New Fracture Risk and FRAX 10-Year Probability of Fracture in HIV-infected Adults

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BACKGROUND

- Low bone mineral density (BMD) is common among people living with HIV.[1]
- FRAX® (FRAX) reliably predicts 10-year fracture probability for adults in the general population.[2]
- FRAX utility for HIV-infected adults has not been assessed.

OBJECTIVE

- Using Central dual energy X-ray absorptiometry (DEXA, GE Lunar or Hologic) left femoral neck BMD values, calculate baseline FRAX 10-year probability of major osteoporotic fracture (hip, spine, forearm, or shoulder) in our HIV-infected population and contrast these findings with observed incident fractures.

Table 1: Patient characteristics by baseline FRAX 10-year probability (%) (N=1,006)

Patient characteristics: n (%) or median (IQR)	All study patients with FRAX 10-year probability (%) (n=1,006)	FRAX range 0%-1.4% (n=263)	FRAX range >1.4% to 1.9% (n=243)	FRAX range >1.9% to 3.0% (n=231)	FRAX range >3.0% (n=269)	p-value †
Median age*	41.7 (35.2-48.0)	36.4 (29.1-41.7)	36.7 (31.6-41.1)	43.5 (39.8-46.9)	50.6 (46.1-55.4)	< 0.001
Sex						< 0.001
Male	837 (83.2)	178 (67.7)	202 (83.1)	208 (90.0)	249 (92.6)	
Female						
Race/ethnicity						< 0.001
Non-Hispanic white	673 (66.9)	18 (6.8)	201 (82.7)	205 (88.7)	249 (92.6)	
Non-Hispanic black	212 (21.1)	159 (60.5)	26 (10.7)	16 (6.9)	11 (4.1)	
Hispanic	91 (9.1)	65 (24.7)	11 (4.5)	7 (3.0)	8 (3.0)	
Other/unknown	30 (3.0)	21 (8.0)	5 (2.1)	3 (1.3)	1 (0.4)	
HIV Risk						< 0.001
IDU	58 (5.8)	19 (7.2)	10 (4.1)	15 (6.5)	14 (5.2)	
MSM	689 (68.5)	114 (43.4)	179 (73.7)	183 (79.2)	213 (79.2)	
Heterosexual	197 (19.6)	102 (38.8)	43 (17.7)	24 (10.4)	28 (10.4)	
Other	62 (6.2)	28 (10.7)	11 (4.5)	9 (3.9)	14 (5.2)	
Insurance*						< 0.001
Private	589 (58.6)	94 (35.7)	161 (66.3)	153 (66.2)	181 (67.3)	
Public	263 (26.1)	107 (40.7)	47 (19.3)	43 (18.6)	66 (24.5)	
Other/unknown payer	154 (15.3)	62 (23.6)	35 (14.4)	35 (15.2)	22 (8.2)	
Median CD4+ cell count (cells/mm^3)*	408 (254-598)	354 (209-528)	419 (258-588)	430 (294-619)	447 (269-673)	< 0.001
Nadir CD4+ cell count (cells/mm^3)	188 (71-298)	179 (58-275)	195 (86-316)	205 (79-298)	168 (59-305)	0.58
Viral load < 400 copies/mL*	560 (55.7)	114 (43.4)	117 (48.2)	139 (60.2)	190 (70.6)	< 0.001
Current/prior tobacco smoker	546 (54.3)	136 (51.7)	130 (53.5)	130 (56.3)	150 (55.8)	0.28
14+ alcoholic drinks/week	34 (3.4)	10 (3.8)	4 (1.7)	9 (3.9)	11 (4.1)	0.55
HAART type*						0.52
Boosted PI	292 (29.0)	83 (31.6)	73 (30.0)	65 (28.1)	71 (26.4)	
NNRTI	420 (41.8)	111 (42.2)	103 (42.4)	92 (39.8)	114 (42.4)	
Other	260 (25.8)	61 (23.2)	57 (23.5)	63 (27.3)	79 (29.4)	
None	34 (3.4)	8 (3.0)	10 (4.1)	11 (4.8)	5 (1.9)	
TDF-containing HAART	467 (46.4)	114 (43.4)	120 (49.4)	100 (43.3)	133 (49.4)	0.34
HCV co-infection (DX or +Lab)	123 (12.2)	31 (11.8)	23 (9.5)	32 (13.9)	37 (13.8)	0.27
Bone Mineral Density						< 0.001
Normal (hip T-score ≥ -1.0)	611 (60.7)	203 (77.2)	204 (84.0)	127 (55.0)	77 (28.6)	
Osteopenia (hip T-score < -1.0)	366 (36.4)	60 (22.8)	36 (14.8)	101 (43.7)	169 (62.8)	
Osteoporosis (hip T-score < -2.5)	29 (2.9)	0 (0.0)	3 (1.2)	3 (1.3)	23 (8.6)	
Prevalent fracture (before date*)	60 (6.0)	2 (0.8)	6 (2.5)	7 (3.0)	45 (16.7)	< 0.001
Total person-years of observation	5,022	1,394	1,211	1,170	1,248	
Incident fracture	95 (9.4)	19 (7.2)	17 (7.0)	16 (6.9)	43 (16.0)	< 0.001

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
† Yates corrected chi-square test or Fisher Exact test for class variables, Jonckheere-Terpstra test for individual continuous variables, or Cochran-Armitage test for individual categorical variables.
Abbreviations: IQR, interquartile range; IDU, intravenous drug use; MSM, men who have sex with men; PI, protease inhibitor; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; TDF, tenofovir difumarate; HCV, hepatitis-C virus; DX, diagnosis.

Table 1 results: Among 1,006 participants who contributed 5,022 person-years of follow-up, 83% were male, 67% were non-Hispanic white, median age at date of DEXA scan was 42 years, and median CD4+ cell count was 408 cells/mm^3.

METHODS

Study Populations:

- **SUN: Prospective cohort study (CDC-funded) with enrollment in 2004-2006, with 7 clinics in 4 US cities; patients followed from enrollment to last contact with DEXA scans every 6 months, up to June 2012.**
- **HOPS: Open prospective cohort study (CDC-funded) started in 1993, with 9 clinics in 6 US cities. Only 1 HOPS site, Denver Infectious Disease Consultants (DIDC), was included in the analysis, as it offered and performed DEXA scans as part of routine clinical care—these study patients were followed from 2008 or later to last contact, up to 30 September 2012.**

Statistical Methods:

- **Descriptive statistics comparing patients by cohort and FRAX score range at baseline (defined as closest to 3/1/2004 for SUN and 1/1/2008 for HOPS cohort patients).**
- **We created 2 multivariable models, the 1st model including all factors required by the FRAX software and additional disease-specific factors of viral load, HCV co-infections, CD4+ cell counts, and antiviral use; the 2nd model included the FRAX 10-year probability and disease specific factors significant in the first multivariable model and not required by the FRAX tool, if any.**
- **Univariate and multivariable analyses: Cox proportional hazards models, with backward selection for multivariable model.**

Table 2: Incidence of bone fractures by baseline FRAX 10-year probability (%), (N=1,006; 95 incident fractures)

FRAX 10-year probability (%)	0%-1.4%	>1.4% to 1.9%	> 1.9% to <3.0%	≥ 3.0% (max value=26%)
Number of patients	263	243	212	288
Number of incident fractures	19	17	15	44
% w/incident fractures	7.2%	7.0%	7.1%	15.3%
Person-years (py) of observation	1,394	1,211	1,072	1,346
Median (IQR) observation, years	5.7 (2.9-7.9)	4.2 (2.9-7.8)	4.2 (3.0-7.7)	4.0 (3.1-7.6)
Mean (min-max) observation, years	5.3 (0.1-8.5)	5.0 (0.0-8.5)	5.1 (0.2-8.5)	4.7 (0.0-8.5)
Incidence per 100 py	1.36	1.40	1.40	3.27

Abbreviation: IQR, interquartile range.

Table 2 results: During a median of 4.2 years of observation after initial DEXA, 95 (9.4%) of patients had an incident fracture, 7.1% with FRAX 10-year probability <3% (1.39/100py) and 15.3% with FRAX 10-year probability ≥3% (3.27/100py). New major osteoporotic fractures observed among 1.5% with FRAX 10-year probability <3% (0.3/100py) and among 4.9% (1.04/100py) with FRAX 10-year probability ≥3%.

Figure 1: FRAX 10-year probability (%) distribution and occurrence of new fracture among 1,006 HIV-infected patients

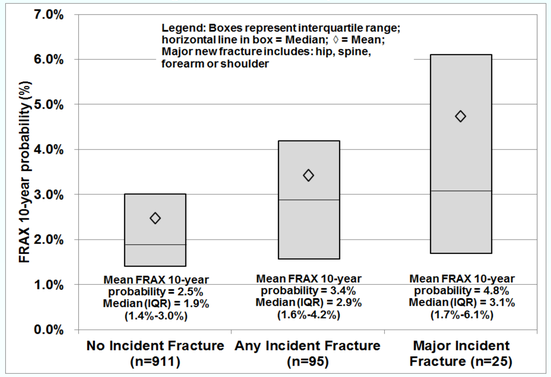


Figure 1 results: The mean FRAX 10-year probabilities among patients with no incident fracture (n=911), any incident fracture (n=95), or incident major osteoporotic fracture (n=25) were 2.5%, 3.4%, and 4.8%, respectively.

Figure 2: SUN/DIDC-HOPS incident fracture proportion and rate by FRAX 10-year probability (%) range (N=1,006; 95 incident fractures)

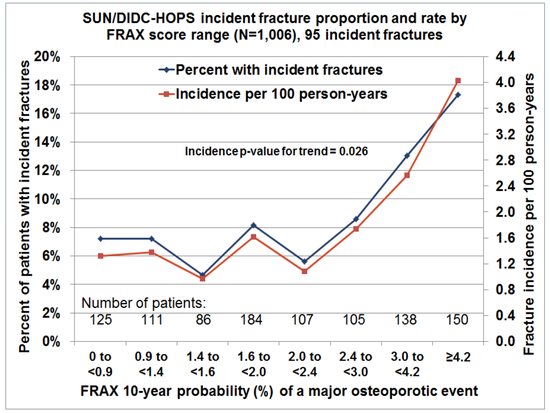


Figure 2 results: Incidence of fracture was statistically greater among those with FRAX 10-year probability of 3.0% or greater.

Table 3: Cox proportional hazards analyses of factors associated with incident fractures (N=1,006; 95 incident fractures)

Independent variables	Univariate HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
MODEL 1				
FRAX tool risk factors				
Age per 10 years	1.41 (1.13-1.76)	0.002	1.30 (1.04-1.62)	0.022
Male sex	1.51 (0.84-2.72)	0.17		
Weight in kg.	1.00 (0.99-1.01)	0.81		
Height in cm.	1.00 (0.98-1.02)	0.85		
Previous fracture	2.42 (1.32-4.43)	0.004	2.02 (1.09-3.71)	0.025
Current/prior tobacco smoker	1.59 (1.04-2.43)	0.031		
Taking glucocorticoids > 90 days	1.40 (0.44-4.43)	0.57		
Rheumatoid arthritis	1.11 (0.15-7.93)	0.92		
Secondary osteoporosis	1.09 (0.68-1.74)	0.72		
14+ alcoholic drinks/week	0.83 (0.26-2.63)	0.75		
BMD in g/cm^2	0.09 (0.02-0.37)	< 0.001	0.14 (0.03-0.59)	0.007
Disease specific factors				
Viral load < 400 copies/mL*	1.16 (0.77-1.75)	0.48		
HCV co-infection	1.63 (0.99-2.70)	0.06		
Nadir CD4 cell count per 100	1.00 (0.88-1.14)	1.00		
CD4 cell count per 100 cells/mm^3*	1.04 (0.97-1.11)	0.24		
TDF-containing HAART, years*	0.94 (0.74-1.19)	0.59		
MODEL 2				
FRAX 10-year probability (%)				
0% to < 3%	referent			
≥ 3%	2.31 (1.54-3.46)	< 0.001		

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
Abbreviations: CI, confidence interval; HCV, hepatitis-C virus; BMD, bone mineral density; TDF, tenofovir difumarate;

Table 3 results: In multivariable analysis, having a prior fracture, older age, and lower BMD were associated with incident fracture. In a second model, having a FRAX 10-year probability ≥3% vs. FRAX 10-year probability <3% was associated with any new fracture.

LIMITATIONS

- Fractures occurring before entry into HOPS or SUN studies may be missing from medical records.
- Incident fractures may be incompletely captured, if not diagnosed by or reported to HOPS or SUN clinics.
- FRAX tool risk factor of parent fractured hip unavailable in HOPS and SUN data.
- In HOPS and SUN, we have all fractures incidence, while FRAX focuses on risk of major osteoporotic fractures only.
- Incomplete reporting of anatomical site of fracture and limited number of major osteopathic fractures (n=25) precluded site-specific analyses.
- Relatively few women were studied.

CONCLUSIONS

- Increasing baseline FRAX 10-year probability was consistently associated with increased rates of incident fractures in our HIV-infected populations.
- Participants with FRAX 10-year probability of ≥3% had over 2-fold higher rates of incident fracture than those with lower FRAX scores.

REFERENCES

1. Overton ET, Mondy K, Bush T, et al. Factors Associated with Low Bone Mineral Density in a Large Cohort of HIV-infected US Adults: Baseline Results from the SUN Study. *14th Conference on Retroviruses and Opportunistic Infections*. Los Angeles, California 2007.
2. FRAX® World Health Organization Fracture Risk Assessment Tool. http://www.shef.ac.uk/FRAX/.

The findings and conclusions from this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.