbar spine (LS), total hip (TH), femoral neck (FN) and total body (TB) BMD in all (n = 114), black (n = 52) and white (n = 62) Cohort 2 patients

BMD site	All patients (n = 114)				Black patients (n = 52)				White patients (n = 62)			
	FRAX® major HIV as 2y RF		FRAX® hip HIV as 2y RF		FRAX® major HIV as 2y RF		FRAX® hip HIV as 2y RF		FRAX® major HIV as 2y RF		FRAX® hip HIV as 2y RF	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
LS	-.271	**.004**	-	-	-.348	**.012**	-	-	-.237	.064	-	-
TH	-.328	**.001**	-.334	**.001**	-.189	.181	-.282	**.043**	-.360	**.016**	-.227	.077
FN	-.413	**.001**	-.412	**.001**	-.404	**.003**	-.460	**.001**	-.241	.059	-.174	.177
TB	-.256	**.006**	-	-	-.240	.087	-	-	-.213	.097	-	-

By incorporating HIV into FRAX® as a "secondary osteoporosis" risk factor, the correlation between FRAX® and BMD was less good in PLWH of black race and and between "FRAX® hip" and total hip and femoral neck BMD in PLWH of white race, but improved between "FRAX® major" and all BMD sites in PLWH of white race (significant for total hip BMD) (Table 5).

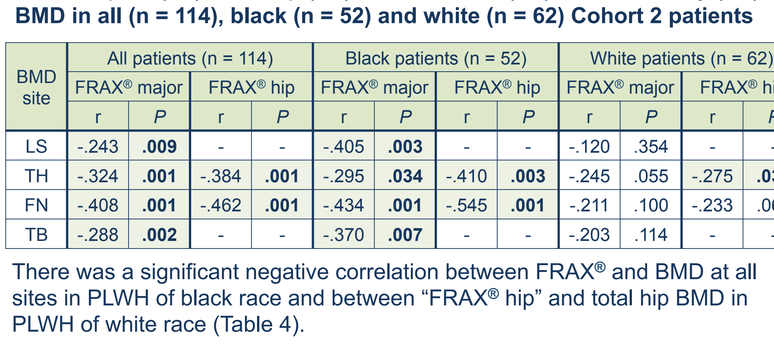


Figure 1. Differences in total hip BMD and in femoral neck BMD between Cohort 2 patients with either low (n = 51), intermediate (n = 32) or high (n = 31) FRAX® 10-year probability of hip fracture

There was a significant difference in both hip and femoral neck BMD between Cohort 2 patients with low *versus* high and intermediate *versus* high FRAX® 10-year probability of hip fracture (Figure 1).

Figure 2. Percentage change in FRAX® 10-year probability of major osteoporotic fracture when calculated with femoral neck BMD compared to without femoral neck BMD in black (A) and white (B) Cohort 2 patients

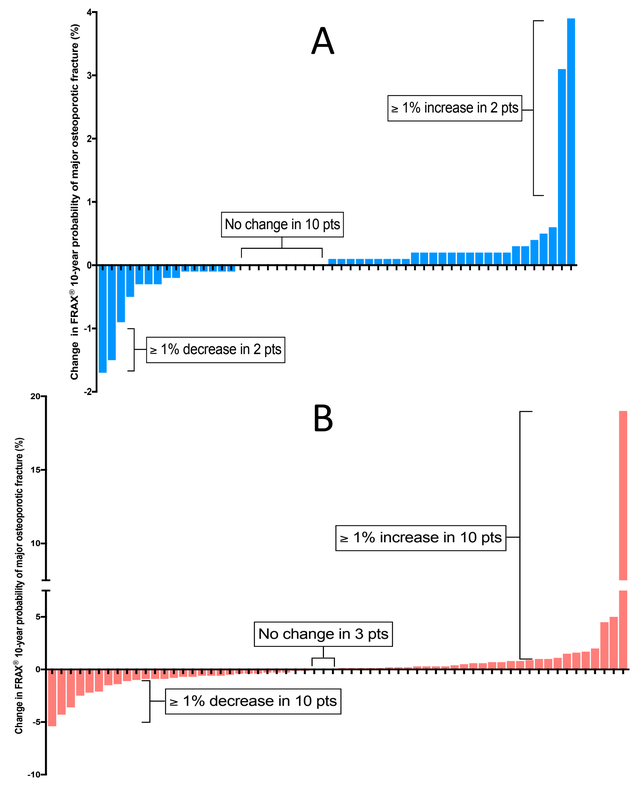


Table 6. National Osteoporosis Guideline Group (NOGG) clinical guidance based on FRAX® 10-year probability of major osteoporotic fracture and hip fracture when calculated without or with femoral neck BMD in white British and Irish patients within Cohort 2 (n = 57)

NOGG clinical guidance		Number of patients (%)
Based on FRAX® without BMD	Based on FRAX® with BMD	
Lifestyle advice and reassure	Lifestyle advice and reassure	36 (63.2)
	Treat with bone replacement therapy	0 (0.0)
Measure BMD	Lifestyle advice and reassure	15 (26.3)
	Treat with bone replacement therapy	4 (7.0)
Treat with bone replacement therapy	Lifestyle advice and reassure	0 (0.0)
	Treat with bone replacement therapy	2 (3.5)

FRAX® scores calculated with femoral neck BMD only increased significantly in a minority of patients with baseline high FRAX® scores calculated without BMD (Figure 2), however this did not alter clinical outcomes (Table 6).

Conclusions and Recommendations

1. FRAX®-incorporated GFRFs and not HIV disease-specific factors were the main determinants of reduced BMD
2. FRAX® scores correlated well with BMD at all sites in patients with low FRAX® scores, in black patients and with hip BMD in white patients (without incorporating HIV as a "secondary osteoporosis" risk factor and without femoral neck BMD): FRAX® should be used **without** incorporating HIV as a "secondary osteoporosis" risk factor to assess fracture risk in PLWH of black race and to assess hip fracture risk in PLWH of white race
3. FRAX® scores correlated less well with lumbar and total body BMD in white patients: correlation was slightly improved by incorporating HIV as a "secondary osteoporosis" risk factor, which could be considered when assessing major osteoporotic fracture risk using FRAX® in PLWH of white race
4. By adding femoral neck BMD, FRAX® scores only increased significantly in a minority of patients who already had high baseline FRAX® scores calculated without BMD; in white patients, BMD measurements did not alter the clinical outcome determined by baseline FRAX® scores calculated without BMD: FRAX® can therefore be used as an initial fracture risk screening tool in PLWH **without** direct BMD measurements in specific patient risk groups

References

1. Brown, TT and Qaqish, RB. *AIDS* 2006; 20(17): 2165-74.
2. Goh, SSL, Lai, PSM, Tan, ATB and Ponnampalavanar, S. *Osteoporos Int* 2016; 29(3): 595-613.
3. Triant, VA, Brown, TT, Lee, H and Grinspoon, SK. *Clin Endocrinol Metab* 2008; 93(9): 3499-504.
4. British HIV Association. British HIV Association guidelines on the routine investigation and monitoring of HIV-1-positive adults. 2016.
5. European AIDS Clinical Society. European guidelines for treatment of HIV-infected adults in Europe. 2015.

Acknowledgments

This work was supported with funding from **ViiV Healthcare (GSK Limited)** and **Sheffield Hospitals Charity**

Correspondence: benjamin.stone@sth.nhs.uk