Title

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Journal

AIDS, 32(12)

ISSN

0269-9370

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Publication Date

2018-07-31

DOI

10.1097/qad.0000000000001864

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2019 July 31.

Published in final edited form as:

AIDS. 2018 July 31; 32(12): 1699–1706. doi:10.1097/QAD.0000000000001864.

Improved fracture prediction using different fracture risk assessment tool adjustments in HIV-infected women

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Abstract

Objectives: A fracture risk assessment tool (FRAX) using clinical risk factors (CRFs) alone underestimates fracture risk in HIV-infected men. Our objective was to determine whether accuracy of FRAX would be improved by considering HIV as a cause of secondary osteoporosis, and further improved with addition of dual-energy X-ray absorptiometry parameters in HIV-infected women.

Design: Subgroup analysis of Women's Interagency HIV Study.

Methods: We included 1148 women (900 HIV-infected and 248 uninfected) over age 40 with data to approximate FRAX CRFs and 10-year observational data for incident fragility fractures; 181 (20%) HIV-infected women had dual-energy X-ray absorptiometry data. Accuracy of FRAX was evaluated by the observed/estimated ratios of fracture in four models: CRFs alone; CRFs with HIV included as a cause of secondary osteoporosis; CRFs and femoral neck bone mineral density (FN BMD); and CRFs, FN BMD and trabecular bone score.

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Author contribution: J.Y. and M.T.Y. were involved in the study conception, design, implementation and writing of the article. J.Y. conducted the statistical analyses. A.S., Q.S., K.A., M.H.C., E.T.G., D.G., D.M., W.J.M., P.C.T. and J.N. were involved in significant editing of the article. All authors approve of the final version of the article.

Conflicts of interest

There are no conflicts of interest.

Results: FRAX using CRFs were less accurate in HIV-infected than uninfected women for major osteoporotic (observed/estimated ratio: 5.05 vs. 3.26, $P < 0.001$) and hip fractures (observed/estimated ratio: 19.78 vs. 7.94, $P < 0.001$), but improved when HIV was included as a cause of secondary osteoporosis. Among HIV-infected women, FRAX accuracy improved further with addition of FN BMD (observed/estimated ratio: 4.00) for hip fractures, but no further with trabecular bone score.

Conclusion: FRAX using CRFs alone underestimated fracture risk more in older HIV-infected women than otherwise similar uninfected women. Accuracy is improved when including HIV as a cause of secondary osteoporosis for both major osteoporotic and hip fractures, whereas addition of FN BMD only improved accuracy for hip fracture.

Keywords

bone mineral density; fracture; fracture risk assessment tool; HIV infection; secondary osteoporosis; trabecular bone score

Introduction

As combined antiretroviral therapy has allowed individuals with HIV to live longer, the burden of aging-associated conditions experienced by people living with HIV has increased [1,2]. Studies have reported greater prevalence of low bone mineral density (BMD) and osteoporosis, as well as significantly higher risk of fragility fracture in HIV-infected individuals compared with age-matched and sex-matched uninfected controls [3–5]. From a recent review, HIV-infected women had 42% higher 10-year fracture incidence when compared with uninfected women [6]. Although the pathogenesis of fracture among HIV-infected individuals has not been clearly established, it is likely related to both traditional and HIV-specific risk factors for fractures [7].

The fracture risk assessment tool (FRAX) incorporates traditional risk factors to estimate the 10-year probability of both major osteoporotic and hip fractures [8]. FRAX can be calculated based upon clinical risk factors (CRFs) alone or combined with femoral neck BMD (FN BMD) as determined by dual-energy X-ray absorptiometry (DXA). To capture other skeletal factors that also influence bone strength, such as the microarchitecture of trabecular bone [9], the FRAX algorithm incorporated lumbar spine trabecular bone score (TBS) in 2015 [10]. TBS is a novel texture measurement that evaluates pixel gray-level variations in the spine DXA image, which has been proposed as a surrogate measure of bone microarchitecture [11,12]. In postmenopausal women, a TBS score less than 1.2 represents degraded microarchitecture [13]. Studies have suggested that TBS helps predict osteoporotic fractures and complements BMD and CRFs for FRAX prediction and monitoring of treatment effect [14–16]. Moreover, TBS may play an even greater role in assessing fracture risk in people with causes of secondary osteoporosis, including HIV infection [17–19].

Due to the variations in fracture epidemiology and mortality across regions, FRAX is geographically calibrated [20]. However, FRAX has shown poor calibrations for certain disease states. For example, FRAX appears to underestimate fracture risk in individuals with diabetes [21,22] and in older HIV-infected men [23]. Therefore, the objective of current

study was to evaluate the predictive accuracy of FRAX using CRFs alone among HIV-infected and uninfected women over 40 years and the predictive accuracy of FRAX calculated when considering HIV as a secondary cause of osteoporosis. Among HIV-infected women who had FN BMD and TBS measures available, the predictive accuracy of FRAX was evaluated sequentially when calculated using CRFs with addition of FN BMD and CRFs with addition of both FN BMD and TBS.

Methods

Study population

The Women's Interagency HIV Study (WIHS) is an ongoing, multicenter prospective cohort study of the natural history of HIV infection in women. Women with and without HIV infection were enrolled from similar sources and frequency matched on demographic characteristics and HIV-related risk factors [24]. A total of 4982 women (3678 HIV-infected and 1304 uninfected) were enrolled between 1994 and 2015 from eleven US cities in four waves of enrollment (1994–1995, 2001–2002, 2011–2012 and 2013–2015). WIHS methods and baseline cohort characteristics have been described previously [25]. Semiannual visits include a comprehensive physical examination, collection of biologic specimens and completion of an interviewer-administered questionnaire that collects information on demographics, disease characteristics and medication use. Institutional review boards at each center approved study protocols and consent forms, and each study participant gave written informed consent. The 3766 women enrolled into WIHS from 1994–1995 to 2001–2002 contributed to the current study.

Risk factors and incident fracture

Starting April to September 2003 (visit 18), all WIHS participants were asked about personal history of fracture of the spine, hip, forearm and other sites, both ever and within the past 6 months. In all subsequent study visits, participants were asked if they had fractures of the spine, hip, forearm and/or other sites since the last visit. Fractures were determined to be fragility (resulting from fall from standing height or less) or nonfragility fractures based upon self-reported history. For the present analysis, we included all incident fragility fractures at the spine, hip, forearm and upper arm/shoulder reported between 2003 and 2012, providing a 10-year observation period for incident fractures at the same body sites as in FRAX prediction. For this analysis, Visit 17 (October 2002–March 2003) was designated as the index visit as incident fractures were only recorded after Visit 17. Fracture-related CRFs used in FRAX were extracted from the WIHS database at the index visit: age, race/ethnicity, personal history of fracture, parental history of fracture, weight, height, current use of cigarettes, glucocorticoid use (ever), excessive alcohol intake (greater than two drinks/day of alcohol) and other causes of secondary osteoporosis (e.g. untreated long-standing hyperthyroidism, premature menopause with onset before age 45, hypogonadism, chronic malnutrition, or malabsorption and chronic liver disease). History of rheumatoid arthritis (RA) was not included as we were unable to confirm accurate diagnoses of RA in the database. Hepatitis C virus (HCV) infection was determined as HCV seropositive with HCV RNA confirmation. We were not able to obtain information on history of type 1 diabetes or osteogenesis imperfecta in adults. Of the 3766 participants, 2517 women had

data on CRFs used in the FRAX calculation. Participants who seroconverted during follow-up (n=18) or who had incomplete information on the 10-year fracture incidence (n=1351) were excluded. The resulting analytic sample was 1148 women (Fig. 1).

Radiographs and dual-energy X-ray absorptiometry scanning

BMD at the lumbar spine (L1–L4) and at the nondominant femoral neck and total hip were assessed by DXA in 181 women with HIV and 39 women without HIV using the Lunar Prodigy densitometer (GE Lunar Corp., Madison, Wisconsin, USA). The DXA BMD measurement was obtained as part of the WIHS Metabolic Substudy within 1 year of the index visit from which the FRAX CRFs were obtained and have been previously reported [26,27]. TBS was determined by reanalyzing deidentified spine DXA files using iNsight software (v1.9; Medimaps, Geneva, Switzerland) as previously described [11]. Femoral neck BMD T scores (FN BMD) and mean TBS measurements for vertebrae L1–L4 were utilized in the FRAX calculation.

Statistical analysis

Descriptive statistics were summarized as appropriate. Student t test and Chi-square test or Fisher's exact test were performed for continuous variables and categorical variables, respectively, to compare variables by HIV serostatus. Incident fracture risk was evaluated based on the occurrence of a new fracture at a major osteoporotic fracture site and hip alone for each participant between 2003 and 2012, consistent with the 10-year FRAX-predicted fracture risk.

The predictive accuracy of FRAX was evaluated by sequentially examining the calibrations of FRAX computed with CRFs alone in both women with and without HIV and computed with consideration of HIV as a secondary cause of osteoporosis [28]. This was performed by calculating the FRAX score for each HIV-infected woman after entering 'Yes' for secondary osteoporosis from the FRAX website calculator. Lastly, among the subset of HIV-infected women whose DXA measures were available, FRAX was computed with CRFs and FN BMD, and computed with CRFs and both FN BMD and TBS. HIV-uninfected women with DXA data (N=39) were excluded from this analysis as there was no observed fracture events. In addition, FRAX was validated sequentially between HIV/HCV coinfected women and HIV monoinfected women, using FRAX with CRFs alone or with the addition of DXA parameters. The magnitude of potential miscalibration of FRAX was evaluated by calculating ratios for the observed 10-year incident fracture probability to the expected 10 year fracture probability predicted by FRAX according to the above four algorithms. Chi-square tests were used to test the differences between the observed/expected ratios between groups, and the Hosmer– Lemeshow chi-square statistic was used to compare the observed/expected ratios over deciles of estimated risk. All analyses were performed using Stata 14.0 (StataCorp, College Station, Texas, USA).

Results

Study population

A total of 1148 women (900 HIV-infected and 248 uninfected) aged above 40 years were included in the current study. Mean±SD age of the cohort was 47±6 years. HIV-infected women were more likely to be African American or infected with HCV than uninfected women, but had lower weight, and were less likely to report current smoking, prolonged glucocorticoid use or excessive alcohol intake. There were no statistically significant differences in age, height, previous fragility fracture and parental hip fracture between HIV-infected and uninfected women (Table 1). Among women with DXA parameters available (N=220), similar demographic characteristics in the HIV-infected and uninfected were observed (data not shown).

The 10-year observed and fracture risk assessment tool-estimated fracture risks

Over the 10-year follow-up, the incidence of fragility fractures was 8.3%. With respect to the type of fractures, 24 participants (2.1%) had spine fractures, 27 (2.4%) had hip fractures, 45 (3.9%) had forearm fractures and 10 (0.9%) had upper arm/shoulder fractures. Among women with DXA parameters, four (1.8%) had spine fractures, six (2.7%) had hip fractures, eight (3.6%) had forearm fractures and one (0.5%) had upper arm/shoulder fractures. Neither the observed risk of fracture nor the mean FRAX-estimated 10-year risk of fracture was significantly different between HIV-infected and uninfected women for major osteoporotic (observed: 9.0 vs. 5.7%, P=0.090, FRAX-estimated: 2.2 vs. 2.0%, P=0.092) and hip fractures (observed: 2.7 vs. 1.2%, P=0.238, FRAX-estimated: 0.2 vs. 0.2%, P=0.156).

Accuracy of fracture risk assessment tool with different adjustments

There were 900 HIV-women with 248 uninfected women included in the FRAX calculated with CRFs alone. FRAX based upon CRFs alone underestimated the 10-year fracture risk more in HIV-infected than uninfected women for both major osteoporotic fractures (observed/expected: 5.05 vs. 3.26, P<0.001) and hip fracture (observed/expected: 19.78 vs. 7.94, P<0.001).

When FRAX was calculated with the consideration of HIV infection as a secondary cause of osteoporosis in the HIV-infected women, the observed/expected ratio was reduced for both major osteoporotic (observed/expected: 3.76) and hip fractures (observed/expected: 14.58). However, FRAX including HIV as a secondary cause of osteoporosis still significantly underestimated the 10-year hip fracture risk more in HIV-infected than uninfected women (P<0.001).

To examine the added benefit of DXA parameters, the analysis was restricted to a subset of HIV-infected women with FN BMD and TBS measures (N=181). For comparability, we recalculated the FRAX scores with CRFs only and with CRFs including HIV as a cause of secondary osteoporosis in this subset. In comparison with the full cohort, observed/expected ratios in the subset were slightly lower for major osteoporotic fractures, but similar for hip fracture (Fig. 2). The addition of FN BMD or both FN BMD and TBS did not further reduce

the observed/expected ratio of FRAX for major osteoporotic fractures compared with the observed/expected calculated when considering HIV as a cause of secondary osteoporosis (Fig. 2). However, the addition of FN BMD greatly improved the accuracy of FRAX for hip fracture among HIV-infected women. We did not observe any further improvements in accuracy for hip fracture prediction by including TBS (Fig. 2).

HIV and hepatitis C virus coinfection

There were 353 (31%) HIV/HCV coinfected and 527 (46%) HIV monoinfected women; among those with DXA parameters, 84 (24%) were coinfected with HIV/HCV and 93 (18%) were monoinfected with HIV. FRAX with CRFs alone and with addition of DXA parameters as described above were assessed in women coinfected with HIV/HCV and monoinfected with HIV, respectively (Table 2). Among the women monoinfected with HIV, the observed/expected ratios were lower when FN BMD was included, compared with FRAX with CRFs alone, and further reduction in observed/expected ratios were seen by adding TBS for both major osteoporotic and hip fractures. Notably, the observed/expected ratio was approximately 1 when FN BMD was included for the prediction of major osteoporotic fractures among women monoinfected with HIV. By contrast, in women coinfected with HIV/HCV, FRAX underestimated the risk of both major osteoporotic and hip fractures, even with the addition of DXA parameters (Table 2).

Discussion

FRAX using CRFs alone underestimated fracture risk more in HIV-infected women over age 40 when compared with uninfected women, but improved by including HIV as a cause of secondary osteoporosis, which is particularly true for the prediction of major osteoporotic fractures. Among women with HIV, the predictive accuracy of FRAX for hip fracture improved with addition of femoral neck BMD, but did not further improve with addition of TBS. Although other studies have demonstrated that FRAX calculated using only CRFs underestimated observed fracture rates in individuals with HIV [23,29,30], to our knowledge, this is the first study demonstrating the complementary role of FN BMD and TBS to CRFs for fracture prediction in HIV-infected women.

Our data revealed that FRAX calculated with inclusion of HIV as a cause of secondary osteoporosis improved the predictive accuracy. Currently, HIV infection is not within the list of accepted causes of secondary osteoporosis [20], but several studies have evaluated improvements in fracture prediction with this adjustment in FRAX calculation. Gazzola *et al.* [31] conducted a crosssectional study in 50 HIV-infected individuals aged at least 40 years; in patients with low BMD, the sensitivity of FRAX as a case-finding tool for pharmacologic interventions was only 22%, but increased to 38% after including HIV as cause of secondary osteoporosis. Our findings were also consistent with findings from a cohort of 24 451 HIV-infected and uninfected men aged 50–70 years in the Veterans Aging Cohort Study [23]. The accuracy of the modified-FRAX was less for HIV-infected men with [observed/expected = 1.62, 95% confidence interval (CI): 1.45–1.81] than uninfected men (observed/expected = 1.29, 95% CI: 1.19–1.40), but improved when HIV was included as a secondary cause of osteoporosis (observed/expected = 1.20, 95% CI: 1.08–1.34) [23]. Our

data add further support for the recommendation to include HIV as a secondary cause of osteoporosis when utilizing the FRAX calculator for HIV-infected individuals [32–34].

The predictive accuracy of FRAX improved with addition of femoral neck BMD for hip fracture, but not for major osteoporotic fractures. This makes sense as the predictive ability of BMD for fracture risk is usually maximized when BMD is used to predict the fracture risk at that same site [35]. Although mounting data suggest that TBS improves prediction of incident major osteoporotic and hip fractures beyond FRAX combined with FN BMD [12,15,16,36], we did not observe this in our study. TBS is likely to be more important in certain causes of secondary osteoporosis which may have differential impact on bone microarchitecture that are not reflected by decreases in bone mineral density [19,37]. Most studies examining the impact of HIV and antiretrovirals on bone strength have found a decrease in areal BMD by DXA [6,26,38], and studies that have examined microarchitecture have found both decreased BMD and disruptions in cortical and trabecular microarchitecture [39,40]. In the current study, our limited sample size may explain the lack of TBS benefit or the addition of TBS may not significantly improve the characterization of bone strength in HIV-infected individuals beyond what is already captured by BMD.

It is noteworthy that among women with HIV/HCV coinfection, the magnitude of the improvement in FRAX accuracy with addition of DXA parameters to CRFs was much smaller than the amount of improvement in women with HIV monoinfection, although this was based on a small sample size. HCV infection is a known risk factor for fracture in both individuals with and without HIV [41,42]. According to a large retrospective cohort study of Medicaid enrollees, women and men coinfected with HCV/HIV had a 76 and 36% increased risk of hip fracture compared with individuals monoinfected with HIV, respectively [43]. From a meta-analysis that included 15 studies, individuals coinfected with HCV/HIV had 77% higher risk of fragility fracture than individuals with HIV monoinfection [44]. Although the pathogenesis of increased fracture risk among patients coinfected with HCV/HIV is not completely understood, proposed mechanisms include increased bone resorption due to chronic HCV-associated inflammatory cytokines [45,46] and impaired bone formation due to hepatic decompensation [47,48].

Although DXA-based parameters greatly improve FRAX prediction, access to DXA is still limited, and therefore, improvements to fracture prediction calculators such as the inclusion of HIV-specific parameters or common laboratory parameters should still be pursued. For example, inclusion of HCV infection as an additional risk factor is likely to improve the fracture prediction [42,49], although the impact of treated HCV infection on fracture prediction is unclear. In addition, specific information about the use of antiretrovirals [50], fall risk [51] and changes in body composition [52], which have known effects on BMD and fracture risk may also improve prediction. Future studies are required to develop and validate a HIV-specific fracture prediction model incorporating some of these additional factors

Our study has several strengths, including the availability of almost all CRFs and 10-year data on fracture incidence in a cohort of well matched HIV-infected and uninfected women in the WIHS. The major limitation of the current study was that only one-fifth of the women

with HIV had DXA measurements. Larger studies are required to further validate the added benefit of DXA parameters to FRAX in people with HIV. Second, we did not have sufficiently accurate data to include RA in the FRAX calculations, and the glucocorticoid use was likely to be an overestimate as we were not able to quantify dose thresholds. Third, the relatively small number of observed hip fracture events (2.4%) over the 10-year follow-up may limit our power to validate the predictive accuracy of FRAX for hip fractures. Lastly, our study sample consisted of mainly (75%) women between 40 and 50 years. The data for FRAX are more robust in individuals at least 50 years. However, our data are responsive to the European AIDS Clinical Society guidelines which recommend fracture risk assessments using FRAX without BMD among individuals aged at least 40 years [20].

Conclusion

In summary, adjusted-FRAX, including the consideration of HIV as a cause of secondary osteoporosis, improves the predictive accuracy of FRAX calculated with CRFs alone in HIV-infected women, and addition of DXA parameters improves fracture prediction at the hip. Current guidelines recommend DXA screening for all individuals with HIV aged above 50 years or FRAX with CRFs after age 40. Our data support the use of DXA parameters for fracture risk stratification in HIV-infected women, but further improvements in fracture prediction may require the development of HIV-specific prediction tools for fracture.

Acknowledgements

Data in this article were collected by the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). WIHS (principal investigators): UAB-MS WIHS (Mirjam-Colette Kempf and Deborah Konkle-Parker), U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun and Gina Wingood), U01-AI-103408; Bronx WIHS (Kathryn Anastos and Anjali Sharma), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), U01-AI-034993; Metropolitan Washington WIHS (Seble Kassaye), U01-AI-034994; Miami WIHS (Margaret Fischl and Lisa Metsch), U01-AI-103397; UNC WIHS (Adaora Adimora), U01-AI-103390; Connie Wofsy Women's HIV Study, Northern California (Ruth Greenblatt, Bradley Aouizerat and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590; Southern California WIHS (Joel Milam), U01-HD-032632 (WIHS I-WIHS IV). The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA) and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and other Communication Disorders (NIDCD) and the NIH Office of Research on Women's Health. WIHS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR000454 (Atlanta CTSA) and P30-AI-050410 (UNC CFAR).

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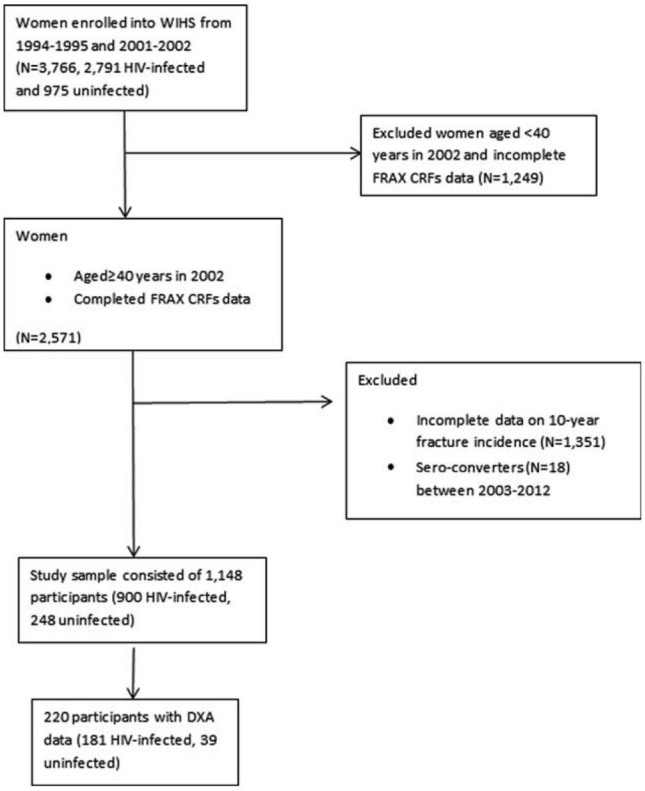

Fig. 1.
Flowchart of the Women's Interagency HIV study cohort.

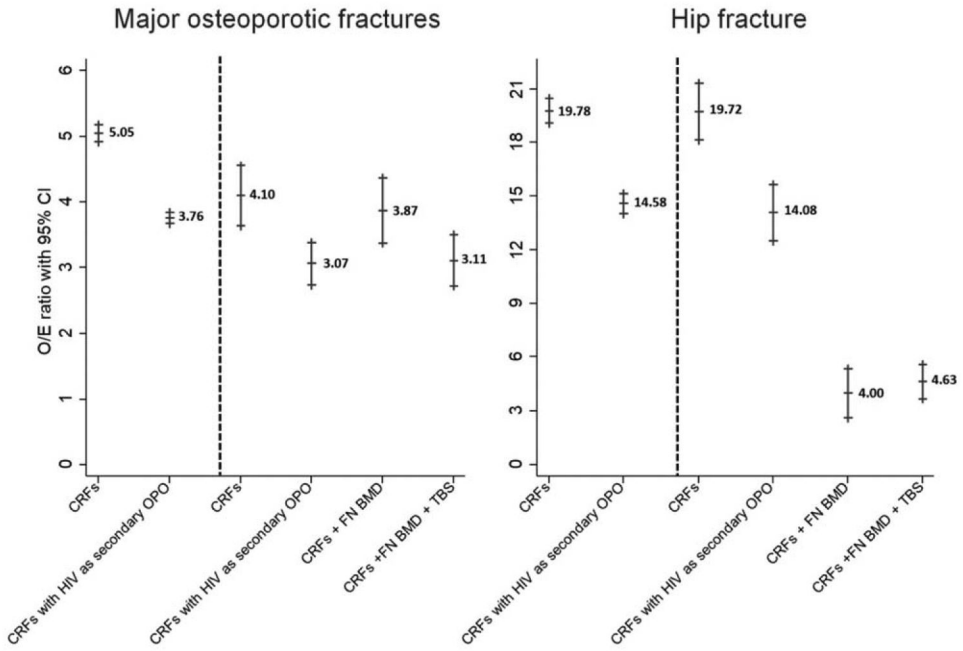

Fig. 2.

Comparison of predictive accuracy of fracture risk assessment tool adjustments in HIV-infected women with clinical risk factor data (left of the dotted line, *N*=900) and in the subset with dual-energy X-ray absorptiometry data (right of the dotted line, *N*=181).

Table 1.

Demographic characteristics of the study population by HIV status.

Characteristics	All, *N*=1148	HIV-infected, *N*=900	HIV-uninfected, *N*=248	*P* value
Age (years), mean±SD	47.2±5.6	47.2±5.6	46.8±5.6	0.331
Race, *N*(%)				0.005
White	15.5	153 (17.0)	25 (10.1)	
Black	58.4	502 (55.8)	168 (67.7)	
Hispanic	23.5	220 (24.4)	50 (20.2)	
Asian	2.6	25 (2.8)	5 (2.0)	
Weight, mean±SD	73.3±17.2	71.8±16.7	78.8±17.9	<0.001
Height, mean±SD	1.6±0.1	1.6±0.1	1.6±0.1	0.537
Previous fracture, *N*(%)	59 (5.1)	47 (5.2)	12 (4.8)	0.809
Family history of fracture, *N*(%)	55 (4.8)	38 (4.2)	17 (6.9)	0.086
Current smoker, *N*(%)	624 (54.4)	466 (51.8)	158 (63.7)	0.001
Glucocorticoid use (in last 6 months), *N*(%)	169 (14.7)	119 (13.2)	50 (20.2)	0.006
Alcohol use, *N*(%)	59 (5.1)	40 (4.4)	19 (7.7)	0.042
Secondary osteoporosis, *N*(%)	99 (8.6)	87 (9.7)	12 (4.8)	0.016
HCV infection, *N*(%)[a]	418 (37.3)	353 (40.1)	65 (27.1)	<0.001

HCV, hepatitis C virus.

[a]28 (2.4%) women had missing/unknown HCV status.

Table 2.

Comparison of accuracy of fracture risk assessment tool adjustments in women with HIV/hepatitis C virus coinfection and HIV monoinfection.

	HIV/HCV coinfection			HIV monoinfection			
	N	**O/E ratio**	**95% CI**	***N***	**O/E ratio**	**95% CI**	***P* value**
FRAX with CRFs							
Major osteoporotic fracture	353	6.04	5.49, 6.59	527	4.07	3.90, 4.24	<0.001
Hip fracture	353	15.95	15.45, 16.44	527	23.56	22.04, 25.07	<0.001
Subset of HIV-infected women with DXA measurements							
FRAX with CRFs							
Major osteoporotic fracture	84	5.92	4.95, 6.88	93	1.29	0.93, 1.65	<0.001
Hip fracture	84	35.70	33.23, 38.17	93	6.94	3.87, 10.02	<0.001
FRAX with CRFs and FN BMD							
Major osteoporotic fracture	84	6.11	4.74, 7.47	93	1.01	0.72, 1.30	<0.001
Hip fracture	84	5.31	2.85, 7.78	93	2.90	1.35, 4.45	0.099
FRAX with CRFs, FN BMD and TBS							
Major osteoporotic fracture	84	4.67	3.90, 5.45	93	0.88	0.64, 1.12	<0.001
Hip fracture	84	5.41	3.57, 7.25	93	2.86	1.43, 4.28	0.030

CI, confidence interval; CRF, clinical risk factor; DXA, dual-energy X-ray absorptiometry; FN BMD, femoral neck bone mineral density; FRAX, fracture risk assessment tool; HCV, hepatitis C virus; O/E, observed/estimated; TBS, trabecular bone score.