

RESEARCH INITIATIVE

Treatment Action!

INTERVIEW WITH:



Michael T. Yin, MD, MS

Clinical insights on HIV-related bone disease risk, screening, and care

Articles by **Mark Mascolini**

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When to use FRAX and DXA — and what they mean

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Bisphosphonates for bone — and advice on ARVs, calcium, vitamin D, glitazones

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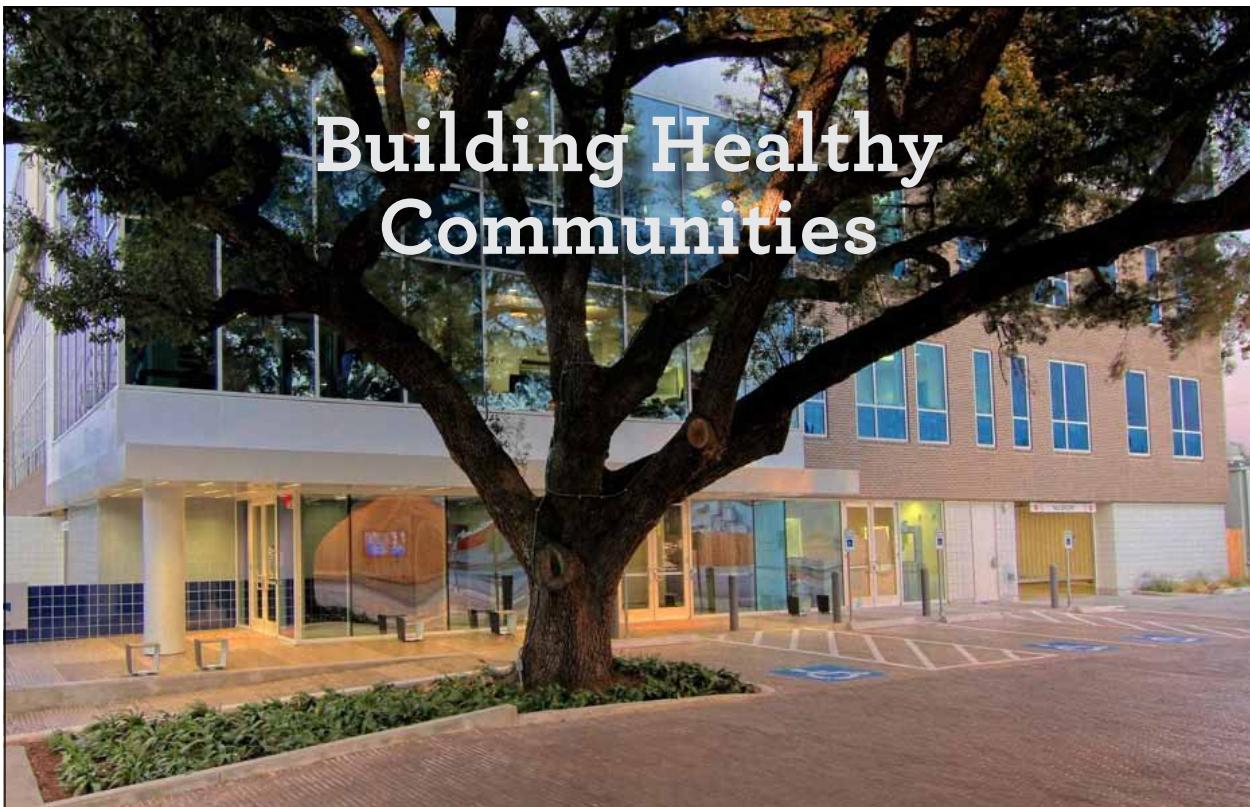
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Fracture facts: prevalence and incidence higher with HIV

By Mark Mascolini

Abstract: Bone disease has affected people with HIV since the early days of the epidemic. Over the years, low bone mineral density has proved frequent in HIV-positive people, who bear a high burden of traditional bone loss risk factors. Accumulated evidence from the United States, Canada, and Western Europe indicates that people with HIV run a higher risk of fracture than comparison groups. Five cross-sectional studies confirmed significantly higher fracture prevalence in people with HIV than in comparison groups. Ten longitudinal comparative studies all found higher fracture incidence in HIV populations, and the higher fracture rate with HIV proved significant in seven of these studies, independently of certain classical risk factors. In one US study, fracture incidence rose steadily over the years in people with HIV but not in the general population.

It all started with a bad tooth. A very bad tooth. In November 1989—a scant 5 years after researchers discovered the AIDS virus—specialists in Copenhagen described what appears to be the first published case of bone disease in an HIV-positive person: tooth loss and necrosis of the alveolar (tooth socket) bone in a patient with trigeminal herpes zoster.¹

Alveolar necrosis (bone death) did not emerge as a prominent complication of HIV infection, but over the next several years groups in the UK and France reported avascular necrosis of the hip² and femoral head³ in people with HIV. In 1993 researchers in Spain compared 16 HIV-positive people with 27 healthy HIV-negatives and charted significantly lower levels of osteocalcin—a bone formation

marker—in the HIV group.⁴ Bone mass also proved lower in the group with HIV. Although that difference lacked statistical significance, scores of later studies would confirm significantly lower bone mineral density (BMD) in people with HIV than in HIV-negative comparison groups.

BMD offers a convenient signal of bone health, but HIV clinicians and the people they see care more about the ultimate consequence of waning bone density: fractures. And plenty of research, detailed in this article, records higher fracture rates in people with than without HIV. The published history of broken bones in HIV-positive people dates back at least to 2001, when Italian clinicians reported fractures “after trivial trauma” in two men with AIDS—one with osteopenia, the other with osteoporosis.⁵ One man was 49 and the other 51, and both had central and peripheral lipodystrophy. Both men had taken indinavir plus stavudine/lamivudine, both had well-controlled HIV infection, and neither had abnormal lipids.

Twelve years later meta-analysis of seven studies comparing fracture incidence in people with and without HIV calculated a 58% higher incidence of all fractures in the HIV group (pooled incidence rate ratio [IRR] 1.58, 95% confidence interval [CI] 1.25 to 2.00) and a 35% higher incidence of fragility fractures (pooled IRR 1.35, 95% CI 1.10 to 1.65).⁶ (Fragility fractures are those following minimal trauma and usually affecting the hip, spine, or wrist.⁷) Published from 2007 through 2012, these studies confirmed several traditional fracture risk factors in people with

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HIV—older age, white race, low weight, alcohol or substance use, diabetes, and liver disease.⁶ Six of seven studies in the meta-analysis figured that hepatitis C virus (HCV) infection inflated fracture risk.

Researchers who ran the meta-analysis rate the 58% higher all-fracture risk and the 35% higher fragility-fracture risk “modest” surges in risk with HIV.⁶ A review of five cross-sectional studies (**Table 1**) and new longitudinal studies published since the meta-analysis (**Table 2**) add weight to the conclusion that HIV makes broken bones more likely.

All five cross-sectional studies, which span 1996 through 2010, found significantly higher fracture prevalence with HIV than in comparison populations.⁸⁻¹² Two of these cross-sectional studies took place in Italy and one each in Canada, the UK, and the US. Three focused on fragility fractures⁸⁻¹⁰ and two on all fractures.^{11,12} The Canadian study included only women,⁸ one Italian study included only men,¹⁰ and the remaining three studies considered both women and men. The Canadian⁸ and US⁹ studies found 60% to 70% higher fragility fracture prevalence in HIV populations than in comparison groups—rates close to the 58% higher all-fracture incidence calculated in the meta-analysis.⁶

These cross-sectional analyses involve almost 12,000 people with HIV and over 2 million controls. The largest review—a population-based comparison in Boston’s Partners HealthCare System—focused on 8525 people with HIV and 2.2 million without an HIV diagnosis (**Table 1**).⁹ Women made up one third of the HIV group, and 72.5% of them were younger than 50. Among men, 64% were under 50. Whites, who run a higher fracture risk than blacks, accounted for 39% of women with HIV and 55% of men.

Prevalence of vertebral, wrist, and hip fractures (all fragility fracture sites) stood at 2.87 per 100 persons in the HIV group, 62% higher than the 1.77 per 100 rate in the HIV-negative comparison group.⁹ In both women and men, fracture prevalence was higher with than without HIV in every 10-year age group analyzed, starting with 20 to 29 for men and with 30 to 39 for women, though these differences were not always statistically significant. Fracture prevalence remained higher with than without HIV when the researchers looked at three nonoverlapping periods, 1997-1999, 2001-2003, and 2005-2007.

As one would expect, fracture prevalence rose with age in the Boston study.⁹ But the relative difference between people with and without HIV also rose with age (see **Figure 2** on page 26). Among 60- to 69-year-old women and men with HIV, prevalence exceeded 5.5 per 100 people, compared with rates of 2.15 per 100 for women and 1.58 for men the same age in the general population. With more HIV-positive people surviving into their 60s and beyond, these findings suggest HIV clinicians will be spending more time helping older patients recover from debilitating fractures.

The 10 studies of fracture incidence ran from 1993 through 2009 (**Table 2**),¹³⁻²² and four were not in the 2013 fracture incidence meta-analysis.⁶ Seven studies took place in the United States, two in Denmark,^{20,21} and one in Spain.¹⁹ One study involved only children in the Pediatric AIDS Clinical Trials Group (PACTG),¹³ two involved only men in the New York CHAMPS cohort¹⁴ or the US Veterans Aging Cohort Study (VACS),¹⁷ one included only women in the US Women’s Interagency HIV Study (WIHS),¹⁵ and the rest studied both men and women.

Of these 10 fracture incidence analyses, three did not find a significantly higher fracture rate with than without HIV, five did find a significantly higher fracture rate with HIV, and three found a higher fracture rate with HIV/HCV or HIV/HBV than without infection. Of the three studies that saw no more incident fractures with than without HIV, a 1993-2007 study involved 5- to 10-year-old US children with or exposed to HIV,¹³ a 2002-2006 US study involved only men ($n = 559$),¹⁴ and a 2002-2008 US study involved only women ($n = 2391$).¹⁵ In all three of these studies, fracture incidence was higher in the HIV group (from 9% to 29% higher) but not significantly higher.

In the 1997-2009 all-male VACS analysis, only 34% of veterans with or without HIV were older than 50, and 55% were black or Hispanic (whites have a higher fracture risk).¹⁷ Median body mass index (BMI) measured 25 kg/m² in the HIV group, significantly lower than the 28 kg/m² in the HIV-negative group but still on the lower end of the overweight spectrum. An analysis adjusted for demographics, comorbid disease, smoking, and alcohol abuse determined that men with HIV had a 24% higher fragility fracture rate than men without HIV (**Table 2**). After further adjustment for BMI, veterans with HIV had a 10% higher fragility fracture rate, but now the difference from the comparison group fell short of statistical significance.

HIV Outpatient Study (HOPS) investigators measured all-fracture incidence in 5826 people with HIV from 2000 through 2008 and indirectly standardized those numbers to a general-population cohort by age and sex through 2006.¹⁸ The HIV group had a median age of 40 (interquartile range [IQR] 34-46), 79% were men, and half were white. Standardized all-fracture incidence proved higher with HIV in every year analyzed from 2000 to 2006

and significantly higher with HIV in 2001, 2002, 2003, 2004, 2005, and 2006 (**Figure 1**). Incidence rose significantly from 2000 to 2008 in the HIV group but not in the comparison group. The HOPS team noted that the rising fracture incidence through the years could reflect improved fracture record keeping as providers became more aware of bone problems in people with HIV, it could reflect a true jump in incidence as people lived longer with HIV, or it could reflect both factors.

Among reports not included in the meta-analysis, a nationwide case-control study in Denmark compared 124,655 people with a new fracture from January through December 2000 and 373,962 people without fractures in that period.²¹ With matching for age and gender, age averaged 43.4 in both cases and controls and 52% were women. People with fractures included a significantly higher proportion who abused alcohol (7.1% versus 2.5%) or ever used steroids (54.3% versus 50.7%).

In this age- and gender-matched comparison, HIV prevalence stood significantly higher among people who had a fracture during the study year than among no-fracture controls (0.04% versus 0.01%, $P < 0.01$).²¹ Odds of any fracture stood almost 3 times higher with HIV, while HIV raised chances of breaks at fragility-fracture sites even higher: 9 times at the hip, 3.5 times at the forearm, and 9 times at the spine (**Table 2**). All of these analyses factored in fracture history, alcoholism, use of medications affecting fracture risk, and annual income. The strength of these associations held true in men and women and in younger and middle-aged populations. The Danish team concluded their overall result “is in line with other recent publications and adds to a growing body of evidence suggesting that HIV-infected patients should be assessed for fracture risk as part of their routine care.”²¹

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Research in the general population indicates that every 1 standard deviation lower bone mineral density measure approximately doubles fracture risk.²³ Together, findings from these cross-sectional and longitudinal comparisons of HIV-positive and negative people confirm that lower bone density with HIV does mean

a higher fracture rate. In 2015 recommendations for evaluating and managing bone disease in people with HIV (see page 31 of this issue), eight experts concur that “patients with HIV infection have a higher risk of low bone mineral density and fragility fracture than the general population.”²⁴

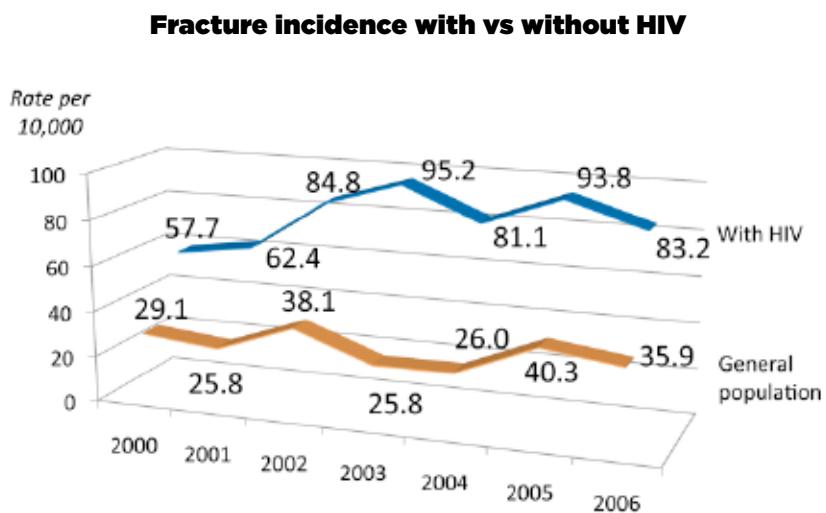


Figure 1. Standardized all-fracture incidence per 10,000 population proved consistently higher in HIV-positive men and women in the HIV Outpatient Study (HOPS) than in the general population from 2000 through 2006 and significantly higher in every year after 2000.¹⁸

Table 1. Cross-sectional studies of fracture with versus without HIV

First author	Year(s), site(s), study type	n HIV+/HIV-	Risk factors HIV+/HIV-	Fracture prevalence HIV+/HIV-
Prior ⁸ ↑ Higher Fx prevalence with HIV	2007, Canada, cross-sectional case-control	138/402 women matched for age and region; 100/138 HIV+ on ART	Age 37.7/38.0, BMI 25.0/26.2, Aboriginal 12.5%/2%, black 16.2%/1%; HIV+ smoked, injected drugs, used steroids more	Fragility Fx prevalence 26.1%/17.3%,* OR 1.7 (1.1-2.6);* BMD similar HIV+/HIV-
Triant ⁹ ↑ Higher Fx prevalence with HIV	1996-2008, Boston, population-based comparison	8525/2,208,792; female 34.9%/55.8%; male 65.2%/44.1%	<i>Female:</i> Age 27.5%/32.4% >50; 39.3%/62.5% white, 30.6%/6.4% black <i>Male:</i> Age 36.3%/25.4% >50; 55.1%/64.3% white, 17.9%/6.1% black	Vertebral, wrist, hip fracture prevalence 2.87/1.77 per 100 persons,* overall Fx 2.49/1.72 female,* 3.08/1.83 male*
Torti ¹⁰ ↑ Higher Fx prevalence with HIV	1998-2010, Italy, case-control	160/163 men matched for age		Vertebral Fx prevalence 26.9%/12.9%;* any Fx 29.6%/12.9%* on ART, 17.1%/12.9%*
Guaraldi ¹¹ ↑ Higher Fx prevalence with HIV	2002-2009; Italy, case-control	2854 HIV+/8562 general population; 37% women; all HIV+ on ART	Age 46 overall	All Fx prevalence 10.8%/0.7% <40 y,* 15.2%/0.9% 41-50 y,* 14.8%/1.3% 51-60 y,* 12.5%/2.5% >60*; higher prevalence with HIV independent of age, sex, hypertension
Peters ¹² ↑ Higher Fx prevalence with HIV	2009-2010, London, case-control	222/222 matched for age; 133/44 men, 89/178 women	<i>Female:</i> Age 44.6/45.2; BMI 27.9/25.1*; smokers 12.4%/19.7%; heavy alcohol 1.1%/1.1% <i>Male:</i> Age 46.2/46.9; BMI 24.3/26.9*; smokers 35.3%/22.7%; heavy alcohol 18%/0%* <i>Overall:</i> 48% white, 38% black	Osteoporosis prevalence 17.6%/3.6%;* Fx prevalence 20.3%/7%,* OR 3.27*

*Statistically significant.

ART, antiretroviral therapy; BMD, bone mineral density; BMI, body mass index; Fx, fracture; OR, odds ratio; py, person-years.

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Table 2. Longitudinal studies of fracture with versus without HIV

First author	Year(s), site(s), study type	n HIV+/HIV-	Risk factors HIV+/HIV-	Fracture prevalence HIV+/HIV-
Siberry¹³ ↔ No higher Fx risk with HIV (Not in meta-analysis ⁶)	1993-2007, US PACTG 219/219C, prospective cohort; 4.97 y F/U	1326 HIV+/649 HIV-exposed; 51% female in both groups; all HIV+ on ART	Age 7.1/5.8 y; 11%/11% white, 62%/53% black; 24%/35% Hispanic; steroids ever 2%/1%	Fx incidence 1.2/1.1 per 1000 py (NS), IRR 1.1 (0.2-5.5); no difference by BMI or steroid use 11% higher incidence with HIV
Arnsten¹⁴ ↔ No higher Fx risk with HIV	2002-2006, NYC, CHAMPS cohort	328/231 men; 87% of HIV+ with ART experience	All 49+ years, median 55; 12%/19% white, 61%/50% black, 23%/28% Hispanic; 52%/70% overweight or obese; 61%/75% smokers; 86%/94% ever drug use	Fx incidence 3.1/2.6 per 100 py (NS); femoral neck and lumbar BMD significantly lower in HIV+ 19% higher incidence with HIV
Yin¹⁵ ↔ No higher Fx risk with HIV	2002-2008, US prospective WIHS cohort, 5.4 y F/U	1728/663 women; 66% HIV+ on ART at index visit	Age 40.4/36.1;* postmenopause 19.6%/11.2%;* 13.3%/10.7% white, 56.3%/58.4% black, 27.2%/27.0% Hispanic; BMI 28.5/30.0;* 45.3%/50.8% smokers;* 2.1%/3.9% heavy drinkers;* HCV 25.4%/14.5%;*	Fx incidence 1.8/1.4 per 100 py (NS); fragility Fx incidence 0.58/0.53 per 100 py (NS) 29% higher all-Fx incidence with HIV; 9% higher fragility Fx incidence
Lo Re¹⁶ ↑ Higher Fx risk with HCV/HIV vs no infection	1999-2005; US Medicaid system; F/U 5.2 y HCV+/HIV+, 2.3 y HCV+ only; 3.7 y HIV+ only, 2.2-2.7 y HCV/HIV-	36,950 HCV/HIV+, 276,901 HCV+ only, 95,827 HIV+ only, 3,110,904 HCV/HIV-; women 29.3% HCV/HIV+, 46.4% HCV+ only, 36.9% HIV+ only, 29.3-46.5% HCV/HIV-	Age 42 HCV/HIV+, 47 HCV+ only, 39 HIV+ only, 42-48 HCV/HIV-; 27.8% HCV/HIV+, 46.1% HCV+ only, 27.3% HIV+ only, ~39% HCV/HIV- white; respective % black 39.8%, 21.3%, 44.4%, ~18%, respective % smoker 10.1%, 11.6%, 4.6%, ~3%	Hip Fx incidence 3.06 per 1000 py HCV/HIV+, 2.69 HCV+ only, 1.95 HIV+ only, 1.29 HCV/HIV-; HCV/HIV+ aHR 1.38 vs HCV+ only,* 1.76 vs HIV+ females only, 1.36 vs HIV+ males only,* 2.65 vs HCV/HIV- females,* 2.20 vs HCV/HIV- males*

First author	Year(s), site(s), study type	n HIV+/HIV-	Risk factors HIV+/HIV-	Fracture prevalence HIV+/HIV-
Womack ¹⁷ ↑ Higher Fx risk with HIV	1997-2009; US VACS-VC prospective cohort; F/U 6.0/6.9 y*	40,115/79,203 men; 75% HIV+ with ART experience	Age at enrollment 34%/34% over 50; age at fracture 54/53;* 55%/55% black/Hispanic; BMI 25/28;* alcohol abuse 16%/15%;* smoker 61%/54%;* steroid use 5%/3%*	aHR for fragility Fx 1.24 (1.11-1.39);† aHR after further adjustment for BMI 1.10 (0.97-1.25) (NS)
Young ¹⁸ ↑ Higher Fx risk with HIV	2000-2008; US HOPS prospective cohort compared with age- and sex-matched general-population cohort; F/U 3.8 y	5826 HIV+; 79% men; 73% with ART experience	Age 40 y; 51.8% white, 33.0% black, 11.7% Hispanic; BMI 24.4	Standardized all-Fx incidence per 10,000 HIV+/HIV- 57.7/29.1 in 2000; 84.8/38.1 in 2002;* 81.1/26.0 in 2004;* 83.2/35.9 in 2006;* in HIV+ (but not HIV-) incidence rose significantly from 2000 to 2008
Güerri-Fernandez ¹⁹ ↑ Higher Fx risk with HIV (Not in meta-analysis ⁶)	2007-2009; Catalonia, Spain; population-based cohort comparison; F/U 3.0 y	2489/1,115,667 40 y or older; 75.3%/47.8% male*	Age 50.0/61.3;* BMI 24.5/28.4;* smoker 53.3%/ 18.9%;* heavy alcohol 2.7%/1.8%*	Fx incidence 8.03/7.93 per 1000 py; aHR 4.7 (2.4-9.5) for hip Fx,* aHR 1.8 (1.2-2.5) for osteoporotic Fx*
Hansen ²⁰ ↑ Higher Fx risk with HIV or HIV/HCV	1995-2009; Denmark; population-based matched cohort comparison; F/U 6.5 y HIV+, 9.6 y population controls	5306/26,530; 76%/76% male; 78% of HIV+ started ART in study period	Age 36.7/36.7; 80% HIV+ white; 16% HIV+ also HCV+	Fx incidence 21.0/13.5 per 1000 py;* for all Fx IRR 1.5 (1.4-1.7) for HIV+, 1.3 (1.2-1.4) for HIV+ only, 2.9 (2.5-3.4) for HIV/HCV+, 1.6 (1.4-1.8) for low-energy Fx in HIV+ and 3.8 (3.0-4.9) HIV/HCV+ (all comparisons vs population controls)

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First author	Year(s), site(s), study type	n HIV+/HIV-	Risk factors HIV+/HIV-	Fracture prevalence HIV+/HIV-
Prieto-Alhambra ²¹ ↑ Higher Fx risk with HIV (Not in meta-analysis ⁶)	Jan-Dec 2000; Denmark; nationwide case-control study	124,655 Fx cases/373,962 age- and gender-matched controls without Fx	Age 43.4 Fx cases and no-Fx controls; 48.2% cases and controls men; Charlson comorbidity index 1-2 in 16.8% of cases and 12.8% of controls, * 3-4 in 4.4% of cases and 2.4% of controls;* alcoholism 7.1% vs 2.5%;* ever use steroid 54.3% vs 50.7%*	0.40 per 1000 with Fx had HIV vs 0.14 per 1000 without Fx; OR for any Fx with vs without HIV 2.89 (1.99-4.18)*, for hip Fx OR 8.99 (1.39-58.0)*, forearm Fx OR 3.5 (1.26-9.72)*, spine Fx OR 9.00 (1.39-58.1)*
Byrne ²² ↑ Higher Fx risk with HIV/HBV vs no infection (Not in meta-analysis ⁶)	1997-2007; US Medicaid cohort comparison; F/U 5 y	4156 Medicaid patients treated for HBV/HIV, 2053 treated with HBV only, 96,253 treated with HIV only, 746,794 randomly sampled Medicaid clients	Medicaid clients	Hip Fx incidence HBV/HIV vs HIV only aHR 1.37 (1.03-1.83)*; vs HBV only aHR 2.62 (0.92-7.51, NS), vs no infection aHR 1.35 (1.03-1.84)*

*Statistically significant.

†After adjustment for demographics, comorbid disease, smoking, alcohol abuse.

aHR, adjusted hazard ratio; ART, antiretroviral therapy; BMD, bone mineral density; BMI, body mass index; F/U, follow-up; HOPS, HIV Outpatient Study; IRR, incidence rate ratio; NS, not significant; OR, odds ratio; PACTG, Pediatric AIDS Clinical Trials Group; py, person-years; VACS-VC, Veterans Aging Cohort Study Virtual Cohort; WIHS, Women's Interagency HIV Study.



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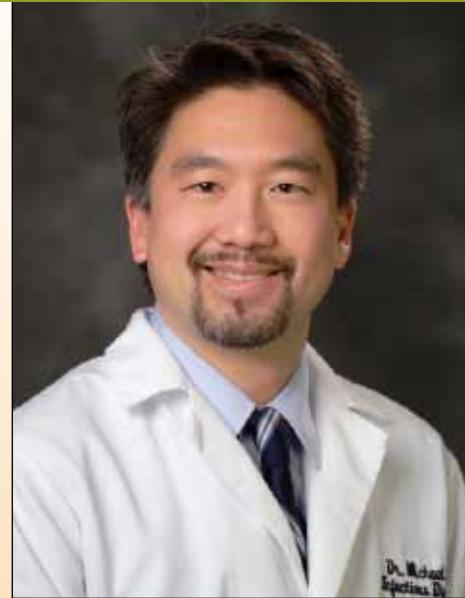
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Clinical insights on HIV-related bone disease risk, screening, and care

An interview with Michael T. Yin, MD, MS

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Dr. Yin is well recognized for research on bone disease and other metabolic complications of HIV infection and antiretroviral therapy. The coauthor of several dozen publications on these issues, he is also a member of the Osteo Renal Exchange Program, which issued the 2015 recommendations for evaluating and managing bone disease in people with HIV. Dr. Yin is principal investigator of a NIAID-funded initiative to study the impact of menopause on bone and muscle in the Women's Interagency HIV Study (WIHS). And he is co-principal investigator of a NICHD-funded study examining bone health in antiretroviral-treated children in South Africa. Dr. Yin is also a member of Bone and Metabolic Working Groups for the WIHS, the Veterans Aging Cohort Study (VACS), and the AIDS Clinical Trials Group (ACTG). He earned his MD at the Columbia College of Physicians and Surgeons and added a Masters in Epidemiology at the Columbia University Mailman School of Public Health.

Focusing on modifiable risk factors

Mascolini: Aside from age, what are the most important bone risk factors in people with HIV?

Yin: The biggest risks are prior fracture, white race, and low body weight.

Mascolini: You can't do anything about fracture history or race, but what about low weight? Should HIV clinicians aggressively try to get underweight people to add pounds?

Yin: I think that's a reasonable approach. You hit upon an important point. There are some modifiable risk factors and some that are not. Controlling body weight, gaining muscle mass with exercise, quitting smoking, and limiting alcohol drinking to moderate amounts are all things that are modifiable and are probably important in people who are at high risk of bone disease. For people who have really low body weight, especially if they are prone to falls, strength training and improvement in muscle mass function would be helpful.

For the majority of patients who are in a reasonable weight range, we don't know how much benefit they'll get from strength training and other exercise. But in older folks, fraailer folks, those who are more prone to falls, that kind of intervention is probably going to be beneficial.

Mascolini: The lifestyle risk factors you just mentioned—smoking, heavy alcohol drinking, and lack of exercise—those are all habits that are pretty hard for people to change. Do you have any advice on how HIV clinicians can motivate people to address those factors?

Yin: Changing ingrained habits can be difficult, but many people do find the motivation to change. The United States, for example, now has more former smokers than current smokers.¹ For some patients, understanding and seeing the short-term benefits of modifying their behavior are strong motivators. Clinicians can help patients find this motivation by mapping out and tracking gains from changed behavior.

Gray zones in interpreting DXA and FRAX

Mascolini: When are DXA scans and the FRAX algorithm appropriate screening tooling for low bone mineral density in people with HIV?

Yin: DXA screening is recommended for all HIV-positive people over 50.² It's a logical extrapolation from screening guidelines in the general population, but I think it will result in lots of test results that are in the gray area. Interpreting results will require a discussion between patient and provider about whether to monitor with a follow-up DXA in 1 year after lifestyle modification, or to switch antiretrovirals and monitor, or to start bisphosphonates or other bone-specific therapy. The thresholds for each of those decisions are not clearly defined, and we hope research will provide results to help guide us in the future.

FRAX—the algorithm based on a list of clinical factors³—can be used in HIV patients. Guidelines from the European AIDS Clinical Society (EACS) recommend FRAX for men in their 40s and premenopausal women over 40 without fragility fracture risk.⁴ This is an extrapolation from screening guidelines for the general population in Europe, which differ from those followed in the United States. Available data suggest that FRAX underestimates risk in HIV-infected individuals.⁵ Some of that underestimation can be corrected if you consider HIV a cause of secondary osteoporosis in the FRAX calculation, but whether it is an accurate enough predictor of fracture risk in HIV to use it as a screening tool is still not clear.

Mascolini: You pointed out that recent HIV bone guidelines call for FRAX screening starting at age 40,^{2,4} but one of your studies found that young men with HIV have lower peak bone mass than young HIV-negative men.⁶ [See “Substance use, old age, young age” on page 26] Should HIV clinicians be on the lookout for signs of bone problems in people in their 20s and 30s?

Yin: That's a good question. If we look, we're going to find evidence of bone deficiency in younger people with HIV, just as we did in that study. The problem with using a risk factor measure such as the FRAX—and even bone mineral density (BMD) by DXA—is that they are useful for predicting fracture only in older individuals. FRAX is well validated for people older than 50, although the calculator itself lets you go down to age 40. Those tools are less useful in younger people because fracture risks are generally low in younger individuals; even if a younger person has low BMD, their fracture risk is still much lower than that of an older person with the same BMD value.

So the question is, in HIV-infected people who are infected at a very early age, including those infected perinatally, whether another kind of screening measure

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is indicated. We don't have good data to answer that question yet. The study that you pointed out and some others are just starting to assemble that data.

Mascolini: Your Veterans Aging Cohort Study analysis found that FRAX underestimates fracture risk in HIV-positive men 50 and older.⁵ Does that finding also raise concerns about the predictive power of FRAX in men in their early or later 40s?

Yin: That's an issue that we really wanted to address with that analysis. It's not a perfect analysis because we didn't have all the risk factors that are necessary to calculate FRAX. So the data we presented are illustrative but not definitive of how accurate FRAX could be in the HIV-infected population if you had all the variables. From our analysis, it appears that a modified-FRAX (calculated with all but two of the FRAX variables) has poor predictive value for fracture using commonly accepted thresholds for pharmacologic therapy (greater than 3% 10-year fracture risk at the hip). However, defining the true predictive value of FRAX in people with HIV still requires a definitive study in which all the variables are utilized.

Bisphosphonates—and before—and beyond

Mascolini: What are the strongest indications for bisphosphonate therapy in people with HIV?

Yin: Prior fracture is the strongest indication. In the general population when someone has a prior fracture, you don't even need to get a FRAX. A fracture alone is indication enough that a patient should be on bisphosphates or some other bone-specific medication. Otherwise, bisphosphonate therapy should be considered for a patient with very

low bone density. The osteoporosis cutoff is bone density at 2.5 standard deviation below that of a person the same sex and race at a young age. If a patient is below that cutoff, then the fracture risk is relatively high and the patient should be on therapy.

The issue is that now, with the guidelines to screen early,² we see a lot of relatively young people—around age 50—who have a bone density right around that osteoporosis cutoff. And if you look at their risk prediction by FRAX, which we understand is not perfect, the FRAX score is relatively low, suggesting they're not at high risk for fracture. And because they're in their early 50s, you don't know whether you want to begin a bisphosphonate that you might have to use for a relatively long time.

For such patients, one strategy that has emerged is to look at the patient's other modifiable risk factors—such as low weight, low vitamin D, exercise, et cetera—and see if we can modify those factors. Switching their antiretrovirals could be an option, if they're taking antiretrovirals that may contribute to low bone density risk. The data on switching off tenofovir suggest that you can gain 1% to 3% in bone density within a year just by trading tenofovir for abacavir or raltegravir.

Addressing some of these factors first and seeing if bone density has stabilized a year or 2 later could allow you to defer bisphosphonate therapy. That's something we're beginning to explore. We think it's a safe strategy for relatively young patients who just received DXA screening and who are not at a significant risk for fracture within 1 year, and we're trying to do some studies to validate that approach.

Mascolini: How long do HIV-negative people typically take bisphosphonates before the drugs start to cause problems?

Yin: The data indicate that bisphosphonate-related toxicities are quite rare. Atypical femoral fractures are devastating because they don't repair well, but they're very rare.⁷ Data on who gets these fractures indicate that very few people with less than 5 years of exposure to bisphosphonates have this problem. That's why the recommendation is that around the 5-year point you can consider having a drug holiday or switching off the bisphosphonates.² The practice of giving a bisphosphonate drug holiday has become recognized only in the last few years. Before that, people who started bisphosphonates stayed on them for life.

Mascolini: When switching from bisphosphonates to another medication is an option, what are the switch possibilities for people with HIV?

Yin: There are several other agents. One is injectable teriparatide, or Forteo, which is an anabolic agent that stimulates osteoblasts to increase bone formation. So its mechanism is completely different from that of bisphosphonates, which work by inhibiting bone resorption by osteoclasts. There are reports of Forteo being used in HIV patients with good success without toxicity,⁸ so that is probably the second-line agent for HIV-infected individuals whose BMDs do not improve with bisphosphonates..

There are newer agents, such as injectable denosumab,⁹ a monoclonal antibody against RANK-ligand that has been approved for use in postmenopausal osteoporosis and is also being studied for corticoid-induced osteoporosis. Denosumab, however, has not been used in HIV patients because of a concern about increased infectious risks, since the treatment arm had more cases of skin and soft tissue infection in one of the pivotal approval trials for use in postmenopausal women.

Switching antiretrovirals, supplementing with calcium or vitamin D

Mascolini: When is it appropriate to switch from tenofovir disoproxil fumarate (TDF) or a ritonavir-boosted protease inhibitor (PI) because of low bone density?

Yin: Evidence is emerging for avoidance of TDF and possibly PIs in favor of raltegravir in patients with prior fracture and osteoporosis.² Clinicians might also consider avoiding or switching from these antiretrovirals in certain high-risk patients—those with fractures, older patients, and potentially those with HCV coinfection.

BMD data in people starting tenofovir alafenamide (TAF), the investigational tenofovir prodrug, are encouraging,¹⁰ so TAF may become an option for patients in whom TDF is not indicated. Data on the potential merits of switching from TDF to TAF are pending.^{11,12} Data on antiretroviral initiation with raltegravir or switching from TDF to raltegravir are also very encouraging. There are no data yet on changes in BMD with dolutegravir, but bone turnover marker findings are encouraging.

Mascolini: The new HIV bone guidelines are clear in suggesting when to switch people off TDF or boosted protease inhibitors in favor of other drugs.² How strong is that evidence?

Yin: I think data are strong for less bone loss with initiation of certain regimens and improvements with switches to other regimens. But I don't think those antiretroviral switches are necessarily indicated for everybody. I think we should consider switches in patients already at higher fracture risk—older

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Controlling body weight, gaining muscle mass with exercise, quitting smoking, and limiting alcohol drinking to moderate amounts are all . . . probably important in people who are at high risk of bone disease.

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people, certainly people who've already had a fracture, certainly those with low bone density. Those are the types of scenarios in which clinicians might want to get a patient off these antiretrovirals.

With the new antiretrovirals coming into use, and with the awareness of risk posed by TDF, in the future we are probably going to be prescribing first-line regimens that don't contain TDF. That change, in and of itself, may help prevent low bone density in some people with HIV. But right now there are a lot of patients taking TDF and doing quite well. We shouldn't switch everyone off TDF without a strong indication, because we probably would not see any benefit from doing that. But in select populations who are at higher risk for fracture or bone loss, I think we have good data to make that switch.

Mascolini: Where do calcium and vitamin D supplementation fit into the management picture?

Yin: We have clear data from a recently published study showing that supplementation with 4000 IU of vitamin D3 daily and 500 mg of calcium carbonate twice daily decreased bone loss with initiation of TDF/FTC/efavirenz (Atripla) in antiretroviral-naïve individuals.¹³ However, we're not certain what the ideal doses are, whether both vitamin D and calcium supplementation are necessary, whether supplementation will have the same effect when used with other antiretroviral regimens, or how long you

have to supplement for maximal impact. Aside from supplementation during antiretroviral initiation, it is prudent to supplement during puberty and older age or after the menopause.

When to get an endocrinologist's help

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Mascolini: What we've been talking about so far—screening and basic management of bone loss—are things most HIV clinicians will handle on their own. What are the scenarios in which clinicians should think about referring to a specialist?

Yin: When patients are not responding to straightforward interventions, you should consider referral. Let's say you switch someone off an antiretroviral and their bone density doesn't improve, and you're concerned and want to start a bone-specific therapy. That's not a bad indication for having an endocrinologist evaluate the patient to select the most appropriate therapy, such as which particular bisphosphonate to prescribe. Many primary care providers are comfortable making that first choice, and that's perfectly fine, but others will want an endocrinologist's help.

Most referrals involve people who don't respond to the bisphosphonates or who fracture while taking a bisphosphonate. Other scenarios in which an endocrinologist can help involve patients with

bisphosphonate toxicity, or patients who have taken a bisphosphonate for a number of years and may be a candidate for a drug holiday.

Mascolini: What else do you see looking ahead?

Yin: Management of low bone density and fracture risk is an area that will continue to evolve as new agents become available and as we gain a better sense of what risk factors are truly specific for HIV patients.

One HIV-related risk factor we haven't talked about is hepatitis C coinfection. Some observational studies make it clear that hep C is a very strong additive risk for fractures in HIV patients.^{14,15} [See "Heightened bone risk with HCV or HBV" on page 25] Whether treatment of hepatitis C will diminish that risk is still unclear. I think that will be a very interesting area to watch over the next few years as we begin to treat more patients with the new oral hep C agents.

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Bone density risk factors in people with HIV: a long, familiar list

By Mark Mascolini

Abstract: A list of osteoporosis risk factors compiled by the National Osteoporosis Foundation is long and detailed, yet it omits two factors confirmed by research and highly prevalent in people with HIV: HCV or HBV infection and opioid substance abuse or opioid substitution therapy. The National Osteoporosis Foundation does count HIV infection as a risk factor, a determination confirmed by plentiful research. Numerous classical risk factors are prevalent in some HIV populations, including low weight, smoking, heavy alcohol drinking, diabetes, kidney disease, stroke, depression, steroid use, and low testosterone. Bone mineral density drops 2% to 6% in the first 2 years of antiretroviral therapy, but continuing treatment does not appear to pose a further threat to bone health. New HIV bone guidelines suggest avoiding tenofovir disoproxil fumarate and protease inhibitors in people with a high fracture risk (previous fragility fracture, DXA-derived T score at or below -2.5, FRAX at or above 20%).

If you consult the National Osteoporosis Foundation web site (www.nof.org), you can count no fewer than 69 osteoporosis risk factors, including six uncontrollable risks, seven controllable risks, 16 medications, and 40 diseases or conditions (**Tables 1, 2, and 3**). Thorough, but hardly a handy checklist you can keep at your fingertips. And if you consult the HIV literature, you learn this 69-item tally has a few holes. The uncontrollable-risk list does not include white or Asian race (which the CDC and the Mayo Clinic do count). The controllable-risk list overlooks opioids and substance use. And the menu of diseases mentions liver disease but does not specify hepatitis C or B infection (HCV, HBV), amply documented as low bone mineral density risk factors in studies of people with and without HIV.

Table 1. National Osteoporosis Foundation: uncontrollable and controllable osteoporosis risk factors

Uncontrollable	Controllable
<ul style="list-style-type: none"> ■ Being over age 50 ■ Being female ■ Menopause ■ Family history of osteoporosis ■ Low body weight/being thin or small ■ Broken bones or height loss ■ White/Caucasian/Asian* 	<ul style="list-style-type: none"> ■ Not getting enough calcium and vitamin D ■ Not eating enough fruits and vegetables ■ Getting too much protein, sodium, and caffeine ■ Having an inactive lifestyle ■ Smoking ■ Drinking too much alcohol ■ Losing weight ■ Opioids or opioid substitution therapy/ substance abuse†

*Not listed by National Osteoporosis Foundation but counted by the Centers for Disease Control and Prevention (CDC) and the Mayo Clinic.

†Not listed by National Osteoporosis Foundation; established in studies of people with HIV.

Table 2. National Osteoporosis Foundation: medications linked to osteoporosis

<ul style="list-style-type: none"> ■ Aluminum-containing antacids ■ Antiseizure medicines (only some) such as Dilantin or phenobarbital ■ Aromatase inhibitors (for breast and ovarian cancer) such as Arimidex, Aromasin, and Femara ■ Cancer chemotherapeutic drugs ■ Cyclosporine A and FK506 (Tacrolimus) ■ Gonadotropin-releasing hormones (GnRH) such as Lupron and Zoladex ■ Heparin ■ Lithium ■ Medroxyprogesterone acetate for contraception (Depo-Provera, DMPA) 	<ul style="list-style-type: none"> ■ Methotrexate ■ Proton pump inhibitors (PPIs) such as Nexium, Prevacid, and Prilosec ■ Selective serotonin reuptake inhibitors (SSRIs), for depression such as Lexapro, Prozac, and Zoloft ■ Steroids (glucocorticoids) such as cortisone and prednisone ■ Tamoxifen (premenopausal use) ■ Thiazolidinediones (glitazones, for diabetes) such as Actos and Avandia ■ Thyroid hormones in excess
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Medications in **bold** are often taken by people with HIV infection.

Table 3. National Osteoporosis Foundation: diseases linked to osteoporosis

<p>Autoimmune disorders</p> <ul style="list-style-type: none"> ■ Rheumatoid arthritis ■ Lupus ■ Multiple sclerosis ■ Ankylosing spondylitis <p>Digestive and gastrointestinal disorders</p> <ul style="list-style-type: none"> ■ Celiac disease ■ Inflammatory bowel disease ■ Weight loss surgery and gastric bypass surgery ■ Gastrectomy ■ Gastrointestinal bypass procedures <p>Endocrine/hormonal disorders</p> <ul style="list-style-type: none"> ■ Diabetes ■ Hyperparathyroidism ■ Hyperthyroidism ■ Cushing syndrome ■ Thyrotoxicosis ■ Missing periods ■ Premature menopause ■ Low testosterone or estrogen in men <p>Hematologic/blood disorders</p> <ul style="list-style-type: none"> ■ Leukemia and lymphoma ■ Multiple myeloma ■ Sickle-cell disease 	<ul style="list-style-type: none"> ■ Blood and bone marrow disorders ■ Thalassemia <p>Neurologic/nervous system disorders</p> <ul style="list-style-type: none"> ■ Stroke ■ Parkinson disease ■ Multiple sclerosis ■ Spinal cord injuries <p>Mental illness</p> <ul style="list-style-type: none"> ■ Depression ■ Eating disorders <p>Cancer</p> <ul style="list-style-type: none"> ■ Breast cancer ■ Prostate cancer <p>Other diseases/conditions</p> <ul style="list-style-type: none"> ■ AIDS/HIV ■ Chronic obstructive pulmonary disease ■ Female athlete triad ■ Kidney disease ■ Liver disease ■ HCV or HBV infection* ■ Organ transplants ■ Polio and postpolio syndrome ■ Poor diet including malnutrition ■ Scoliosis ■ Weight loss
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Conditions in **bold** are highly prevalent in people with HIV infection.

*Not specified by National Osteoporosis Foundation but established in medical literature.

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Does HIV alone heighten low bone-density risk?

More than a few major risk factors highly prevalent in many HIV populations show up in the National Osteoporosis Foundation inventory, including smoking, heavy alcohol drinking, low weight, steroid use, diabetes, kidney disease, liver disease, stroke, depression, and low testosterone in men. And the Foundation cites HIV infection as a risk factor. Almost a dozen studies over the past decade implicate HIV infection as an independent risk factor for low bone mineral density (BMD) or fracture. Three other studies also found HIV an independent predictor—until weight got factored into the analysis.

A meta-analysis scrutinizing 11 cross-sectional studies published from 2000 through 2004 (five in the United States and the rest in Western Europe or Argentina) calculated that HIV infection independently bolstered chances of osteoporosis 3.7-fold (95% confidence interval [CI] 2.3 to 5.9).¹ The pooled analysis involved 884 people with HIV and 654 without HIV, about two thirds of them men and most in their mid-30s to mid-40s.

Ten studies published after the meta-analysis figured that HIV infection independently raised chances of lower BMD or fracture.²⁻¹¹ These studies include prospective and cross-sectional cohort surveys and case-control analyses. Eight of them took place in the United States,^{2-8,10} one in Switzerland,⁹ and one in Ireland.¹¹ Ages usually averaged in the 40s, though two studies involved postmenopausal US women^{6,7} and one involved US men 49 or older.³ Two other studies assessed only women.^{4,5}

What explains the higher bone-thinning risk in HIV-positive people in these studies? Two factors leap out as key contributors because adjustment for those factors

dimmed the impact of HIV on risk: shifts in bone metabolism and low weight. The bone-metabolism study involved 474 HIV-positive and negative people with similar demographic backgrounds in Dublin's UPBEAT Study Group.¹¹ Many study participants were women, 41%, with HIV and 56% without HIV; 40% and 25% with and without HIV were African, and median ages stood at 39 and 42. Among people with HIV, the largest proportion, 47%, got infected during heterosexual sex, 25% during gay sex, and 19% while injecting drugs.

Statistical analysis adjusted for body mass index and demographic and lifestyle factors independently linked HIV infection to lower BMD at the femoral neck (-0.62 g/cm^2 , $P < 0.0001$), total hip (-0.078 g/cm^2 , $P < 0.0001$), and lumbar spine (-0.060 g/cm^2 , $P = 0.0002$).¹¹ HIV remained independently associated with reduced BMD after further adjustment for bone biomarkers, though the impact dwindled. People with HIV had significantly higher bone turnover rates than HIV-negative controls ($P < 0.0001$).

Veterans Aging Cohort Study (VACS) investigators compared incident fragility fractures in male veterans with and without HIV.¹² More than half of the group, 55%, was black or Hispanic, and 34% were 50 or older. Statistical analysis adjusted for demographics, comorbid disease, smoking, and alcohol abuse figured that vets with HIV had a 24% higher fracture risk (adjusted hazard ratio [aHR] 1.24, 95% CI 1.11 to 1.39). But further adjustment for body mass index rendered the risk difference nonsignificant (aHR 1.10, 95% CI 0.97 to 1.25).

A 2007 meta-analysis considered 10 studies comparing HIV-positive adults with HIV-negative controls of comparable age and gender, all with weight or body mass index data.¹³ HIV-positive people averaged 5.1 kg lower in weight than negative

controls, a highly significant difference ($P < 0.001$). Unadjusted analyses found significantly lower BMD at all skeletal sites, ranging from 4.4% to 7.0% lower, in people with HIV ($P < 0.01$). After adjustment for weight, those differences became nonsignificant for the total body and lumbar spine and were smaller though still significant at the total hip (-0.02 g/cm^2 , 95% CI -0.04 to 0.00 , $P = 0.031$) and femoral neck (-0.04 g/cm^2 , 95% CI -0.07 to -0.01 , $P = 0.013$).

A 2015 study in the Netherlands compared osteoporosis rates in 581 people with HIV and 520 HIV-negative people with similar demographics, all of them 45 or older.¹⁴ Prevalent osteoporosis proved significantly more frequent in the HIV group, 13.3% versus 6.7% ($P < 0.001$). But statistical adjustment for body weight and smoking diluted this difference to nonsignificance.

Impact of antiretrovirals on weak-bone risk

Volumes could be written—indeed, volumes have been written—on whether antiretrovirals individually or en masse directly lower BMD. The bottom line: some do, but no one suggests avoiding or delaying antiretroviral therapy because it sends people to the hospital with fragility fractures.

The National Osteoporosis Foundation pointedly omits antiretrovirals from its 16-drug list of medications that make osteoporosis more likely (**Table 2**). And new HIV bone guidelines advise following national protocols on when to start antiretroviral therapy because treatment benefits “far outweigh the potential negative long-term effects on bone mass and metabolism, and fracture risk.”¹⁵ For people with a high fracture risk (previous fragility fracture, T score at or below -2.5 , FRAX at or above 20%), the guidelines suggest avoiding tenofovir disoproxil fumarate (TDF) and protease inhibitors (PIs) in first-line regimens and switching from those drugs if treatment has begun. (For findings on tenofovir alafenamide—TAF—and BMD, see page 41 of this issue).

Perhaps because many people start therapy with TDF, a PI, or both, BMD does drop 2% to 6% in the first 2 years of treatment, the bone guidelines acknowledge.¹⁵ But after that not much happens, according to a 6-year study comparing 44 men with HIV and 37 without HIV.¹⁶ The HIV group averaged 49 years in age and the control group 46. The groups did not differ significantly in weight or body mass index, but a significantly higher proportion of the HIV group smoked (37% versus 3%, $P < 0.001$). Men with HIV had been infected for an average 8 years.

HIV-positive men had DXA scans when antiretrovirals began and 2 and 6 years later. HIV-negative controls also had three DXA scans over 6 years. Six-year change in total body BMD did not differ significantly between men with and without HIV (+0.3% and +0.5%, $P = 0.15$), and the same proved true for total hip BMD (-0.6% and -0.1%, $P = 0.8$). Men with HIV gained significantly more lumbar spine BMD than did seronegative men through 6 years (+5.3% versus +0.3%, $P < 0.001$).

Anyone still wavering on whether to start (or continue) antiretroviral therapy in someone with a high fracture risk should consider the plentiful reports linking low CD4 count or high viral load to lower bone density or fracture. At least two studies tied higher viral load to lower BMD. The older study involved 161 consecutive HIV-positive people in Italy who completed a rigorous demographic questionnaire and testing for bone-related disease.¹⁷ Twenty-two of 48 antiretroviral-naïve people (46%) and 58 of 113 taking antiretrovirals (51%) had osteopenia or osteoporosis—a slim difference. Three classic risk factors—female gender, older age, and lower body mass index—individually predicted osteopenia or osteoporosis. And every 10-fold higher viral load at DXA scanning doubled chances of osteopenia or osteoporosis (adjusted odds ratio [aOR] 1.97, 95% CI

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1.16 to 3.34, $P = 0.01$) (**Figure 1**). Compared with antiretroviral-naïve people, the treated group did not run a higher risk of low bone density.

A more recent analysis pooled data from 796 participants in AIDS Clinical Trials Group (ACTG) studies in which everyone had whole-body DXA before starting first-line therapy and 96 weeks later.¹⁸ Participants lost an average 2% of BMD through 96 weeks of treatment.

The same three classic risk factors identified in the Italian study¹⁷—female gender, older age, and lower body mass index—emerged as independent predictors of a greater 96-week BMD drop. Higher pretreatment viral load independently predicted greater BMD loss (-0.56% lower per 10-fold higher viral load, $P = 0.02$) (**Figure 1**). Treatment with TDF or a PI also made losing more BMD more likely.

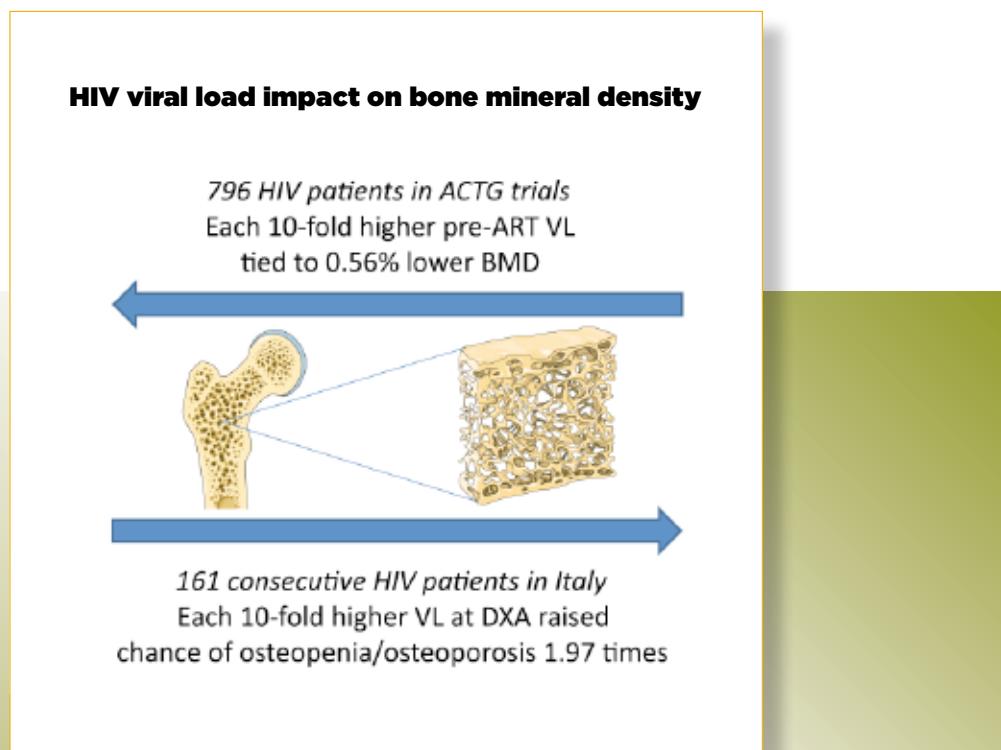


Figure 1. An ACTG analysis linked every 10-fold higher HIV load before antiretroviral therapy (ART) to 0.56% lower bone mineral density (BMD).¹⁸ In a series of 161 consecutive HIV patients in Italy, every 10-fold higher viral load before or during ART doubled chances of osteopenia or osteoporosis.¹⁷ (Osteoporosis images from Servier PowerPoint Library, <http://servier.com/Powerpoint-image-bank>.)

A half-dozen studies link lower baseline^{18,19} or nadir²⁰⁻²³ CD4 count to low BMD or fracture. In a single-center Australian case-control study of HIV patients with and without fractures, a current CD4 count below 500 cells/mm³ doubled the risk of fragility fracture.¹⁹ A count below 200 cells/mm³ (versus above 500) inflated fracture risk almost 7-fold. In the US HIV Outpatient Study (HOPS), a nadir CD4 count below 200 raised the risk of incident fracture 60%.²⁰ Together these studies show that uncontrolled HIV infection—signaled by high viral loads or low CD4 counts—threaten bone health more than antiretroviral therapy.

Heightened bone risk with HCV or HBV

Neither the National Osteoporosis Foundation nor the CDC counts hepatitis virus infection as an osteoporosis risk factor, though the Foundation more broadly lists “liver disease.” But plentiful evidence from recent meta-analyses and other studies confirms that either HCV or HBV adds to the bone-thinning risk with HIV. Testing for these viruses should be routine for people with HIV, regardless of bone risk, because both can be treated and HBV can be prevented by vaccination. The added bone risk with hepatitis virus infection should offer an extra prod to test HIV patients for these viruses.

Two recent meta-analyses established a tie between HCV/HIV coinfection and osteoporosis or fracture compared with HIV alone or no infection. The more recent analysis considered studies published up to April 2013 that assessed endpoints of BMD or incident fracture in HCV/HIV-coinfected people compared with HIV-monoinfected people or HCV/HIV-negative individuals.²⁴ The investigators found 13 studies—six considering BMD and seven fracture—involving 427,352 people. Compared with HIV-monoinfected individuals (but not uninfected people), HCV/HIV-coinfected people had a doubled chance of low bone density (pooled OR 1.98, 95% CI 1.18 to 3.31). Fracture risk proved more than 50% higher

with coinfection than with HIV alone (pooled relative risk [RR] 1.57, 95% CI 1.33 to 1.86). Fractures were more than twice as likely with HCV/HIV coinfection than with neither infection in cohort studies (pooled RR 2.46, 95% CI 1.03 to 3.88) or in cross-sectional studies (pooled OR 2.30, 95% CI 2.09 to 2.33).

Exploring 15 studies presented through 2013—nine focused on BMD and six on fracture—another team reached similar conclusions.²⁵ HCV/HIV-coinfected people had 63% higher odds of osteoporosis than HIV-monoinfected people (OR 1.63, 95% CI 1.27 to 2.11). Coinfected individuals had a 77% higher overall fracture incidence than HIV-monoinfected people (pooled incidence rate ratio [IRR] 1.77, 95% CI 1.44 to 2.18) and almost a tripled fracture incidence compared with uninfected people (pooled IRR 2.95, 95% CI 2.17 to 4.01). This analysis confirmed the importance of classical bone risk factors in these populations—older age, lower BMI, smoking, and alcohol and substance abuse.

These investigators noted that people with HCV/HIV may run a higher fracture risk because of behaviors that boost chances of bone-breaking trauma.²⁵ But they doubted such dangerous behavior completely explains the inflated risk because adjustment for alcohol and substance use did not eliminate the higher fracture risk with HCV. Rather, they observed, research shows that chronic liver disease upsets healthy bone remodeling.²⁶⁻²⁸ Other research suggests chronic inflammation resulting from HIV infection promotes bone resorption (breakdown).²⁹ Reason suggests that the added inflammation due to HCV coinfection would compound that process.

Less work addresses the interplay between HBV infection—with or without HIV—and bone risk. A recent study compared incident hip fracture in four US Medicaid populations—4156 people dually

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treated for HBV and HIV, 2015 treated only for HBV monoinfection, 96,253 treated for HIV monoinfection, and 746,794 HBV/HIV-negative people.³⁰ Through 5 years the HBV/HIV group had a 37% higher risk of hip fracture (aHR 1.37, 95% CI 1.03 to 1.83) than HIV-monoinfected people and a 35% higher risk than uninfected people (aHR 1.35, 95% CI 1.03 to 1.84).

Substance use, old age, young age

Apart from drinking too much alcohol and smoking, substance use—particularly with opioids or opioid substitutes—figures prominently in bone-risk research but has not earned a place on the 69-item National Osteoporosis Foundation risk list. Here's some of the evidence:

A prospective study of 245 middle-aged women with HIV and 219 women without HIV—about half of them opioid or cocaine users—determined that methadone therapy independently predicted waning BMD at the femoral neck.⁵ Current methadone use also predicted falling BMD (at the total hip) in a

study of 230 men with HIV and 159 without HIV, all of them 49 or older and nearly all of them opioid or cocaine users.³¹ This prospective study linked heroin use plus AIDS to falling BMD at the total hip or femoral neck. Two other studies tied methadone treatment to lower spine BMD in 495 middle-aged women with or without HIV² and 559 men 49 or older and with or without HIV.³

Incidence of diverse major chronic diseases ratchets relentlessly upward with age, and osteoporosis is no exception. As prevalence of predisposing comorbid diseases climbs and bone mass dwindle with age, risk of osteoporosis and osteoporotic fracture grows apace. And fracture risk with age appears to climb faster with age in people with HIV than in HIV-negative people, suggest results of a large cross-sectional study at Boston's Partners HealthCare System.³² The analysis compared 8525 HIV-positive adults with 2.2 million HIV-negative people in the same system, all of them seen at some point between October 1996 and March 2008. Fragility fracture prevalence rose steeply starting at age 40 in both the HIV-positive and negative groups, but the climb was steeper among both women and men with HIV than in their HIV-negative counterparts (**Figure 2**).

Difference in fragility fracture prevalence with age in HIV+ vs HIV-women and men

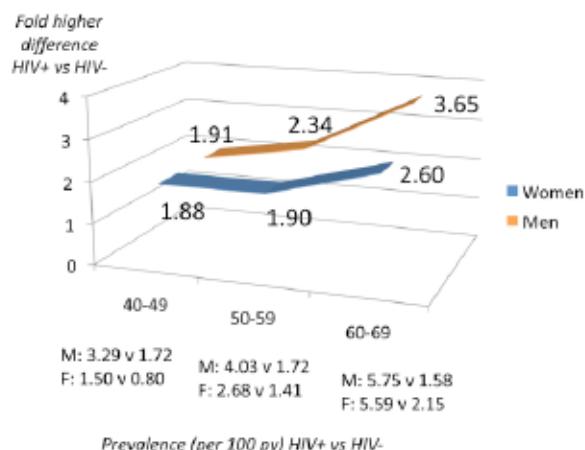


Figure 2. Fragility fracture prevalence in a Boston healthcare system rose faster with age in women and men with HIV than in those without HIV.³²



The risk imbalance between people with and without HIV may begin early in life—even before people reach peak bone mass in their early 20s—if children are infected at birth or in adolescence. The impact of early HIV infection came clear in a three-way comparison involving perinatally and behaviorally HIV-infected young men and healthy controls.³³

The researchers cited five previous studies that recorded lower BMD in perinatally and behaviorally infected children and adolescents than in HIV-negative controls, even after adjustment for sexual maturation stage, height, and weight. But they noted that DXA has limitations in growing children that may make comparisons between HIV-positive and negative youngsters unreliable. Thus they used both DXA and high-resolution peripheral quantitative CT (HR-pQCT) to measure BMD in this cross-sectional study of 15 perinatally HIV-infected men, 15 men infected during adolescence, and 15 healthy HIV-negative controls.³³ Everyone was between 20 and 25 years old, everyone had reached Tanner stage 5, and all HIV-positive men were on antiretroviral therapy. People usually attain peak bone mass by age 20. Among men with HIV, 60% were black and 40% Hispanic. Among controls, 20% were black and 80% Hispanic. Height, weight, body mass index, smoking status, and alcohol use did not differ significantly between study participants with and without HIV.

Men with and without HIV had similar bone size, but DXA-derived BMD Z scores proved significantly lower in HIV-positive men than in healthy controls at the spine, hip, and radius. HR-pQCT showed significantly lower total and trabecular volumetric BMD at the radius (forearm) and tibia (shin) in men

with HIV. Cortical and trabecular thickness were also significantly lower in men with HIV at the radius and tibia. Other bone measures also favored men without HIV. No DXA or HR-pQCT results differed significantly between perinatally and behaviorally infected men with HIV.

The investigators believe their data “suggest that men infected with HIV early in life have lower peak bone mass, a thinner cortical shell, markedly abnormal trabecular bone microstructure with deficiencies in trabecular plates and axial bone volume fraction, and reduced bone strength.”³³ They proposed that “these deficits may place them at higher risk of fractures as they age than uninfected individuals and HIV-infected individuals who were infected later in life, after acquisition of peak bone mass.”

Osteoporosis risk pieces not so puzzling

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With the National Osteoporosis Foundation 69-item risk lists (**Table 1, 2, and 3**) as a starting point, findings outlined in this article suggest a simpler schema for judging and lowering risk in people with HIV. The blueprint hinges on six immutable risk factors (**Figure 3**, center), with the understanding that low weight can be improved if its cause is poor nutrition or eating disorders. Six lifestyle changes (**Figure 3**, left) can lower chances of poor bone health regardless of fixed risk factors. Six comorbidities prevalent in people with HIV (**Figure 3**, top right) add to the risk of osteoporosis, but all these diseases can be prevented or treated. Five types of nonantiretroviral medications often taken by people with HIV (**Figure 3**, bottom right) can hike the risk of bone disease and should be considered in the risk equation.

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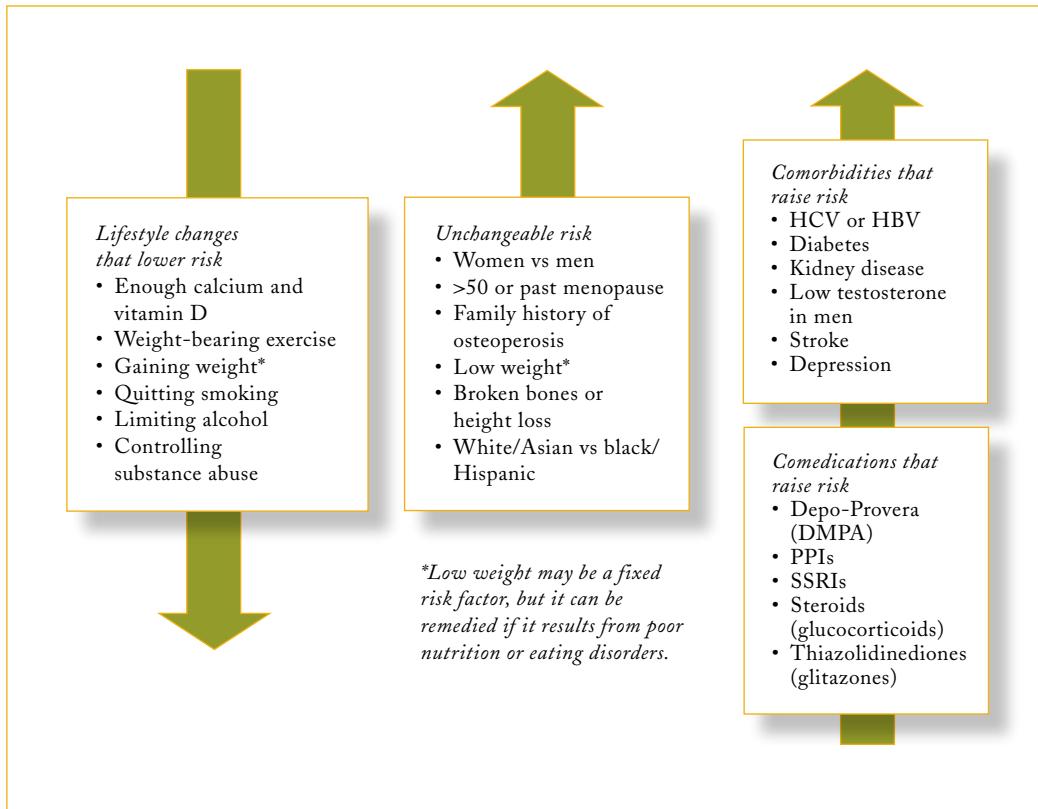


Figure 3. A simplified osteoporosis risk schema for people with HIV considers fixed risk factors (center), lifestyle changes that can lower risk (left), and diseases and medications common in many HIV populations (right). PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors. (Based mainly on National Osteoporosis Foundation risk lists, www.nof.org.)

The Figure 3 framework abridges the National Osteoporosis Foundation risk factor list by focusing on those most often pinpointed in studies of people with HIV. Still, it remains too lengthy for most to memorize. But anyone can keep in mind the three prime risk factors HIV bone guidelines list for fragility fracture:¹⁵

1. History of fragility fracture
2. Glucocorticoids for more than 3 months (≥ 5 mg of prednisone daily or equivalent)
3. High risk for falls

The following article in this issue covers fragility fracture risk assessment according to the new guidelines.¹⁵

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When to use FRAX and DXA—and what they mean

By Mark Mascolini

Abstract: New guidelines for evaluating and managing osteoporotic bone disease in people with HIV recommend FRAX screening for men 40 to 49 years old and for premenopausal women over 40. DXA scanning should be deployed for men 50 or older, postmenopausal women, and people with certain fragility fracture risk factors. A FRAX result predicting a 10% or lower fragility-fracture risk in the next 10 years means patients should be counseled on calcium and vitamin D intake and on lifestyle issues that may affect bone changes. People with a FRAX result above 10% should have DXA to measure bone mineral density. Repeat FRAX or DXA screening depends on initial results and whether a person starts bisphosphonate therapy. Analysis of 50- to 70-year-old male veterans with or without HIV determined that FRAX underestimates fracture risk in older men with HIV.

Detailed up-to-date advice on screening and monitoring HIV-positive people for weak bones—with an eye toward preventing fracture—had gone lacking until US, European, and Australian collaborators published thorough and lucid guidelines early in 2015.¹ Reflecting briefer prior recommendations from the European AIDS Clinical Society (EACS),² the new guidelines endorse the simple Fracture Risk Assessment Tool (FRAX) without DXA scanning for HIV-positive men 40 to 49 years old and for premenopausal women 40 or older (**Figure 1**). Men 50 or older, postmenopausal women, and people with certain fracture risk factors (**Figure 1**) should undergo DXA. Research presented just after these guidelines appeared found

that FRAX underestimates fracture risk in HIV-positive men over 50, as discussed below.³

How FRAX and DXA work

World Health Organization (WHO) experts devised a simple online algorithm that lets clinicians plug in easily obtained clinical variables (see Note 4), click a button, and get a 10-year prediction of (1) hip fracture risk and (2) major osteoporotic fracture risk (spine, hip, wrist, upper arm). Femoral neck bone mineral density (BMD) can be added to the algorithm, but the calculation works without it. In people with HIV, FRAX does not predict DXA-determined osteoporosis or *prevalent* fracture.³

DXA—short for dual-energy x-ray absorptiometry—beams low-dose x-rays with two distinct energy peaks through the target bone.⁵ Soft tissue absorbs one peak while bone absorbs the other. Subtracting the soft-tissue value from the total value yields BMD. A DXA T score compares a patient's BMD with that of a young adult of the same gender, as follows:

- A value above -1 means normal BMD
- A value between -1 and -2.5 means osteopenia
- A value below -2.5 means osteoporosis

A DXA Z score indicates a person's BMD compared with people the same age, the same size, and the same gender. Z scores at or below -2 indicate low BMD for age, but Z scores are not used to diagnose osteoporosis.¹

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When and how to use FRAX and DXA

New bone screening guidelines for adults with HIV start by dividing people into those with no fragility-fracture risk factors and those with risk factors, which include (1) history of fragility fracture, (2) glucocorticoid treatment for more than 3 months, and (3) a high risk of falls (**Figure 1**).¹ People with fragility-fracture risk factors should get a DXA scan; people without risk factors should be considered for

FRAX or DXA according to age or menopause status (**Figure 1**). (Fragility fractures are those following minimal trauma and usually affecting the hip, spine, or wrist.⁶)

What do FRAX and DXA results say about planning care and planning follow-up? A FRAX score predicting a 10% or lower fragility-fracture risk in 10 years means patients should be counseled on calcium and vitamin D intake and on lifestyle issues that

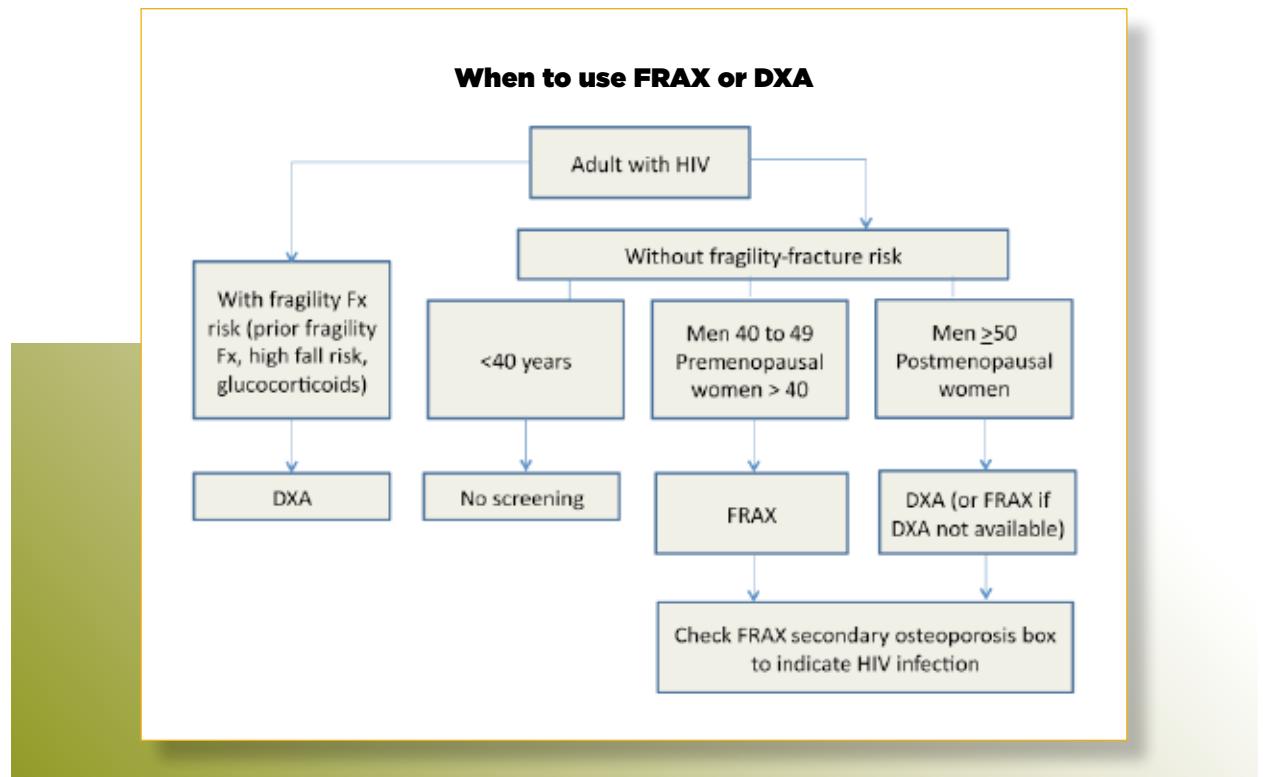


Figure 1. A US-European team recommends FRAX, DXA, or no screening for fragility-fracture risk depending on current risk factors and age.¹ Fx, fracture.

may affect bone changes—like alcohol, smoking, and weight-bearing exercise (**Figure 2**). (See the article starting on page 20.) People with a FRAX result above 10% should have DXA to measure BMD, and those with a FRAX at or above 20% should undergo DXA and may be candidates for bisphosphonate therapy after the clinician excludes secondary causes of osteoporosis.

For people without a prior fracture and a FRAX below 20%, those with a lowest DXA-calculated T score above -2.5 should get calcium, vitamin D, and lifestyle advice (**Figure 2**). In the United States (1) a T score at or below -2.5 at the femoral neck, total hip, or lumbar spine, or (2) a T score between -1.0 and -2.5 and a

FRAX score at or above 20% or at or above 3% at the hip, or (3) a hip or vertebral fracture should lead clinicians to consider bisphosphonates—plus vitamin D, calcium, and lifestyle advice—after excluding secondary causes of osteoporosis or low BMD.

HIV-positive people with a FRAX score at or below 10% should have a follow-up FRAX in 2 to 3 years or if a new fracture risk factor develops (**Figure 3**). People with a FRAX below 20% and no fracture history should have another DXA in 1 to 2 years if they have advanced osteopenia (T score -2.00 to -2.49) and in 5 years if they have mild to moderate osteopenia (T score -1.01 to -1.99). People who start bisphosphonates need a follow-up DXA after 2 years.

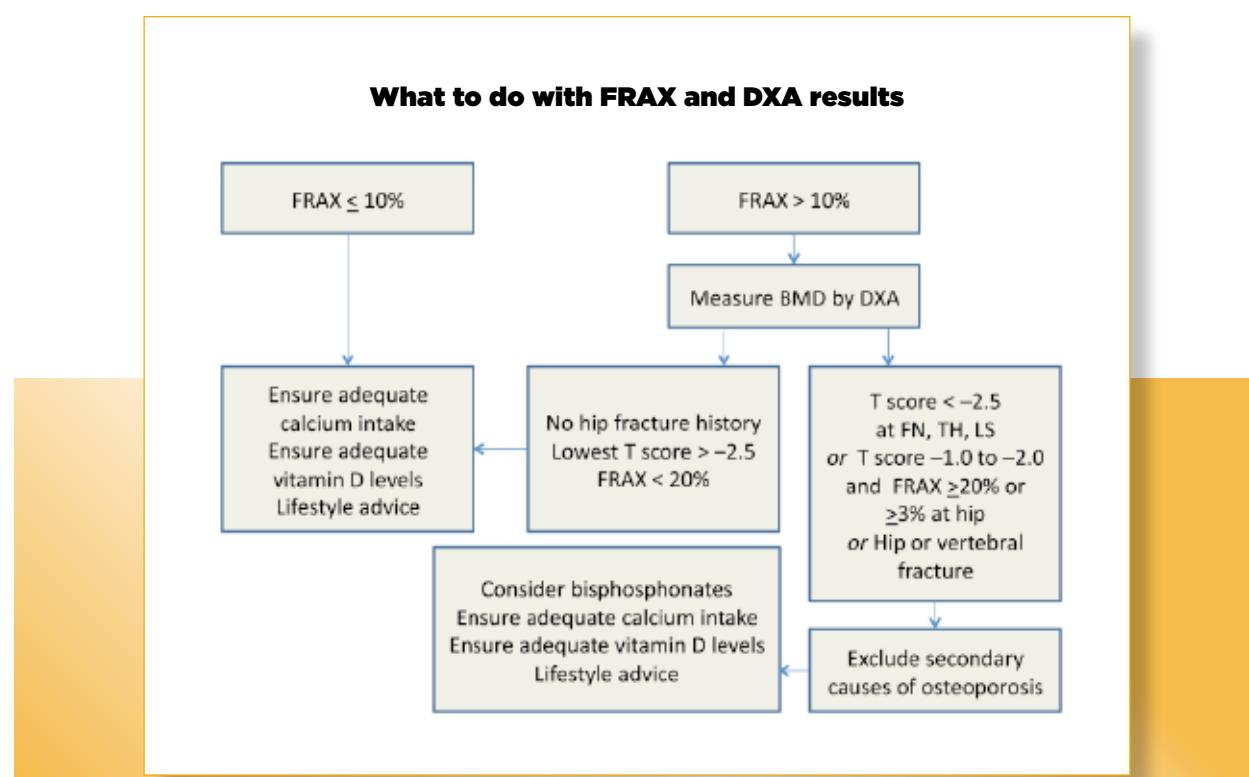


Figure 2. Recent bone guidelines for people with HIV suggest management based on FRAX and DXA results.¹ BMD, bone mineral density; FN, femoral neck; LS, lumbar spine, TH, total hip.

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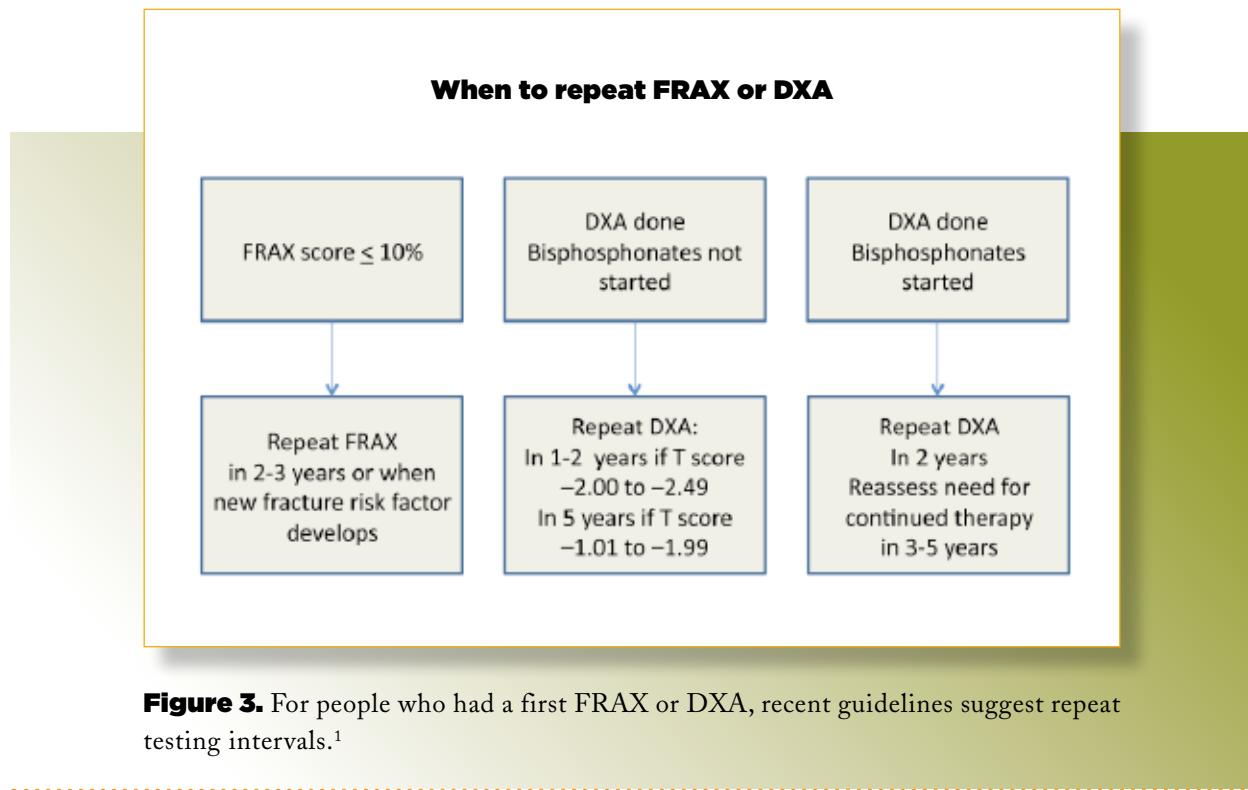


Figure 3. For people who had a first FRAX or DXA, recent guidelines suggest repeat testing intervals.¹

Aiming to figure how often DXA scans should be repeated, Spanish researchers analyzed 1639 DXAs in 391 HIV-positive people to gauge abnormal BMD progression risk.⁷ Everyone in the analysis had at least two DXAs from 2000 through 2009. Initial scans indicated that 29% had normal BMD, 50% had osteopenia, and 22% had osteoporosis. Using these baseline BMD findings, the investigators divided people into tertiles at low risk, middle risk, and high risk of progression from normal BMD to osteopenia and from osteopenia to osteoporosis (**Table 1**). The new HIV bone guidelines¹ suggest repeat DXA intervals prudently within the progression bounds found in the Spanish study.

FRAX underestimates fracture risk in older HIV+ men

Shortly after release of the new HIV bone guidelines,¹ researchers reported results of a large comparison of 50-and-older men with or without HIV indicating that FRAX underestimates fracture risk more in men with HIV “and does not discriminate well between those at risk and not at risk for future fracture.”³ The new guidelines reflect this result in recommending DXA—not FRAX—for men over 49,¹ but the FRAX study raises concern because no one assumes a clean cutoff at age 50 that renders FRAX inaccurate over 50 and accurate under 50.

Table 1. Rates of BMD progression in 391 HIV patients with at least 2 DXAs

	Progression from normal BMD to osteopenia: 35.7% in median 6.7 y		
	Low risk: T score > -0.2	Middle risk: T score -0.2 to -0.6	High risk: T score -0.6 to -1.0
Median time to progression	8.7 y	>7.2 y	1.7 y
Progression from osteopenia to osteoporosis: 23.7% in median >8.5 y			
	Low risk: T score > -1.1 to -1.6	Middle risk: T score -1.6 to -2	High risk: T score -2 to -2.4
Median time to progression	>8.2 y	>8.5 y	3.2 y

Source: Negredo et al.⁷

With a team of US colleagues, Columbia University's Michael Yin (a member of the guideline panel¹) studied 50- to 70-year-old HIV-positive and negative men in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) who had complete data from 2000 for all FRAX algorithm variables except secondary osteoporosis and parental hip fracture. For 7064 men with HIV and 17,387 without HIV, the investigators searched the VACS database to determine how many men had a hip, spine, wrist, or upper arm fracture from 2001 through 2010.

The HIV-positive and negative groups both averaged 56 years in age, and similar proportions were black (48% and 46%) or white (44% versus 45%). Veterans with HIV weighed significantly less than veterans without HIV (average 79 versus 89 kg, $P < 0.01$), and higher proportions of positive men had a previous fracture (2.4% versus 1.8%, $P = 0.003$) and used glucocorticoids (0.3% versus 0.1%, $P = 0.02$). But lower proportions of HIV-positive vets smoked (5.2% versus 6.3%, $P < 0.01$) and had rheumatoid arthritis (2.7% versus 3.5%, $P < 0.01$). (These are all variables in the FRAX equation.)

Osteoporotic fracture incidence in the 10-year study period proved significantly higher in veterans with than without HIV (4.61% versus 3.50%, $P < 0.0001$), as did hip fracture incidence (1.32% versus 0.85%, $P = 0.0008$). FRAX-estimated 10-year fracture rates fell well short of actual fracture rates for both major osteoporotic fractures (2.85% with HIV versus 2.71% without HIV, $P < 0.0001$) and hip fractures (0.29% with HIV versus 0.24% without HIV, $P < 0.0001$). In the interview starting on page 14, Yin characterizes these findings as "illustrative but not definitive" because the analysis had to leave out two FRAX variables.

Next Yin and colleagues refigured FRAX predictions for men with HIV after checking the secondary osteoporosis box in the FRAX form as a surrogate for HIV infection. The 10-year prediction for major osteoporotic fractures rose 31% as a result, and the 10-year prediction for hip fractures jumped 67%. But both resulting predictions still substantially lagged observed fracture rates in HIV-positive vets.

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The investigators calculated FRAX predictive accuracy as the agreement between observed fractures and FRAX-estimated fractures by an observed/estimated (O/E) ratio that indicates perfect accuracy if O/E = 1.0. FRAX accuracy significantly missed the ideal ratio in HIV-negative veterans (O/E ratio 1.29, 95% confidence interval [CI] 1.19 to 1.40) and missed the mark by an even wider margin in men with HIV (O/E ratio 1.62, 95% CI 1.45 to 1.81). Predictive accuracy in men with HIV improved to a level similar to HIV-negative men when the analysis included HIV as a cause of secondary osteoporosis, but even after this correction accuracy lay significantly beyond the ideal mark (O/E ratio 1.20, 95% CI 1.08 to 1.34).

Yin and coworkers concluded that FRAX as they calculated it (leaving out two algorithm variables) has limited accuracy in HIV-positive men over 50. Checking the secondary osteoporosis box as a surrogate for HIV infection improved accuracy but still underestimated the actual fracture rate. They proposed that “the exact role of FRAX for risk stratification in HIV-infected individuals for DXA screening or pharmacologic treatment requires additional study.”³ In the interview starting on page 14, Yin suggests “there’s room for a better prediction algorithm,” but designing a better algorithm that uses only clinical variables won’t be easy.

One way to improve FRAX accuracy in people with HIV may be combining it with the Aging Males Symptoms (AMS) scale, an 18-question form developed by the Berlin Center for Epidemiology and Health Research and available online.⁸ But the findings come from a small cross-sectional study of only 50 antiretroviral-treated men with HIV and 27 controls.⁹

The AMS scale tallies symptoms related to hypogonadism (low testosterone), a recognized secondary cause of osteoporosis. A score at or above

27 is abnormal. All study participants had a DXA scan, spinal x-ray, and hormonal evaluation, and all completed the AMS questionnaire. DXA diagnosed osteoporosis in 24% of men with HIV and 4% of controls ($P = 0.05$); 18% of the HIV group and no controls had radiologic fractures. Calculated free testosterone levels indicated hypogonadism in 26% of men with HIV and 4% of controls ($P = 0.04$). Almost two thirds of men with HIV (62%) had an abnormal AMS score, compared with 41% of controls ($P = 0.04$).

ROC curve analysis indicated that FRAX had only 23% sensitivity but 100% specificity in identifying osteoporosis. (Sensitivity is the ability of a test to identify a condition in people with that condition; specificity is the ability of a test to identify people without a condition as not having that condition.) An abnormal AMS score yielded a sensitivity of 82.6% and a specificity of 42.9%. Combining FRAX with AMS resulted in 77.3% sensitivity and 69% specificity.

The new HIV bone guidelines¹ do not weigh in on the potential value of the AMS score in predicting bone fragility. The guidelines do recommend assessing hypogonadism as a possible cause of osteoporosis in HIV-positive men (evaluated by morning measurement of free testosterone) and women (evaluated by menstrual history, estradiol, follicle-stimulating hormone, prolactin). The guidelines list nine other potential secondary causes of osteoporosis that should be evaluated in people with HIV: vitamin D deficiency, hyperparathyroidism, subclinical hyperthyroidism, Cushing syndrome, phosphate wasting, idiopathic hypercalcuria, celiac sprue, multiple myeloma, and mastocytosis (guidelines Table 5¹).

If FRAX has screening limitations, why not just send everyone for a DXA scan straightaway? That’s what Italian clinicians asked in a study of 163 middle-aged HIV-positive people at their center.¹⁰ This analysis of

universal DXA produced evidence that almost one fifth of HIV-positive adults with low bone density would be missed if screened by risk factor-based guidelines.

The study involved all adults seen from April 2009 through March 2011 who agreed to DXA screening.¹⁰ Most study participants (71%) were men, and age averaged 44.2 (+/-10), so a portion of these people—those younger than 40—would not be considered for DXA or FRAX by the new bone guidelines.¹ Body mass index averaged a healthy 23.7 kg/m², but half of the group smoked, vitamin D levels averaged a deficient 15.2 ng/mL, and only 37% of the group exercised regularly. Defining osteopenia as a femoral or lumbar spine Z score at or below -2, the researchers diagnosed osteopenia in 32 people (19.6%). Six of those 32 (18.8%) would not be offered DXA by current Italian HIV guidelines, which call for DXA scans in anyone with HIV plus two more osteoporosis risk factors. Results were similar when the investigators used EACS guidelines.²

The drawbacks of a DXA-for-all strategy are clear: time and money. The procedure itself takes 10 to 30 minutes,⁵ not counting time for scheduling and preparing a person for scanning. In the United States DXA scanning could cost the patient \$150 to \$250,^{11,12} and staff time must be added to that. Staff time is the only cost for completing the FRAX algorithm. And as Michael Yin points out in the interview starting on page 14, *both* DXA and FRAX are less useful in predicting fracture in younger people because overall fracture risk is lower in younger people.

Screening for subclinical vertebral fracture

Clinicians may be unaware of another strong fracture predictor in people with HIV, according to the

new bone guidelines.¹ One quarter of HIV-positive people break their back and never notice, and these subclinical vertebral fractures boost the risk of later vertebral fracture 5-fold and the risk of other fractures 2- to 3-fold.¹³ US osteoporosis guidelines add that these hidden fractures are linked to pain, disability, deformity, and death.¹³ To uncover subclinical broken vertebrae, providers should measure the height of every HIV patient 50 or older every 1 to 2 years.¹ Losing height suggests covert cracked vertebrae.

HIV bone guidelines¹ suggest lateral x-rays of the lumbar and thoracic spine or DXA-based vertebral fracture assessment to identify subclinical vertebral breaks in three groups:

- Postmenopausal 50- to 64-year old women and 50- to 69-year-old men with fragility risk factors (historical height loss ≥ 4 cm [1.5 inches], prospective height loss ≥ 2 cm [0.8 inches]), or recent or ongoing long-term glucocorticoid treatment)
- Women 65 to 69 years old and men 70 to 79 years old with BMD T score -1.5 or lower
- Women 70 or older and men 80 or older with BMD T score below -1.0 at the spine, total hip, or femoral neck

The guidelines go on offer advice on care for HIV-positive people at risk for fragility fracture, including antiretroviral management, bisphosphonate use, and vitamin D and calcium supplementation.¹ The article starting on page 39 of this issue considers these therapies.

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Bisphosphonates for bone — and advice on ARVs, calcium, vitamin D, glitazones

By Mark Mascolini

Abstract: HIV-positive people with a high fracture risk (indicated by a previous fracture, low bone mineral density, or a high FRAX score) should be considered for bisphosphonate therapy, according to 2015 HIV-bone health guidelines. These guidelines stress that the advantages of antiretroviral therapy far outweigh a possible negative impact on bones, but they advise avoiding tenofovir disoproxil fumarate and ritonavir-boosted protease inhibitors in people with a high fracture risk. HIV-positive people should be advised to get adequate calcium and vitamin D. Research indicates that most people in the United States do not consume enough calcium in their diets and most have insufficient levels of vitamin D. Whether vitamin D supplementation offers clinical benefits to people with HIV remains unclear. Glitazones are linked to bone loss.

New bone health guidelines for HIV providers offer straightforward advice on when to use bisphosphonates, when to use antiretrovirals, and which antiretrovirals to use, based on dual-energy x-ray absorptiometry (DXA)-derived bone mineral density (BMD) and FRAX osteoporotic fracture prediction scores.¹ The guidelines say one of four variables indicates fracture risk in people with HIV and should encourage clinicians to consider bisphosphonate therapy (**Figure 1**): (1) previous fragility fracture, (2) DXA-derived T score at or below -2.5 at the lumbar spine, total hip, or femoral neck in postmenopausal women or older men, (3) T score between -2.5 and -1.0 and a FRAX major osteoporotic fracture score at or above 20% or a FRAX hip fracture score at or above 3% for postmenopausal women or older men, or (4) a FRAX osteoporotic fracture score (without DXA-derived BMD) at or above 20%.

Guideline advice on bisphosphonates and antiretrovirals

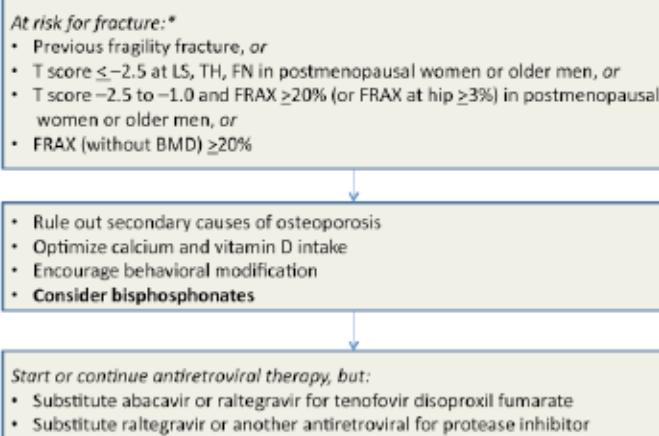


Figure 1. Current bone health guidelines for people with HIV offer clear advice on when to consider bisphosphonates and when to substitute another antiretroviral for tenofovir disoproxil fumarate (TDF) or a ritonavir-boosted protease inhibitor.¹ The guidelines recommend following national or regional protocols on evaluating fracture risk (*US guidelines shown here) and when to start antiretroviral therapy, regardless of fracture risk. FN, femoral neck; LS, lumbar spine; TH, total hip.

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HIV-positive people with one of those traits should be checked for secondary causes of osteoporosis and such causes (Table 5 in guidelines¹), if identified, should be treated. Otherwise, clinicians should optimize calcium and vitamin D intake (discussed below), encourage physical activity (**Table 1**), smoking cessation, and moderate alcohol drinking, and they should consider starting bisphosphonates.

Table 1. Weight-bearing exercise and population-attributable risks

Weight-bearing exercises	Population-attributable risk
<ul style="list-style-type: none"> ■ Walking, jogging, running ■ Tennis or racquetball ■ Field hockey ■ Stair climbing ■ Jumping rope ■ Basketball ■ Dancing ■ Hiking ■ Soccer ■ Weight lifting 	<p>A population-based study in Norway found that population-attributable risk (PAR) for hip fracture was higher for low physical activity than for other risk factors:</p> <ul style="list-style-type: none"> ■ Low physical activity: PAR 0.151 ■ Smoking: PAR 0.081 ■ Excessive alcohol: PAR 0.01 <p>PAR measures the portion of new fractures in the population that can be attributed to an individual factor if there is a causal relationship.</p>

Sources: Centers for Disease Control and Prevention. Nutrition for everyone. Calcium and bone health. <http://www.cdc.gov/nutrition/everyone/basics/vitamins/calcium.html>; Pripp AH, Dahl OE. The population attributable risk of nutrition and lifestyle on hip fractures. *Hip Int.* 2015; 25:277-281.

Antiretrovirals: PIs, TDF, and TAF

Bone variables should not dissuade clinicians from starting or continuing antiretroviral therapy (ART), the guidelines say. As with any patient, “local or national guidelines for initiation and choice of ART regimen should be followed.”¹ But, the guidelines advise, people who meet one of the fracture risk criteria described above should not start tenofovir disoproxil fumarate (TDF) or a ritonavir-boosted protease inhibitor (PI), and those already taking TDF or a boosted PI should switch. The guidelines list abacavir and raltegravir as switch options for TDF and raltegravir as a switch option for PIs. What about other integrase inhibitors? For now, these experts say, evidence supporting use of other integrase agents remains too scant.

Will tenofovir alafenamide (TAF) sidestep the bone and kidney trouble seen with TDF? Forty-eight-week results of a randomized trial suggest it will,^{2,3} though some wary clinicians reserve judgment until TAF builds a record in clinical practice. Combined results of identical phase 3, double-blind, double-dummy trials found TAF virologically noninferior to TDF when either came packed in a single tablet with elvitegravir, cobicistat, and emtricitabine.³ The trials involved 1733 people starting their first regimen, all with an estimated glomerular filtration rate at or above 50 mL/min and none with hepatitis B or C. Concentrations of tenofovir in plasma—where it spells toxicity trouble for people—were 91% lower with TAF than with TDF. Tenofovir levels inside cells—where it spells trouble for HIV—were 4 times higher with TAF.³

Average hip bone mineral density (BMD) fell marginally in the TAF group through 48 weeks (-0.66%) while dropping 4.5-fold more in the TDF arm (-2.95%), a significant difference ($P < 0.001$).² Average spine BMD fell 1.30% with TAF plus the other drugs versus 2.86% with TDF and the other drugs ($P < 0.001$). Almost half of study participants randomized to TDF (45%) endured a 3% or greater decline in spine BMD, compared with 26% randomized to TDF. Respective proportions of participants who lost 3% or more hip BMD were 50% and 17%. Two bone turnover markers—C-telopeptide and P1NP—rose significantly less with TAF than TDF. Signals of kidney toxicity also significantly favored TAF. Results of a trial in which people switch from TDF to TAF will be presented in 2015.

Guidance on bisphosphonates, calcium, vitamin D

Do bisphosphonates work in people with HIV? A 2014 meta-analysis of eight randomized controlled trials showed they boost BMD at the spine and hip through 96 weeks, though the trials did not last long enough to figure whether treatment prevents fracture.⁴ The analysis involved five trials of oral alendronate and three trials of intravenous zoledronate (zoledronic acid). Pooled results showed a mean difference in spine BMD of 6.76% favoring the bisphosphonates over placebo or no treatment and a mean difference of 3.2% in hip BMD favoring the bisphosphonates. No one dropped out of alendronate trials because of drug-related side effects, while 2 of 104 taking zoledronate dropped out for that reason. Guideline-recommended doses are 70 mg orally once weekly for alendronate (plus 1000 mg of calcium carbonate and 400 IU vitamin D daily) and 5 mg of zoledronate intravenously yearly.¹ These guidelines also advise reviewing bisphosphonate therapy after the first 3 to 5 years because of concerns over suppressing bone turnover that long.¹ In the interview starting on page 14, Michael Yin discusses two other bone-preserving agents, teriparatide (Forteo) and denosumab (a monoclonal antibody against RANK-ligand).

The new HIV bone guidelines urge clinicians to ensure adequate daily calcium for postmenopausal women and for men 50 or older.¹ Men 51 to 70 years old should get 1000 mg of calcium daily, while women 51 or older and men 71 or older should get 1200 mg daily, which are the Recommended Dietary Allowances (RDAs) in the United States. The guidelines suggest first advising people on sources of dietary calcium (**Table 2**) and turning to calcium supplements if the dietary approach fails.

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Table 2. Prime dietary sources of calcium

Highest food-group sources

- Dairy products: low-fat or nonfat milk, cheese, yoghurt
- Dark green leafy vegetables: bok choy and broccoli
- Calcium-fortified foods: orange juice, cereal, bread, soy products, tofu products
- Nuts: almonds

Highest individual food sources

- Yoghurt
- Mozzarella cheese
- Sardines
- Cheddar cheese
- Milk

Sources: Centers for Disease Control and Prevention.

Nutrition for everyone. Calcium and bone health.

<http://www.cdc.gov/nutrition/everyone/basics/vitamins/calcium.html>; National Institutes of Health. Calcium.

Dietary supplement fact sheet.

<http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/>

US authorities call for 1000 mg of calcium daily starting at age 4, and that quota jumps to 1300 mg from ages 9 through 18.⁵ For adults 19 to 50 years old, the RDA stands at 1000 mg (and at 1300 mg for pregnant or lactating women 14 to 18 years old).

Most people do not eat enough calcium to meet these requirements, and daily calcium consumed drops with age. A survey of 9475 US adults figured median daily dietary calcium intakes of 968 mg for 31- to 40-year-olds, 852 mg for 41- to 50-year-olds,

777 mg for 51- to 60-year-olds, and 735 mg for 71- to 80-year-olds.⁶ A comparison of 112 HIV-positive adults in Italy and 76 HIV-negative people matched for age and gender measured an average daily calcium consumption of only 454 mg in the HIV group as recorded in weekly food-frequency questionnaires.⁷ Daily total calcium did not correlate with DXA-measured BMD, but in multivariate analysis weekly yoghurt intake emerged as a significant predictor of lumbar spine BMD ($P = 0.04$). When the researchers grouped participants into milk drinkers and milk-plus-yoghurt imbibers, they measured significantly higher rates of osteopenia and osteoporosis in the milk-only group. These findings may reflect yoghurt's status as the highest single-food source of calcium (**Table 2**).

A study of 89 HIV-positive and 95 HIV-negative postmenopausal US women found that three quarters had a vitamin D level below 30 ng/mL, the cutoff indicating insufficient vitamin D.⁸ Insufficiency prevalence proved higher in African-American women (33% of participants) than in Hispanic women (67% of participants). Regardless of HIV status, vitamin D levels were significantly higher in women who took both multivitamins and calcium supplements than in women who took neither (mean 31.5 versus 21.0 ng/mL, $P < 0.0001$), but only 1 in 5 women took both multivitamins and calcium.

A 1778-woman analysis of the Women's Interagency HIV Study (WIHS) found that most women with or without HIV had vitamin D deficiency (25(OH)D < 25 ng/mL), though deficiency prevalence proved significantly lower with than without HIV (60% versus 72%, $P < 0.001$).⁹ Compared with white race, African American race tripled odds of deficiency (adjusted odds ratio [aOR] 3.02, 95% confidence interval [CI] 2.30 to 3.97), while Hispanic ethnicity tended to raise the odds (aOR 1.40, 95% CI 0.99 to

1.96). Every additional 10 years of age cut deficiency risk 16% (aOR 0.84, 95% CI 0.73 to 0.96), a finding contrary to results in the general population. Among the 1268 women with HIV, an undetectable viral load independently trimmed chances of deficiency 31% (aOR 0.69, 95% CI 0.50 to 0.95), while a CD4 count below 200 cells/mm³ versus above 500 cells/mm³ raised chances (aOR 1.66, 95% CI 1.11 to 2.48).

The new HIV bone guidelines recommend measuring vitamin D (25-hydroxy vitamin D) in people with a history of low BMD or fracture.¹ Clinicians may also consider checking vitamin D in people with risk factors for low levels—dark skin, dietary insufficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, or efavirenz use. These experts recommend vitamin D supplementation for people with quotients below 20 ng/mL with a dose that yields 25-hydroxy vitamin D levels of about 30 ng/mL, followed by “a suitable maintenance dose.”¹

The guidelines stress that vitamin D deficiency can stifle responses to bisphosphonates, so people with HIV should get levels up to 30 ng/mL before starting bisphosphonate therapy.¹ But guideline writers caution that research has not firmly established any “health benefit” to spotting low D levels and pumping them up.¹ One exception may be a lower risk of hip fracture or nonvertebral fracture in people 65 or older in the general population (mean age 76, 91% women) taking about 800 IU daily, according to results of an 11-study meta-analysis.¹⁰ Fewer falls may be another benefit of vitamin D supplementation by elderly people. A meta-analysis of eight trials found that high-dose vitamin D cut the risk of falls about 20% in older people in the general population (mean age 65).¹¹

Do glitazones or statins make a bone difference?

Two other drug classes often used by people with HIV—glitazones and statins—may or may not affect BMD, depending on which studies you consult and how you interpret them. New bone guidelines for HIV clinicians suggest avoiding or stopping drugs linked to bone loss—glitazones, corticosteroids, proton pump inhibitors, and antiepileptics—in people who need bisphosphonates, “if appropriate alternatives are available.”¹

A placebo-controlled trial of daily rosiglitazone involved 71 HIV-positive people with lipoatrophy who had stopped stavudine and zidovudine for at least 24 weeks.¹² The researchers found no significant change in total BMD in either arm through 48 weeks. The bone formation marker P1NP dropped significantly at weeks 24 and 48 in rosiglitazone takers, but the difference between the rosiglitazone group and the placebo group was statistically significant only at week 24. Osteocalcin, another bone formation marker, also dropped significantly through 24 weeks in the rosiglitazone arm, but the fall did not differ significantly from the placebo group. Another placebo-controlled trial of rosiglitazone in 63 people taking antiretroviral therapy found that the diabetes drug did not affect BMD through 48 weeks.¹³

The HIV bone guidelines do not mention statins.¹ Some evidence suggests statins improve BMD and lower fracture risk, but other research finds no such benefits. At week 48 of an ongoing 147-person placebo-controlled trial of rosuvastatin in HIV-positive people with normal low-density lipoprotein

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cholesterol, researchers measured small gains in trochanter BMD (mean 0.9%) and total hip BMD (mean 0.6%) with the statin that differed significantly from BMD changes in the placebo arm ($P < 0.05$).¹⁴ Total hip BMD improvement with rosuvastatin remained significant after adjustment for age, sex, race, and smoking ($P = 0.02$).

Meta-analysis of eight observational studies in the general population independently linked statin use to 57% lower odds of hip fracture and 31% lower odds of nonspine fracture.¹⁵ But combined analysis of two clinical trials found no protective benefit with statins. Analysis of 3601 HIV-positive people starting or not starting a statin in an AIDS Clinical Trials Group longitudinal cohort found no evidence that statin therapy prevented nontraumatic fracture.¹⁶ And after a median of 1.9 years in a double-blind placebo-controlled trial of daily rosuvastatin involving almost

18,000 men over 50 and women over 60 in the general population, fracture incidence was nearly identical in statin takers and placebo takers.¹⁷

A note on the new HIV bone guidelines

This issue of *RITA!* reviews key advice in the 2015 “Recommendations for evaluation and management of bone disease in HIV.”¹ But these guidelines have much more to offer. HIV clinicians should get their hands on a copy and read it from start to finish. These comprehensive yet concise recommendations run for only 7 pages, including two algorithms and six tables (and excluding references). Eight HIV-bone experts authored the guidelines with input from 34 specialists working in 16 countries. At this point *Clinical Infectious Diseases* has not made the guidelines freely accessible online, but they are available elsewhere.¹

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