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How to predict risk of fracture in HIV

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Abstract

Purpose of review—Skeletal fractures are more common in HIV, and impact the medical, functional and economic status of frequently vulnerable patients. Identifying asymptomatic patients with low bone mineral density (BMD)/osteoporosis requiring intervention can be expected to reduce fracture risk and complications. Clinical tools are available to determine fracture risk in the general population and are being evaluated in HIV patients. The FRAX calculator, incorporating demographics and risk factors for osteoporosis, with or without BMD results, has been investigated most often in HIV patients.

Recent findings—The few published studies which have calculated the 10-year FRAX risk for both major osteoporosis and hip fractures without BMD generally show limited precision in predicting the presence of osteoporosis severe enough to initiate treatment. It remains uncertain whether using HIV as a secondary risk factor and adding DXA-BMD information improves case-finding compared to using DXA results only. Not incorporating risks relevant to aging HIV patients such as antiretroviral exposure, HCV co-infection and history of falls are other potential limitations.

Summary—Accurate screening tools using clinical risk factors alone to determine fracture risk in HIV are not yet available. Further research and validation studies are necessary.

Keywords

Osteoporosis; HIV; fracture; risk; FRAX

Introduction

The availability of increasingly effective and well-tolerated anti-HIV therapy for almost 20 years has resulted in a significant increase in long-term survival of most treated patients.

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This currently approximates that of the general population and may be similar in a significant minority [1,2]. This achievement has however been tempered by the concurrent increase in the prevalence of several common disorders which typically occur in an older population [3]. The etiology of this unexpected development is multifactorial and it remains uncertain if this represents accelerated or accentuated aging [4]. These conditions include cardiovascular disease, certain metabolic disorders, renal and hepatic dysfunction, non-dementing cognitive decline and bone demineralization.

In the general population the most common bone disease is osteoporosis, and the major complication is skeletal fragility fractures that result in significant medical, functional and economic consequences. Although fractures may occur at any age, the main impact of osteoporosis related to fractures occurs primarily among older persons, the fastest growing segment of the population. In treated HIV-infected males and females the risk of fractures is higher than expected for a given age [5]. The number of HIV patients with incident fractures will increase as the population ages [6]. This will significantly impact this already vulnerable group.

As decreased bone mineral density (BMD) is generally asymptomatic until a fracture occurs, it is expected that identification of patients at increased risk of falls and fractures will decrease the risk. As there are few published treatment studies, treatment of low BMD in HIV patients with bisphosphonates as first line agents currently follows guidelines in the general population and generally increases BMD [7]. However, it remains unknown at present whether fracture risk declines in treated HIV patients. As well, there is limited data available on the use of second line drugs. Therefore it is appropriate to adapt the approach of prevention, detection and treatment of osteoporosis used in the general population to HIV patients [8]. This chapter will focus on recent developments in the detection of asymptomatic HIV patients with low BMD who may benefit from pharmacologic intervention.

Assessment of fracture risk in the general population

Osteoporosis is the major risk factor for skeletal fractures and is more common with age. The extent of bone mass reduction is accurately measured by the dual X-ray absorptiometry (DXA)-determined BMD value at a specific site (traditionally the femoral neck), and is expressed as the T-score. The WHO defines osteoporosis as a T-score at the hip or lumbar spine ≤ −2.5 SD below the average value for young women aged 20–29. Fracture risk has been determined to a large extent by the T-score, although it is recognized that the BMD alone lacks sensitivity in predicting individual risk. Specific clinical risk factors, more than 30 are recognized[8], may affect the risk of having a fracture associated with a fall independently from the BMD. Algorithms have been developed which combine demographic, personal, medication and specific health condition information that cause secondary osteoporosis along with site-specific BMD results to determine fracture risk at specific skeletal sites. The rationale to determine fracture risk is based on evidence that pharmacologic therapy of patients with specific threshold risk at different skeletal sites decreases the risk and prevents fractures.

Most societies recommend screening for fracture risk all women ≥ 65 and men aged ≥ 75 even in the absence of risk factors. Women between 50–65 and men between 50–75 should be screened if they have risk factors. The majority of people < 50 years should be screened only if they have major risk factors [9,10]. Although several fracture risk assessment tools are available the following are the ones commonly used by specialist societies and clinicians caring for people at risk for osteoporosis: the WHO developed web-based fracture risk assessment tool (FRAX™ [11]; the Garvan algorithm based on the Dubbo Osteoporosis Study which has been calibrated in the Australian population[12]; and the QFractureScores, based on a prospective open cohort study among a large number of general practices in England and Wales[13]. This chapter will discuss the use of the FRAX calculator as it is the most widely used metric and there have not been any studies published using either of the other two prediction tools in HIV patients.

The FRAX tool (www.shef.ac.uk/FRAX) is a computer based algorithm which integrates relevant clinical data known to affect fracture risk in men and women to calculate the 10 year probability of both a hip fracture alone (high risk designated ≥ 3%) and a major osteoporotic fracture at the wrist, humerus, spine and hip (low risk < 10%, moderate risk 10–19% and high risk ≥ 20%). Fracture probability is determined by using gender, age (between 40–90 years), BMI, with or without the femoral neck BMD, and the dichotomized risk from the following variables: history of fragility fracture including clinical and asymptomatic vertebral fractures), parent history of hip fracture, current cigarette smoking, current or past history of prolonged oral glucocorticoid use (defined as ≥ 5 mg/d of prednisone for > 3 months [recent updates can adjust for either lower or higher daily doses]), rheumatoid arthritis, alcohol intake ≥ 3 units daily, and other causes of secondary osteoarthritis, of which more than 80 have been recognized. Of relevance to this discussion is that HIV infection has been considered as a secondary cause of osteoporosis [14]. FRAX was developed using clinical outcome data obtained from several large cohorts from different worldwide geographic and ethnic regions. FRAX models have been calibrated for different countries in various regions to take into consideration that fracture risk is variable and is therefore most accurate and relevant to the clinician when the calculated risk reflects the patient's individual characteristics. It is important to recognize that FRAX was developed in order to assist in clinical decision making regarding the risk level at which cost-effective treatment of osteoporosis intervention is most likely to benefit patients by reducing the fracture risk. This brings into consideration related factors including but not limited to treatment effectiveness and cost-benefit issues. In fact randomized controlled studies confirm that FRAX identifies patients who do respond to appropriate pharmacotherapy. FRAX is not a static tool and has evolved as updated clinical data is incorporated and new considerations concerning risk factors have emerged. For example, the possible independent influence of both diabetes and chronic bronchitis and fracture risk may require adjustments to the algorithm.

Controversies with using the FRAX calculator

An important issue concerns the interpretation of the calculated 10-year risk with or without the addition of BMD data. The algorithm was designed to allow for the calculation of risk without the BMD. Possible reasons for this include the non-utilization of DXA scans in geographic regions (eg no or limited DXA units, cost, access of patients to units). The

current status of this issue may be summarized as follows. The ability of basic demographics plus the specific FRAX designated clinical risk factors (CRFs) provides similar prognostic value of fracture risk. The classification of patients as high risk using FRAX with CRFs selects patients with low BMD. Although this may be sufficient to initiate therapy, there is concern that such patients may not respond as well. Although thresholds to begin therapy vary by jurisdiction based on local factors, there is general agreement that some high-risk patients (personal history of fragility fracture at the hip or radiographic evidence of a spinal compression fracture) should be treated in the absence of BMD testing and studies show that this is clinically effective in preventing further fractures. Similarly, some patients at low risk will not benefit from treatment regardless of the BMD. Evidence supports the use of FRAX with CRFs as a screening tool with patients designated as having an intermediate risk being most likely to then benefit from BMD determination and having their fracture risk reassessed [15]. Evidence for this approach was confirmed in a study of a large, well-characterized cohort of patients with available BMD and outcome data. Fracture risk re-classification without BMD showed that most patients classified as low risk would not meet National Osteoporosis Foundation guidelines for treatment while those classified as high risk would qualify for therapy. Knowledge of the BMD was most helpful in determining treatment eligibility in patients initially at moderate risk, although this occurred in only a minority of patients [16,17].

Several limitations concerning the use of the FRAX tool have been considered. A major criticism has been the lack of consideration of falls as a risk factor and the concern that this leads to underestimation of fracture risk in patients with a history of falls. It does not bear repeating that the majority of factures occur in older women and falls are one of the most commonly confirmed risks for fragility fractures. This limitation has been partially explained by the FRAX developers in that data on falls were inconsistently captured in the databases and that there is lack of data on the interaction of falls with the other FRAX risks [18]. Fall recall is a reasonably accurate method of capturing history of falls [19]. Both the Garvan and QFractureScores tools include a history of falls in the previous year in their algorithm. A FRAX working group has officially recommended that falls history be incorporated in the algorithm when reliable data becomes available [20]. Another potential limitation is the lack of bone turnover markers for which data on their association with fracture outcomes is however limited. A more relevant issue has been the inclusion of only the femoral neck BMD and not the lumbar spine BMD in the FRAX calculator. Current data suggests that substituting the LS-BMD for the FN-BMD doe not improve FRAX performance but that incorporating an adjustment factor when there is discordance between the FN and LS BMD (a not uncommon occurrence) results in a small improvement in risk determination, particularly in patients at moderate risk [17]. Finally, the use of parsimonious and clinically simple prediction models may well be appropriate in certain situations such as in older women where age and BMD or age and facture history have similar performance characteristics as the more involved FRAX tool [21]. All developers of fracture risk tools agree that although clinical judgment cannot be entered into computer algorithms its role in the decision making process cannot be discounted.

Data on fracture risk calculators in HIV-infected individuals

In Europe, FRAX is commonly utilized for risk prognostication in the general population to identify individuals over age 40 who should undergo a screening DXA and those at high enough risk of fracture to receive pharmacologic therapy without BMD evaluation based upon age-specific thresholds [22]. In the United States, where DXA is considered the preferred screening modality for older individuals, FRAX is utilized primarily in individuals who do not meet criteria for osteoporosis by DXA but have low bone density/osteopenia (T score< −1.0 but >−2.5) to determine appropriateness of pharmacologic therapy [8]. There are no definitive data on similar use of FRAX for HIV-infected patients. However, there are a few studies, published and in abstract, that may be illustrative.

Several studies address whether FRAX scores calculated with only clinical risk factors (CRFs) discriminate well enough to be utilized for determination of DXA screening in HIV-infected individuals (Table 1).

Calmy et al performed DXAs and calculated FRAX in a cohort of 153 HIV-infected adults (98% men, median age 48) on ART in Australia [23]. The study found that FRAX scores did not differ in those with low BMD (T score<−1) vs normal BMD. In patients with normal BMD (n=74), the mean FRAX score was 0.4% for hip and 4.1% for major osteoporotic fracture. In patients with low BMD (n=65), mean FRAX score was 0.4% for hip and 3.8% for major osteoporotic fracture. With addition of FN BMD data, mean FRAX scores increased to 1.2% for hip and 5.4% for major osteoporotic fracture. Overall, 2.2% of the cohort met criteria for pharmacologic therapy if using the 20% 10-year risk of major osteoporotic fracture threshold and 16% met criteria if using the 7.5% threshold. Grazzola et al. performed a similar study in 50 HIV-infected individuals over age 40 by evaluating whether individuals with low BMD (defined as T score<−1 or Z score<−1 for patients <50 and premenopausal women) had FRAX scores based on CRFs above the intermediate intervention threshold set by the National Osteoporosis Guideline Group for recommending a DXA evaluation [24]. In patients with Low BMD, the sensitivity of FRAX was only 22%. Gazzola et al, also re-calculated the FRAX scores including HIV as a cause of secondary osteoporosis, increasing the sensitivity to 38%. On the other hand, the positive predictive value was 70%, and in patients with normal BMD, the specificity of FRAX with CRF=83%. Pepe et al also examined the test characteristics of FRAX with CRFs in 50 HIV-infected men with a mean age of 49 and found a sensitivity of 23% and specificity of 100% for detecting men with “bone fragility” (T score<−2.5 or T score between −2.5 and −1.0 plus fracture) when using a FRAX threshold of 7%[25].

In contrast, two studies evaluated detection rates for osteoporosis following DXA screening strategies recommended by guidelines instead of FRAX (Table 1). Mary-Krause et al. analyzed data from the ANRS-120 FOSIVIR study in 892 HIV+ adults (median age 45; 78% men), and found that the strategy of DXA screening in all individuals over age 50 resulted in a sensitivity of 52% and specificity of 65% for detection of DXA-defined osteoporosis[26]. Using their proposed strategy, which combines age, BMI and CD4+ T cell count, the sensitivity and specificity increased to 65% and 67%, respectively[26]. On the other hand, Mazzotta et al. found in their cohort of 163 HIV+ adults (mean age 44, 71% men) that

following the Italian DXA screening guideline for screening anyone with 2 risk factors other than HIV resulted in only a sensitivity of 32% and specificity of 81% for detecting a Z score≤−2.0[27].

Other studies have examined the accuracy of the FRAX calculator in HIV-infected individuals for prediction of incident fractures, to determine need for pharmacologic therapies. Yin et al. utilized the Veterans Aging Study Virtual Cohort (VACS-VC) to perform the largest study on the accuracy of FRAX estimates for incident fractures in HIV-infected individuals [7,28]. They included 24451 HIV-infected and uninfected 50–70 year old men with complete data in year 2000 to approximate all but two factors (i.e. history of secondary osteoporosis and parental hip fracture) for modified-FRAX calculation without bone density and 10-year observational data for incident fragility fracture. Accuracy of the modified-FRAX calculation was compared by observed/estimated (O/E) ratios of fracture by HIV status. They found that the accuracy of modified-FRAX was less for HIV-infected (O/E=1.62, 95%CI: 1.45, 1.81) than uninfected men (O/E=1.29, 95%CI: 1.19, 1.40), but improved when HIV was included as a cause of secondary osteoporosis (O/E=1.20, 95%CI: 1.08, 1.34). Since the clinical utility of FRAX is based upon accepted thresholds for intervention, they compared the sensitivity/specificity of the modified-FRAX for fracture prediction using accepted FRAX thresholds for pharmacologic interventions in HIV-infected and uninfected groups: the age-specific thresholds for major osteoporotic fractures endorsed by European osteoporosis societies (6.3% to 13.4% in 50–70 year olds) [22] and the hip threshold (>3%) endorsed by the NOF [8]. Using these thresholds, only 21/326 (6.4%) HIV-infected men with fractures at major osteoporotic sites and 3/93 (3.2%) at the hip were correctly predicted. However, the sensitivity was similarly poor among uninfected men. A limitation of this study was the fact that not all FRAX variables were present in the calculator, therefore, use of a FRAX score with complete risk factors and/or with BMD may improve sensitivity/specificity at these thresholds. Battalora et al. performed a retrospective cohort study on 1006 HIV-infected subjects with DXA data from the Study to Understand the Natural History HIV/AIDS (SUN) and HIV Outpatient Study (HOPS) cohorts and FRAX scores calculated with FN BMD data to rate of incident fracture (fragility and non-fragility) over a median 4.2 years of observation [29]. The majority of the subjects were male (83%) with median age of 42, and median CD4=408 cells/μl. Incident fractures occurred in 15.3% of subjects with FRAX scores >3% as compared to only 7.1% of those with FRAX scores≤3%. Mean FRAX scores in subjects 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.

These studies suggest that FRAX scores based on CRFs are not sufficiently accurate to identify patients at risk of fracture for pharmacologic intervention, even when HIV is included as a cause of secondary osteoporosis. Even though FRAX scores based on CRFs also had poor predictive value for low BMD or osteoporosis by DXA in HIV-infected individuals, perhaps the clearest role for FRAX in HIV-infected individuals is to risk stratify for DXA evaluation. FRAX calculated with femoral neck BMD may improve accuracy, but further studies are necessary to determine whether it adds predictive value beyond DXA alone, and whether the thresholds for intervention should be similar in HIV-infected individuals and the general population or different.

What do current guidelines recommend?

Several guidelines have addressed how to use FRAX in HIV-infected individuals given our limited data. The HIV Medical Association of the Infectious Diseases Society of America (HIVMA/IDSA) guidelines follow the National osteoporosis Foundation (NOF) guidelines for the general population in the United States, and do not offer any recommendation of risk stratification with FRAX, but rather, recommend DXA screening for all postmenopausal women and men over age 50 (Table 2) [30]. The European AIDS Clinical Society (EACS) guidelines updated in October 2015 recommend calculating fracture risk by FRAX based on CRFs for risk stratification in all HIV-infected individuals over age 40, or performing screening DXA for patients with one or more risk factors (Table 2). The Osteo Renal Exchange program (OREP) guidelines [7] recommend performing FRAX calculation based upon CRFs for all HIV-infected individuals between 40–50 without other fracture risk factors, and basing further management on thresholds. Both the EACS and OREP guidelines recommend checking the “secondary cause of osteoporosis” box when using the FRAX calculator tool in HIV-infected individuals. If FRAX score is above>20% at a major osteoporosis site or >3% at the hip, the OREP recommends excluding secondary causes of osteoporosis followed by consideration of bisphosphonate therapy in addition to ensuring adequate calcium/vitamin D intake and lifestyle advice. If the FRAX score is >10%, the OREP recommends obtaining a DXA for further risk stratification. And if the FRAX score is <10%, the OREP recommends re-evaluating by FRAX in 2–3 years (Table 2).

Conclusions and future directions

Given the increased fracture risk among HIV-infected individuals, dietary and lifestyle modifications, antiretroviral modifications, and screening DXAs are indicated in higher-risk older individuals [7]. FRAX is a readily available calculator of fracture risk that can be utilized in HIV-infected individuals. However the studies that are available in HIV-infected individuals suggest that fracture estimates calculated using FRAX based on CRFs likely underestimate true fracture risk. Accuracy is improved if HIV is considered a cause of secondary osteoporosis in FRAX calculation, but still appears to be poor tool for case-finding when utilizing pharmacologic therapy thresholds for the general population. When available, DXA may be a better screening modality to determine whether to start pharmacologic therapy. In areas where DXAs are not readily available, FRAX calculated with CRFs may be best utilized for determining which patients meet criteria for additional risk stratification with a DXA.

Future studies should include prospectively collected CRFs since all existing studies of FRAX test characteristics in HIV-infected individuals are limited by missing CRFs and potential misclassification from retrospective data review. It is also possible that HIV-infected individuals differ so greatly from the FRAX development and validation cohorts that different treatment thresholds will have to defined or separate fracture prediction models with HIV-specific variables created, similar to the VACS-index [32]. Accuracy of fracture prediction models in HIV-infected individuals may also improve greatly with the addition of hepatitis C predictor, given the higher risk of fracture with HIV/HCV co-infection [5]. The difficulty with any HIV-specific risk calculators, however, is that they have to be validated in

other HIV cohorts and the algorithms made widely available. There are significant costs to screening all HIV-infected individuals over the age of 50, including unnecessary pharmacologic therapy and additional DXA testing for monitoring. A cost-effectiveness analysis has never been performed to assess this problem. Lastly, modifications to FRAX that have been demonstrated to improve risk prediction in the general population could also be evaluated amongst HIV-infected individuals. Trabecular bone score (TBS) is a new gray-level textural metric that can be extracted from the 2-dimensional lumbar spine DXA image to estimate trabecular microstructure. TBS has been shown be a helpful adjunct to BMD and FRAX clinical risk factors for fracture detection and prediction [33]. TBS has been studied in patients with secondary osteoporosis, such as diabetes and glucocorticoid use, in which the BMD DXA lacks sensitivity to predict fracture[34], but has not been assessed in HIV-infected individuals.

A fracture prediction calculator based upon clinical risk factors that is accurate, generalizable, and easily accessible does not currently exist for HIV-infected individuals, but is clearly an important agenda for future research.

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Bullet points

- Low bone density (BMD) occurs more often in HIV and is associated with higher fractures rates
- Early detection of low BMD may reduce fracture rates and clinical sequelae
- The FRAX risk can be easily applied to HIV patients but may not be accurate using current FRAX application guidelines
- It is uncertain whether the FRAX calculator can be accurately used in HIV
- Further studies are required to determine how best to screen for fracture risk in HIV

Table 1

Screening for low bone density/osteoporosis in HIV-infected individuals using FRAX scores calculated with only clinical risk factors (CRFs) or following screening guidelines

Study	Study design and population	Outcome	Results
Calmy, 2009[23]	153 HIV+ adults Median age=48 Male (98%)	Low BMD (T score<−1) versus normal BMD	**FRAX with CRFs** did not differ in those with low BMD vs normal BMD Normal BMD (n=74): 0.4% for hip, 4.1% for major osteoporotic fracture Low BMD (n=65): 0,4% for hip, 3.8% for major osteoporotic fracture
Gazzola, 2010[24]	50 HIV+ adults Mean age≥40	Low BMD defined as T<−1 or Z<-1 for patients <50 and premenopausal women	In patients with Low BMD: sensitivity of **FRAX with CRFs** only=22%. Considering HIV as a cause of secondary osteoporosis in FRAX calculation increased sensitivity to 37.5%
Pepe, 2012[25]	50 HIV+ART+ men Mean age=49	“bone fragility” defined by DXA T score<−2.5 or T score between −1 and −2.5 and history of a peripheral fracture	Among HIV+ subjects, considering threshold of 7% threshold for major osteoporotic fracture, **FRAX with CRFs** has sensitivity of 23% and specificity of 100%
Mary-Krause, 2012[26]	892 HIV+ adults (700 men, 192 women) from ANRS-120 FOSIVIR Median age=46 (male); 41 (female)	Osteoporosis defined by WHO extended definition and ISCD definition, or EACS definition.	DXA screening in all HIV+ individuals>50 years results in sensitivity of 52% and specificity of 65% Using proposed strategy of screening age>60 or age<60 and BMI<20 or age<60, BMI=20–23, CD4<200, results in sensitivity of 65% and specificity of 67%
Mazzotta, 2015[27]	163 HIV+ adults Mean age=44 Male (71%)	Z score≤−2.0	DXA screening based upon Italian Guidelines (2 risk factors other than HIV) results in sensitivity of 32.1% and specificity of 81.2%

Table 2

Current guidelines on fracture risk stratification in HIV-infected individuals

	HIV Medicine Association/ Infectious Diseases Society of America (**HIVMA/ IDSA**), 2014 [30]	European AIDS Clinical Society (**EACS**) version 8.0, 2015 [31]	Osteo Renal Exchange Program (**OREP**), 2015 [7]
DXA screening	Postmenopausal women and men over 50 years	Postmenopausal women and men over 50 years	Postmenopausal women and men over 50 years
FRAX based on Clinical Risk Factors (CRFs)	N/A	Risk assessment in persons >40 years	Risk assessment in persons >40 years **If≤10%** for major osteoporosis fracture, repeat every 2–3 years or when new risk factor develops **If >10%** obtain DXA **If>20%,** obtain DXA, exclude secondary causes of osteoporosis, consider pharmacologic therapy