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More than Osteoporosis: Age-Specific Issues in Bone Health

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Abstract

Purpose of Review—The interaction between fall and fracture risk factors is an area of increasing clinical relevance, but little is known about the age-specific issues in bone health unique to HIV-infected adults. This review will focus on what is known about falls and fall risk factors among HIV-infected adults, and then review the association between decreased muscle, increased adiposity, and frailty with both low BMD and falls

Recent Findings—The rate of falls among middle-aged HIV-infected adults is similar to that of HIV-uninfected adults 65 years and older. Many of the clinical factors that contribute to low BMD overlap with risk factors for falls, resulting in a high risk of a serious fall among older adults with the greatest risk for a fracture. Low muscle mass, increased adiposity and metabolic syndrome, physical function impairment and frailty, common among older HIV-infected adults, contribute to an increased risk for low BMD and falls, and subsequently, may increase the risk of fracture among HIV-infected older adults.

Summary—Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

Keywords

Osteoporosis; sarcopenia; obesity; frailty; falls; fracture

Introduction

Clinical Vignette

A 65 year old HIV-infected man was evaluated in the HIV clinic for a routine follow-up visit. He was diagnosed with HIV and cryptococcal encephalitis in 1989. His CD4 nadir was 21 cells/ μ L, and most recent CD4 lymphocyte count was 585 cells/ μ L. His HIV-1 viral load was suppressed on lamivudine, maraviroc, and boosted atazanavir. Comorbid illnesses included type 2 diabetes mellitus, hypertension, and benign prostatic hyperplasia;

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Conflicts of Interest:

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medications included metformin, lisinopril, tamsulosin, aspirin, pravastatin, and vitamin D. On further questioning, the patient reported 3 falls during the prior month. On examination, he exhibited orthostatic hypotension, his waist circumference was 102 cm, his body mass index (BMI) was 26.3 kg/m² but arms and legs were notably thin, and he had difficulty rising from a chair without use of his arms. A dual-energy x-ray absorptiometry (DEXA) scan was notable for a lumbar T-score -2.5 and femoral neck T-score -1.8; risk for a major osteoporotic fracture risk within 10 years was 7% using the FRAX algorithm [1]. *What unique issues should be addressed when evaluating the older adult with osteoporosis?*

Decreased muscle, increased adiposity, and frailty are integrally related to bone mineral density (BMD). However, the clinical consequence of low BMD is the fracture that results following a fall. Thus, rather than focus on low BMD, this review will first review what is known about falls and fall risk factors among HIV-infected adults, and then describe the associations between decreased muscle, increased adiposity, and frailty with both low BMD and falls. Due to the increasing age and comorbidity burden of treated HIV patients, research is commonly focused on the interactions between HIV, antiretroviral therapy (ART), and low BMD. Indeed, PubMed includes over 4000 publication citations in reference to “HIV and bone”. In contrast, the risk of falls in HIV has been minimally described. As of January 25, 2016 only 12 PubMed citations included “HIV and ‘accidental falls’ ” and 3 of these reported rates of falls or characteristics of HIV-infected fallers [2–4]. As the proportion of HIV-infected adults aged 50 or older is projected to reach nearly 70% by 2030 [5], the interaction between falls and fracture risks is an area of increasing clinical relevance. Little is known, however, about the issues unique to HIV-infected adults.

Falls and Fall Risk Factors in HIV

A “fall” is most often defined as “an unexpected event in which the participant comes to rest on the ground, floor, or lower level”[6]. In the clinical setting, falls are most commonly assessed by retrospective self-report which may underestimate the actual number of falls, particularly if a fall is non-injurious [7, 8]. An individual’s own assessment of his or her risk of falling using tools such as the Activities Specific Balance Confidence [9] or Falls Efficacy Scale [10] is also highly predictive of falls [11]. Objective, standardized tests including the timed-up-and go (TUG) test, a 10-time chair rise test, or tandem stand can identify patients with balance or mobility problems suggestive of high fall risk [12, 13].

Self-reported falls were described among 359 middle-aged, HIV-infected adults on effective ART in a Colorado cohort; 30% sustained at least 1 fall during the prior year, similar to fall rates reported among HIV-uninfected adults aged 65 or older [3]. In a similar cross-sectional analysis from the University of California San Francisco SCOPE cohort, 26% of 155 HIV-infected adults (94% male) aged 50 or older on ART reported at least 1 fall in the prior year [2]. To further explore the effect of HIV serostatus on fall risk, falls were compared between HIV-infected and HIV-uninfected men and women in the Multicenter AIDS Cohort (MACS) and the Women’s Interagency HIV Study (WIHS)[14]. In these cohorts, no significant differences were found by HIV status in falls described retrospectively (24% HIV-infected versus 18% of HIV-uninfected participants reported at least 1 fall in the prior year, $p=0.27$). The lack of falls risk attributable to HIV may reflect that the HIV-infected and uninfected

MACS and WIHS participants are demographically similar in regards to overall burden of fall risk factors, while comparisons to the general population data reported by the CDC reflects a different demographic. The lower fall rate compared to prior studies in HIV-infected adults may be explained in part by healthier individuals agreeing to participate in the study, compared to a routine clinical assessment in the Colorado and SCOPE Cohorts. To further understand fall prevalence and risk factors, standardized assessment of self-reported falls are now being captured across multiple cohorts.

Falls are a common geriatric syndrome, and are the consequence of multiple interrelated factors including comorbidities (arthritis, diabetes, pain, depression), physical impairments (vision, cognition, neuropathy, strength, gait), and polypharmacy (Figure) [15]. A high prevalence of comorbidities, physical impairments, and polypharmacy associated with falls are also seen among HIV-infected older adults [16]. Similarly, many of the clinical factors that contribute to low BMD overlap with risk factors for falls, resulting in a high risk of a serious fall among older adults with the greatest risk for a fracture. For example, use of antidepressants, sedatives, and opiates are established risk factors for low BMD and were some of the strongest predictors of falls in the Colorado cohort [3]. Similarly, a greater number of prescribed medications were associated with an increased risk of falling in both the Colorado and MACS/WIHS Cohorts [14, 17]. In contrast to the strong associations between HIV-specific factors and low BMD discussed in prior articles in this journal issue, HIV-related characteristics and substance abuse appear to have minimal effect on fall risk. Outside of increased fall risk with current tobacco use or prior didanosine [3], and decreased fall risk with current protease inhibitor use (MACS/WIHS cohort)[14], no association was found with other HIV-specific variables or with substance abuse-related factors (hepatitis C, alcohol use, current illicit drug use).

Sarcopenia as a Risk for Low BMD and Falls

In healthy adults, a decline in both muscle quality (function) and quantity (mass) begins in the fourth or fifth decade of life [18]. Without intervention or if hastened by concomitant disease, the decline in muscle may result in *sarcopenia*, a term which refers to the loss of muscle mass alone, but has been more recently defined as a condition consisting of both impaired muscle function and low muscle mass. Although sarcopenia and osteoporosis are two distinct processes, there is increasing evidence of important interactions which significantly impact on fracture risk. Sarcopenia is independently associated with an increased risk of low BMD in both Caucasian and Asian middle-aged and elderly individuals [19, 20]. Sarcopenia contributes to the development of frailty which itself increases the risk of disability and falls in the elderly. Studies suggest that individuals with both sarcopenia and osteoporosis have more comorbidities, as well as impaired mobility, diminished quality of life [21], and an increased risk of falls [22]. New terminology including osteosarcopenia, sarco-osteoporosis, and musculoskeletal frailty highlight the integrated mechanisms of loss and similar risk factors underlying both disease processes [23].

The interconnectedness of bone and muscle are seen at several levels from direct muscle-bone interactions to shared pathways including endocrine influence, nutrition and lifestyle factors, demographics, and genetic features. Muscle and bone cells share a common

progenitor in the mesenchymal stem cell, and thus are susceptible to similar genetic or epigenetic influences [24]. Muscle and bone develop in parallel throughout adolescence, and decline similarly with older age. The mechanical loading force of muscle on bone is well-recognized: increasing levels of acute, dynamic stress creates greater muscle contractions, and stimulate cortical bone formation. In contrast, in situations of prolonged bedrest with very limited muscle contraction or among astronauts with zero gravity and no mechanical loading, marked losses in both BMD and muscle result [25, 26]. The molecular and cellular mechanisms that underlie the muscle-bone crosstalk and whether bone provides a similar stimulus to muscle are less understood research questions [27]. Endocrine pathways such as the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis are critical in the regulation of both muscle and bone growth [28]. Both the concentration and effectiveness of serum and bone IGF-1 decrease with age, and lower levels of IGF-1 are associated with a lower BMD [29–32]. Low IGF-1 or variations in the GH/IGF-1 gene have also been associated with low lean body mass (LBM) or impaired muscle function [33–36] and frailty [37, 38].

Sarcopenia has been evaluated in HIV in the absence of the AIDS wasting syndrome and malnutrition. Although some studies have suggested that the rate of lean muscle mass loss may not differ from that in the general population [39], low muscle mass is not uncommon, with 20–35% of HIV-infected participants meeting the DXA-defined criteria for low appendicular lean mass [40, 41]. As the FRAM study previously confirmed that both sarcopenia and visceral adiposity are independent predictors of mortality in treated HIV-infected persons [42], the potential for clinically important consequences of low LBM is evident. Furthermore, the impact of greater total body mass on BMD of HIV-infected persons is described in multiple cohorts [43–45]. The association between LBM, in particular, and bone density was first described early in the AIDS era [46]. Subsequent cross-sectional and longitudinal studies have corroborated these findings [47]. Among HIV-infected naïve participants initiating ART through the AIDS Clinical Trials Group Study 5224s, a greater increase in LBM after 96 weeks of ART was independently associated with greater week 96 increases in both hip and lumbar spine BMD [48]. Among participants with available follow-up DXA scans, low LBM was a significant predictor of subsequent decline in BMD over an average of 7 years of follow-up [49].

In addition to the decline in muscle mass and function, an increase in the amount of fat content within and surrounding skeletal muscle is seen with aging among HIV-uninfected populations [50]. The fatty infiltration of skeletal muscle, as defined by lower attenuation on computed tomography (CT), has been associated with fall and fracture risk beyond that predicted by muscle mass or low BMD. In the Health, Aging, and Body Composition (Health ABC) study of HIV-uninfected adults > 70 years, low CT-attenuation of skeletal muscle was associated with increased risk of hip fracture independent of BMI, percentage body fat, age, height, race, gender, and bone mineral density. Furthermore, skeletal muscle fat infiltration was the only significant muscle parameter of fracture risk in models including muscle strength, physical performance score, and thigh muscle cross-sectional area [51]. Subsequent studies within the Health ABC Cohort and other cohorts have found similar, independent associations between skeletal muscle fat infiltration and fracture risk [52–54]. Although the mechanisms for this association have not been delineated, greater fatty muscle

infiltration may lead to weaker mechanical loading forces on bone, may be associated with poorer postural stability, or could increase local inflammation with a detrimental effect on bone resorption. In the MACS, middle-aged HIV-infected men had significantly greater fatty muscle infiltration of the mid-thigh musculature compared to uninfected men, and greater fat correlated with decreased grip strength. Furthermore, this measurement of muscle quality decreased with increasing age among the HIV-infected men, but not the uninfected men [55].

Obesity, Diabetes, and Metabolic Syndrome as Risk for Low BMD and Falls

Metabolic diseases, including type II diabetes mellitus, dyslipidemia, obesity, and the metabolic syndrome occur with increasing frequency among older adults. These disorders often occur together and may share underlying pathogenic features. The concept of an “allostatic load” suggests that the accumulated dysregulation across physiologic systems including chronic inflammation, cardiovascular disease, lipid and glucose disorders, is associated with decreased bone strength, despite the lack of an independent effect of each condition on BMD [56]. Although obesity is generally associated with greater BMD, the distribution of fat may be a better predictor of BMD and bone quality than the amount of total body fat described by the BMI alone. Indeed, some studies have demonstrated an increased hip BMD among both men and women with visceral obesity [57–59], while visceral obesity had either a weak or negative correlation with lumbar spine BMD [59–61]. Visceral adiposity has been negatively associated with bone density, strength, and structure in the majority of studies, presumably due in part to heightened inflammation and altered adipocyte-secreted or converted hormones [62]. Adipose tissue within the bone marrow also appears to be a strong predictor of low BMD [63]. Although diabetes does not appear to be associated with low BMD, an increased rate of bone loss [64] or abnormal micro- and macro-architecture of diabetic bone may explain the greater hip fracture risk among diabetics [65].

The relationship between obesity, diabetes, and metabolic syndrome with fall or fracture risk is more complex. Obesity has commonly been considered as protective against fractures [66, 67], due to the mechanical loading effects of increased body weight on BMD and the shock-absorption of additional adipose tissue, particularly over the greater trochanter [68]. In contrast, obese individuals may have greater postural and gait instability, predisposing to a higher fall risk [69]. Indeed, obesity is consistently associated with disability, impaired mobility, impaired physical performance, and frailty [70–72], which are themselves risk factors for falls. More recent studies have suggested that the relationship between obesity and fracture risk appear to differ between genders and across fracture site [73]. Comorbidities associated with obesity, including hypertension, inactivity, and neurocognitive disease add additional fall risk [74]. Type II diabetes mellitus may increase fall risk via peripheral neuropathy, visual impairment, and autonomic dysfunction. Similarly, metabolic syndrome has been associated with impaired exercise capacity [75] and may be an independent risk factor for falls [76].

Similar to HIV-uninfected populations, among HIV-infected participants, higher body weight has been a consistently protective factor for BMD [45, 77], while the effect of

visceral adiposity differs: in one cohort, both visceral adiposity and hyperglycemia were associated with low BMD [78]. Increased visceral fat over 96 weeks following ART initiation was associated with increased BMD at the hip but decreased BMD at the lumbar spine in the AIDS Clinical Trials Group study A5224s [48]. Similar to the effects on BMD, diabetes, but not obesity, was an independent contributor to recurrent falls in the Colorado Cohort [3]. In a separate cohort, abdominal obesity was strongly associated with frailty, and thus could subsequently increase the risk of falls [79]. Changes in body fat including both peripheral lipoatrophy and central lipohypertrophy contribute to reduced hand grip strength [80], a risk factor for falls.

Frailty and Physical Function Impairment as Risks for Low BMD and Falls

Frailty is a geriatric syndrome often overlapping with obesity and/or sarcopenia, and is characterized by decreased physiologic reserve. Several diagnostic criteria are used to define frailty clinically. Regardless of the definition, frailty is considered the end result of multiple potential insults including alterations in hormones (growth hormone, estrogen, testosterone), heightened inflammation, low physical activity, and poor or under-nutrition. These alterations are associated with the clinical manifestations of slowness, weakness, and fatigue. Thus, many of the risk factors for frailty overlap with the risks for low BMD, sarcopenia, and falls, which may subsequently result in fractures. Not surprisingly, frailty and other impairments in physical function such as balance impairment, slow gait speed, or weakness, are also strong predictors of both falls and fractures in cohorts of older, HIV-uninfected adults [81–86]. The association between frailty and low BMD in HIV-uninfected populations is not well-established and may depend on the definition of frailty used and the prevalence of osteoporosis in the population under investigation [87–91]. Most existing data is cross-sectional but a recent study of older women found that while baseline osteoporosis was not associated with frailty, frail participants were more likely to develop osteoporosis in follow-up [87].

Relatively little is known about the relationships between frailty or physical function impairment and falls, low BMD, and fracture among HIV-infected older adults, outside of the studies previously mentioned. Recent evidence suggests that impaired locomotor function, as determined by routine functional tests of the lower extremities, is both common and increases over time in older HIV patients with comorbidities [92, 93]. This is an important risk for falls and interacts closely with the decline in gait speed which also occurs in older HIV patients [94]. In the Colorado cohort, nearly 70% of HIV-infected participants with functional impairment or frailty also had osteopenia or osteoporosis at the hip or lumbar spine compared to <40% of participants in the high-function group [41]. Furthermore, the frailty components of exhaustion and unintentional weight loss, as well as objective difficulty with balance were all significantly associated with a greater odds of falling [3]. In the MACS/WIHS cohort, the presence of imbalance symptoms was one of the strongest predictors of falls, even after adjusting for comorbidities, polypharmacy, and HIV-related characteristics [14]. In a subsequent Multicenter AIDS Cohort Study, Brown, et al found that lower self-reported balance confidence was a significantly better predictor of falls than objective tests of strength or balance [95]. As all these studies are observational, the cause and effect relationships cannot be determined. Persons with frailty or impaired

physical function are less likely or less able to engage in more strenuous regular physical activity. The resultant decline in muscle mass from physical inactivity may amplify the fall risk and BMD decline. Furthermore, chronic pain, fatigue, and altered sleep are additional risks for falls. These conditions occur commonly in HIV patients, and are known risk factors for polypharmacy, but are infrequently considered in routine care settings [96–99].

Testosterone and Vitamin D on Falls and Fracture Risk

Testosterone decreases with age and is a known risk factor for both sarcopenia and visceral adiposity [100]. The potential contribution of hypogonadism to risk of falls remains uncertain. This relates partly to the study design limitations related to whether the condition is defined on the basis of total, free or bioavailable testosterone. Although hypogonadism may contribute to frailty via its effect on sarcopenia, the evidence is unclear whether this refers to frailty as defined by the frailty phenotype or only to some of its components [101, 102]. This distinction is of more than academic interest, as numerous interventional studies in hypogonadal patients have not clarified whether the clinical manifestations of hypogonadism presumed to be related to physical function in the elderly can be improved with judicious use of function promoting anabolic therapies [103]. In HIV, hypogonadism is more pronounced in both untreated and effectively treated patients compared to HIV-uninfected men [104–106].

Vitamin D plays an important role in bone health and physical performance [107] possibly via effects on muscle function and strength [108, 109]. Vitamin D deficiency is as common in HIV, as it is in the general community and is of multifactorial etiology [110]. Although some studies suggest that the widespread adoption of universal vitamin D supplementation will prevent falls in the general elderly population, careful meta-analyses do not support this recommendation [111]. Similarly, although studies show an association between vitamin D deficiency and frailty, evidence for a causal effect and whether supplementation can prevent its occurrence are lacking [112]. Furthermore, two recent studies suggest that vitamin D supplementation may increase the risk of falls or functional decline [113, 114]. Among HIV-infected persons initiating ART with efavirenz/emtricitabine/tenofovir disoproxil fumarate, high dose vitamin D3 (4000 IU/day) and calcium supplementation significantly attenuated BMD losses [115], suggesting a beneficial effect on fracture risk reduction. No association between 25-hydroxy vitamin D levels and physical function/frailty was found in the Colorado cohort [41], but whether high dose vitamin D supplementation could attenuate fall risk, decrease frailty, and improve muscle function in HIV is unknown.

Clinical Vignette Continued...

In discussion of the risks and benefits of therapy with the patient, he and his provider changed his tamsulosin to finasteride to decrease his orthostatic hypotension. Testosterone levels were low-normal, but therapy was held due to his additional cardiac risk factors. Vitamin D supplementation was continued but increased to 2000 IU daily, calcium supplementation was initiated, and bisphosphonate therapy was held. Occupational therapy completed a home safety evaluation to reduce extrinsic fall risks (i.e., loose rugs, cords, low lighting). The patient began physical therapy for balance and resistance training, followed by

a regular indoor walking regimen and weekly tai chi. He had only 1 fall during the subsequent year, his lumbar T-score improved to -2.0 , and femoral to -1.6 .

Conclusions

The combination of increased fall risk and lower BMD highlights the importance of evaluating, monitoring, and modifying risks for both falls and fracture. In the context of the aging HIV population, we have expanded the perspective of low BMD as a diagnosis or surrogate of a specific organ disease, to that of falls as a geriatric syndrome. Considering falls as a geriatric syndrome allows for a broader, multifactorial approach. Although no data exists on specific fall or fracture prevention in HIV-infected populations, successes with other populations or other treatment outcomes can be extrapolated to develop falls prevention guidelines for the clinical or research setting. The evaluation, prevention, and treatment of falls and fractures in the older, HIV-infected adult should be multifactorial and encompass the medical, social, and psychological aspects. Brief standardized assessments for falls, fear of falling, and/or fall risk factors should be incorporated into the routine clinical assessment. Ideally, those at risk of falling can be identified before a fall, and the particular risk profile minimized. Among other benefits, this will serve to less the fear of falling that may subsequently limit activities. Low BMD is one of many risk factors for fracture, and should be evaluated together with anthropometric changes, functional impairment, and environmental risks. Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

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References

1. FRAX WHO Fracture Risk Assessment Tool. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield; UK: Available at: <http://www.shef.ac.uk/FRAX/index.aspx?lang=En> [Accessed 1/3/2013]
- 2*. Greene M, Covinsky KE, Valcour V, Miao Y, Madamba J, Lampiris H, et al. Geriatric Syndromes in Older HIV-Infected Adults. *J Acquir Immune Defic Syndr*. 2015; 69:161–167. This is the first study which analyzes geriatric syndromes including falls, urinary incontinence, functional impairment, frailty, sensory impairment, depression, and cognitive impairment in older, HIV-infected adults. It underlines that geriatric syndrome needs a multifactorial approach. [PubMed: 26009828]
3. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, MaWhinney S, Kohrt WM, et al. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012; 61:484–489. [PubMed: 23143526]
4. Ruiz MA, Reske T, Cefalu C, Estrada J. Falls in HIV-infected patients: a geriatric syndrome in a susceptible population. *J Int Assoc Provid AIDS Care*. 2013; 12:266–269. [PubMed: 23719236]
- 5*. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem A, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis*. 2015; 15:810–818. This modeling study forecast demographic and characteristics of HIV patients

including the Athena cohort. In 2030, 73% of the patients will be aged >50 years and 54% of HIV-infected patients will be prescribed co-medications. This study goes beyond the description of the aging shift of the cohort and gives the flavor of the clinical aspects and health needs of HIV patients in the near-future. [PubMed: 26070969]

6. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Prevention of Falls Network E, Outcomes Consensus G. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* 2005; 53:1618–1622. [PubMed: 16137297]
7. Fleming J, Matthews FE, Brayne C. Falls in advanced old age: recalled falls and prospective follow-up of over-90-year-olds in the Cambridge City over-75s Cohort study. *BMC Geriatr.* 2008; 8:6. [PubMed: 18366645]
8. Hannan MT, Gagnon MM, Aneja J, Jones RN, Cupples LA, Lipsitz LA, et al. Optimizing the tracking of falls in studies of older participants: comparison of quarterly telephone recall with monthly falls calendars in the MOBILIZE Boston Study. *Am J Epidemiol.* 2010; 171:1031–1036. [PubMed: 20360242]
9. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci.* 1995; 50A:M28–34. [PubMed: 7814786]
10. Tinetti ME, Richman D, Powell L. Falls efficacy as a measure of fear of falling. *J Gerontol.* 1990; 45:P239–243. [PubMed: 2229948]
11. Tinetti ME, Mendes de Leon CF, Doucette JT, Baker DI. Fear of falling and fall-related efficacy in relationship to functioning among community-living elders. *J Gerontol.* 1994; 49:M140–147. [PubMed: 8169336]
12. Centers for Disease Control and Prevention. [Accessed 11/5/2015] Stopping Elderly Accidents, Deaths & Injuries (STEADI)- Older Adult Fall Prevention. <http://www.cdc.gov/steady/materials.html>
13. Simonsick EM, Newman AB, Nevitt MC, Kritchevsky SB, Ferrucci L, Guralnik JM, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. *J Gerontol A Biol Sci Med Sci.* 2001; 56:M644–649. [PubMed: 11584038]
14. Erlandson KM, Plankey MW, Springer G, Cohen HS, Cox C, Hoffman HJ, et al. Fall frequency and associated factors among men and women with or at risk for HIV infection. *HIV Med.* in press.
15. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology.* 2010; 21:658–668. [PubMed: 20585256]
16. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis.* 2008; 47:542–553. [PubMed: 18627268]
17. Marzolini C, Elzi L, Gibbons S, Weber R, Fux C, Furrer H, et al. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther.* 2010; 15:413–423. [PubMed: 20516560]
18. Nedergaard A, Karsdal MA, Sun S, Henriksen K. Serological muscle loss biomarkers: an overview of current concepts and future possibilities. *J Cachexia Sarcopenia Muscle.* 2013; 4:1–17. [PubMed: 22996343]
19. Verschueren S, Gielen E, O'Neill TW, Pye SR, Adams JE, Ward KA, et al. Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men. *Osteoporos Int.* 2013; 24:87–98. [PubMed: 22776861]
20. Wu CH, Yang KC, Chang HH, Yen JF, Tsai KS, Huang KC. Sarcopenia is related to increased risk for low bone mineral density. *J Clin Densitom.* 2013; 16:98–103. [PubMed: 22975297]
21. Kull M, Kallikorm R, Lember M. Impact of a new sarco-osteopenia definition on health-related quality of life in a population-based cohort in Northern Europe. *J Clin Densitom.* 2012; 15:32–38. [PubMed: 22071030]

22. Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Muir SW, et al. Phenotype of osteosarcopenia in older individuals with a history of falling. *J Am Med Dir Assoc*. 2015; 16:290–295. [PubMed: 25512216]
23. Laurent MR, Dubois V, Claessens F, Verschueren SM, Vanderschueren D, Gielen E, et al. Muscle-bone interactions: From experimental models to the clinic? A critical update. *Mol Cell Endocrinol*. 2015
24. Karasik D, Kiel DP. Genetics of the musculoskeletal system: a pleiotropic approach. *J Bone Miner Res*. 2008; 23:788–802. [PubMed: 18269309]
25. Whalen R. Musculoskeletal adaptation to mechanical forces on Earth and in space. *Physiologist*. 1993; 36:S127–130. [PubMed: 11537418]
26. Cervinka T, Sievanen H, Hyttinen J, Rittweger J. Bone loss patterns in cortical, subcortical, and trabecular compartments during simulated microgravity. *J Appl Physiol* (1985). 2014; 117:80–88. [PubMed: 24812642]
27. Bonewald LF, Kiel DP, Clemens TL, Esser K, Orwoll ES, O’Keefe RJ, et al. Forum on bone and skeletal muscle interactions: summary of the proceedings of an ASBMR workshop. *J Bone Miner Res*. 2013; 28:1857–1865. [PubMed: 23671010]
28. Goldspink G. Loss of muscle strength during aging studied at the gene level. *Rejuvenation research*. 2007; 10:397–405. [PubMed: 17822355]
29. Lindsey RC, Mohan S. Skeletal effects of growth hormone and insulin-like growth factor-I therapy. *Mol Cell Endocrinol*. 2015
30. Tanaka H, Liang CT. Mitogenic activity but not phenotype expression of rat osteoprogenitor cells in response to IGF-I is impaired in aged rats. *Mech Ageing Dev*. 1996; 92:1–10. [PubMed: 9032750]
31. Gillberg P, Mallmin H, Petren-Mallmin M, Ljunghall S, Nilsson AG. Two years of treatment with recombinant human growth hormone increases bone mineral density in men with idiopathic osteoporosis. *J Clin Endocrinol Metab*. 2002; 87:4900–4906. [PubMed: 12414848]
32. Rucker D, Ezzat S, Diamandi A, Khosravi J, Hanley DA. IGF-I and testosterone levels as predictors of bone mineral density in healthy, community-dwelling men. *Clin Endocrinol (Oxf)*. 2004; 60:491–499. [PubMed: 15049965]
33. Yang CW, Li TC, Li CI, Liu CS, Lin CH, Lin WY, et al. Insulinlike Growth Factor-1 and Its Binding Protein-3 Polymorphisms Predict Circulating IGF-1 Level and Appendicular Skeletal Muscle Mass in Chinese Elderly. *J Am Med Dir Assoc*. 2015; 16:365–370. [PubMed: 25548030]
34. Gielen E, O’Neill TW, Pye SR, Adams JE, Wu FC, Laurent MR, et al. Endocrine determinants of incident sarcopenia in middle-aged and elderly European men. *J Cachexia Sarcopenia Muscle*. 2015; 6:242–252. [PubMed: 26401471]
35. Volpato S, Bianchi L, Cherubini A, Landi F, Maggio M, Savino E, et al. Prevalence and clinical correlates of sarcopenia in community-dwelling older people: application of the EWGSOP definition and diagnostic algorithm. *J Gerontol A Biol Sci Med Sci*. 2014; 69:438–446. [PubMed: 24085400]
36. Cappola AR, Xue QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *The Journal of clinical endocrinology and metabolism*. 2003; 88:2019–2025. [PubMed: 12727948]
37. Fried LP, Xue QL, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci*. 2009; 64:1049–1057. [PubMed: 19567825]
38. Leng SX, Cappola AR, Andersen RE, Blackman MR, Koenig K, Blair M, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. *Aging Clin Exp Res*. 2004; 16:153–157. [PubMed: 15195991]
39. Yarasheski KE, Scherzer R, Kotler DP, Dobs AS, Tien PC, Lewis CE, et al. Age-related skeletal muscle decline is similar in HIV-infected and uninfected individuals. *J Gerontol A Biol Sci Med Sci*. 2011; 66:332–340. [PubMed: 21310810]

40. Freitas P, Santos AC, Carvalho D, Pereira J, Marques R, Martinez E, et al. Fat mass ratio: an objective tool to define lipodystrophy in hiv-infected patients under antiretroviral therapy. *J Clin Densitom.* 2010; 13:197–203. [PubMed: 20347364]
41. Erlandson KM, Allshouse AA, Jankowski CM, MaWhinney S, Kohrt WM, Campbell TB. Functional impairment is associated with low bone and muscle mass among persons aging with HIV infection. *J Acquir Immune Defic Syndr.* 2013; 63:209–215. [PubMed: 23392468]
42. Scherzer R, Heymsfield SB, Lee D, Powderly WG, Tien PC, Bacchetti P, et al. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. *AIDS.* 2011; 25:1405–1414. [PubMed: 21572308]
43. Sharma A, Cohen HW, Freeman R, Santoro N, Schoenbaum EE. Prospective evaluation of bone mineral density among middle-aged HIV-infected and uninfected women: Association between methadone use and bone loss. *Maturitas.* 2011; 70:295–301. [PubMed: 21944566]
44. Bolland MJ, Grey AB, Gamble GD, Reid IR. CLINICAL Review # : low body weight mediates the relationship between HIV infection and low bone mineral density: a meta-analysis. *J Clin Endocrinol Metab.* 2007; 92:4522–4528. [PubMed: 17925333]
45. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab.* 2006; 91:2938–2945. [PubMed: 16735489]
46. Huang JS, Wilkie SJ, Sullivan MP, Grinspoon S. Reduced bone density in androgen-deficient women with acquired immune deficiency syndrome wasting. *J Clin Endocrinol Metab.* 2001; 86:3533–3539. [PubMed: 11502775]
47. Carr A, Miller J, Eisman JA, Cooper DA. Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. *AIDS.* 2001; 15:703–709. [PubMed: 11371684]
48. Erlandson KM, Kitch D, Tierney C, Sax PE, Daar ES, Tebas P, et al. Weight and lean body mass change with antiretroviral initiation and impact on bone mineral density. *AIDS.* 2013; 27:2069–2079. [PubMed: 24384588]
49. Grant, P.; Kitch, D.; McComsey, G.; Collier, A.; Koletar, S.; Erlandson, KM., et al. International AIDS Society. Vancouver, Canada: 2015. Long-term bone mineral density changes in antiretroviral-treated HIV-infected individuals. Abstract UPDB0103.
50. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *J Appl Physiol* (1985). 2001; 90:2157–2165. [PubMed: 11356778]
51. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB, et al. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. *J Bone Miner Res.* 2010; 25:513–519. [PubMed: 20422623]
52. Schafer AL, Vittinghoff E, Lang TF, Sellmeyer DE, Harris TB, Kanaya AM, et al. Fat infiltration of muscle, diabetes, and clinical fracture risk in older adults. *J Clin Endocrinol Metab.* 2010; 95:E368–372. [PubMed: 20668037]
53. Malkov S, Cawthon PM, Peters KW, Cauley JA, Murphy RA, Visser M, et al. Hip Fractures Risk in Older Men and Women Associated With DXA-Derived Measures of Thigh Subcutaneous Fat Thickness, Cross-Sectional Muscle Area, and Muscle Density. *J Bone Miner Res.* 2015; 30:1414–1421. [PubMed: 25644748]
54. Lang T, Koyama A, Li C, Li J, Lu Y, Saeed I, et al. Pelvic body composition measurements by quantitative computed tomography: association with recent hip fracture. *Bone.* 2008; 42:798–805. [PubMed: 18234578]
55. Natsag, J.; Sellmeyer, D.; Haberman, SA.; Margolick, JB.; Jacobson, LP.; Palella, F., et al. HIV infection is associated with increased thigh muscle cross-sectional area and lower muscle attenuation on CT in men age 40–70 years old. In. *ENDO*; Abstract FRI-229; San Diego, CA. 2015.
56. Mori T, Karlamangla AS, Merkin SS, Crandall CJ, Binkley N, Greendale GA, et al. Multisystem dysregulation and bone strength: findings from the study of midlife in the United States. *J Clin Endocrinol Metab.* 2014; 99:1843–1851. [PubMed: 24527715]

57. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S sample. *J Clin Endocrinol Metab.* 2007; 92:4161–4164. [PubMed: 17785365]
58. Szulc P, Varennes A, Delmas PD, Goudable J, Chapurlat R. Men with metabolic syndrome have lower bone mineral density but lower fracture risk--the MINOS study. *J Bone Miner Res.* 2010; 25:1446–1454. [PubMed: 20200928]
59. von Muhlen D, Safii S, Jassal SK, Svartberg J, Barrett-Connor E. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. *Osteoporos Int.* 2007; 18:1337–1344. [PubMed: 17492393]
60. Jankowska EA, Rogucka E, Medras M. Are general obesity and visceral adiposity in men linked to reduced bone mineral content resulting from normal ageing? A population-based study. *Andrologia.* 2001; 33:384–389. [PubMed: 11736801]
61. Blaauw R, Albertse EC, Hough S. Body fat distribution as a risk factor for osteoporosis. *S Afr Med J.* 1996; 86:1081–1084. [PubMed: 8888774]
62. Sheu Y, Cauley JA. The Role of Bone Marrow and Visceral Fat on Bone Metabolism. *Curr Osteoporos Rep.* 2011; 9:67–75. [PubMed: 21374105]
63. Shen W, Scherzer R, Gantz M, Chen J, Punyanitya M, Lewis CE, et al. Relationship between MRI-measured bone marrow adipose tissue and hip and spine bone mineral density in African-American and Caucasian participants: the CARDIA study. *J Clin Endocrinol Metab.* 2012; 97:1337–1346. [PubMed: 22319043]
64. Schwartz AV, Ewing SK, Porzig AM, McCulloch CE, Resnick HE, Hillier TA, et al. Diabetes and change in bone mineral density at the hip, calcaneus, spine, and radius in older women. *Front Endocrinol (Lausanne).* 2013; 4:62. [PubMed: 23755040]
65. Shanbhogue VV, Mitchell DM, Rosen CJ, Bouxsein ML. Type 2 diabetes and the skeleton: new insights into sweet bones. *Lancet Diabetes Endocrinol.* 2015
66. Ensrud KE, Lipschutz RC, Cauley JA, Seeley D, Nevitt MC, Scott J, et al. Body size and hip fracture risk in older women: a prospective study. Study of Osteoporotic Fractures Research Group. *Am J Med.* 1997; 103:274–280. [PubMed: 9382119]
67. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int.* 2005; 16:1330–1338. [PubMed: 15928804]
68. Bouxsein ML, Szulc P, Munoz F, Thrall E, Sornay-Rendu E, Delmas PD. Contribution of trochanteric soft tissues to fall force estimates, the factor of risk, and prediction of hip fracture risk. *J Bone Miner Res.* 2007; 22:825–831. [PubMed: 17352651]
69. Melzer I, Oddsson LI. Altered characteristics of balance control in obese older adults. *Obes Res Clin Pract.* 2015
70. Beavers KM, Hsu FC, Houston DK, Beavers DP, Harris TB, Hue TF, et al. The role of metabolic syndrome, adiposity, and inflammation in physical performance in the Health ABC Study. *J Gerontol A Biol Sci Med Sci.* 2013; 68:617–623. [PubMed: 23109678]
71. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc.* 2005; 53:927–934. [PubMed: 15935013]
72. Armour BS, Courtney-Long EA, Campbell VA, Wethington HR. Disability prevalence among healthy weight, overweight, and obese adults. *Obesity (Silver Spring).* 2013; 21:852–855. [PubMed: 23712989]
73. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res.* 2014; 29:223–233. [PubMed: 23775829]
74. Mitchell RJ, Lord SR, Harvey LA, Close JC. Obesity and falls in older people: mediating effects of disease, sedentary behavior, mood, pain and medication use. *Arch Gerontol Geriatr.* 2015; 60:52–58. [PubMed: 25307955]
75. Senechal M, Bouchard DR, Dionne IJ, Brochu M. Lifestyle habits and physical capacity in patients with moderate or severe metabolic syndrome. *Metab Syndr Relat Disord.* 2012; 10:232–240. [PubMed: 22352681]

76. Liao KC, Pu SJ, Lin CH, Chang HJ, Chen YJ, Liu MS. Association between the metabolic syndrome and its components with falls in community-dwelling older adults. *Metab Syndr Relat Disord*. 2012; 10:447–451. [PubMed: 22994428]
77. Dolan SE, Carpenter S, Grinspoon S. Effects of weight, body composition, and testosterone on bone mineral density in HIV-infected women. *J Acquir Immune Defic Syndr*. 2007; 45:161–167. [PubMed: 17527091]
78. Brown TT, Ruppe MD, Kassner R, Kumar P, Kehoe T, Dobs AS, et al. Reduced bone mineral density in human immunodeficiency virus-infected patients and its association with increased central adiposity and postload hyperglycemia. *J Clin Endocrinol Metab*. 2004; 89:1200–1206. [PubMed: 15001610]
79. Shah K, Hilton TN, Myers L, Pinto JF, Luque AE, Hall WJ. A new frailty syndrome: central obesity and frailty in older adults with the human immunodeficiency virus. *J Am Geriatr Soc*. 2012; 60:545–549. [PubMed: 22315957]
80. Crawford KW, Li X, Xu X, Abraham AG, Dobs AS, Margolick JB, et al. Lipodystrophy and inflammation predict later grip strength in HIV-infected men: the MACS Body Composition substudy. *AIDS Res Hum Retroviruses*. 2013; 29:1138–1145. [PubMed: 23550976]
81. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci*. 2007; 62:744–751. [PubMed: 17634322]
82. Forti P, Rietti E, Pisacane N, Olivelli V, Maltoni B, Ravaglia G. A comparison of frailty indexes for prediction of adverse health outcomes in an elderly cohort. *Arch Gerontol Geriatr*. 2012; 54:16–20. [PubMed: 21339007]
83. Stenhausen M, Ekstrom H, Nordell E, Elmstahl S. Falls in the general elderly population: a 3- and 6- year prospective study of risk factors using data from the longitudinal population study 'Good ageing in Skane'. *BMC Geriatr*. 2013; 13:81. [PubMed: 23919320]
84. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2004; 52:1121–1129. [PubMed: 15209650]
85. Honeycutt PH, Ramsey P. Factors contributing to falls in elderly men living in the community. *Geriatr Nurs*. 2002; 23:250–255. [PubMed: 12386601]
86. Tom SE, Adachi JD, Anderson FA, Boonen S, Chapurlat RD, Compston JE, et al. Frailty and Fracture, Disability, and Falls: A Multiple Country Study From the Global Longitudinal Study of Osteoporosis in Women. *J Am Geriatr Soc*. 2013; 61:327–334. [PubMed: 23351064]
87. Sternberg SA, Levin R, Dkaidek S, Edelman S, Resnick T, Menczel J. Frailty and osteoporosis in older women--a prospective study. *Osteoporos Int*. 2014; 25:763–768. [PubMed: 24002542]
88. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med*. 2008; 168:382–389. [PubMed: 18299493]
89. Ma SL, Oyler J, Glavin S, Alavi A, Vokes T. Self-reported frailty is associated with low calcaneal bone mineral density in a multiracial population of community-dwelling elderly. *Osteoporos Int*. 2009; 20:1837–1846. [PubMed: 19294329]
90. Gerdhem P, Ringsberg KA, Magnusson H, Obrant KJ, Akesson K. Bone mass cannot be predicted by estimations of frailty in elderly ambulatory women. *Gerontology*. 2003; 49:168–172. [PubMed: 12679607]
91. Frisoli A Jr, Chaves PH, Ingham SJ, Fried LP. Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: results from the Women's Health and Aging Study (WHAS) II. *Bone*. 2011; 48:952–957. [PubMed: 21195216]
- 92*. Richert L, Brault M, Mercie P, Dauchy FA, Bruyand M, Greib C, et al. Decline in locomotor functions over time in HIV-infected patients. *AIDS*. 2014 Both this and the subsequent paper provide important information about gait disturbances occurring in aging HIV patients and are of the same magnitude as in older uninfected persons were these are known risk factors for falls, which may improve with interventions.
93. Richert L, Dehail P, Mercie P, Dauchy FA, Bruyand M, Greib C, et al. High frequency of poor locomotor performance in HIV-infected patients. *AIDS*. 2011; 25:797–805. [PubMed: 21330905]

- 94*. Schrack JA, Althoff KN, Jacobson LP, Erlandson KM, Jamieson BD, Koletar SL, et al. Accelerated Longitudinal Gait Speed Decline in HIV-Infected Older Men. *J Acquir Immune Defic Syndr*. 2015; 70:370–376. This longitudinal analysis from the MACS Cohort highlighted the “accelerated aging” process, by clearly demonstrating the separation of gait speed among HIV-infected men after the age of 50. [PubMed: 26102450]
95. Brown, T.; Dobs, AS.; Li, X.; Jacobson, L.; Schrack, JA.; Margolick, JB., et al. Balance confidence predicts falls better than physical function testing in HIV+ men. Conference on Retroviruses and Opportunistic Infections; Abstract #786; Seattle, WA. 2015.
96. Payne BA, Hateley CL, Ong EL, Premchand N, Schmid ML, Schwab U, et al. HIV-associated fatigue in the era of highly active antiretroviral therapy: novel biological mechanisms? *HIV Med*. 2013; 14:247–251. [PubMed: 22998022]
97. Merlin JS. Chronic Pain in Patients With HIV Infection: What Clinicians Need To Know. *Top Antivir Med*. 2015; 23:120–124. [PubMed: 26518396]
98. Vosvick M, Gore-Felton C, Ashton E, Koopman C, Fluery T, Israelski D, et al. Sleep disturbances among HIV-positive adults: the role of pain, stress, and social support. *J Psychosom Res*. 2004; 57:459–463. [PubMed: 15581649]
99. Payne B, Hateley C, Ong E, Premchand N, Schmid M, Schwab U, et al. HIV-associated fatigue in the era of highly active antiretroviral therapy: novel biological mechanisms? *HIV Med*. 2012
100. Bhasin S. Testosterone supplementation for aging-associated sarcopenia. *J Gerontol A Biol Sci Med Sci*. 2003; 58:1002–1008. [PubMed: 14630881]
101. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R, et al. Associations of subclinical cardiovascular disease with frailty. The journals of gerontology Series A, Biological sciences and medical sciences. 2001; 56:M158–166.
102. Afilalo J. Androgen deficiency as a biological determinant of frailty: hope or hype? *J Am Geriatr Soc*. 2014; 62:1174–1178. [PubMed: 24897926]
103. Srinivas-Shankar U, Roberts SA, Connolly MJ, O’Connell MD, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2010; 95:639–650. [PubMed: 20061435]
104. Wunder DM, Bersinger NA, Fux CA, Mueller NJ, Hirschel B, Cavassini M, et al. Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. *Antivir Ther*. 2007; 12:261–265. [PubMed: 17503668]
105. Rochira V, Zirilli L, Orlando G, Santi D, Brigante G, Diazzi C, et al. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. *PLoS One*. 2011; 6:e28512. [PubMed: 22174826]
106. Monroe AK, Dobs AS, Palella FJ, Kingsley LA, Witt MD, Brown TT. Morning free and total testosterone in HIV-infected men: implications for the assessment of hypogonadism. *AIDS Res Ther*. 2014; 11:6. [PubMed: 24450960]
107. Sohl E, van Schoor NM, de Jongh RT, Visser M, Deeg DJ, Lips P. Vitamin D status is associated with functional limitations and functional decline in older individuals. *J Clin Endocrinol Metab*. 2013; 98:E1483–1490. [PubMed: 23864700]
108. Gallagher JC. Vitamin D deficiency and muscle strength: are they related? *J Clin Endocrinol Metab*. 2012; 97:4366–4369. [PubMed: 23223484]
109. Scott D, Sanders KM, Ebeling PR. Vitamin D, muscle function, and falls in older adults: does reduced deposition of intramuscular adipose tissue influence the relationship? *J Clin Endocrinol Metab*. 2013; 98:3968–3970. [PubMed: 23966239]
110. Eckard AR, McComsey GA. Vitamin D deficiency and altered bone mineral metabolism in HIV-infected individuals. *Curr HIV/AIDS Rep*. 2014; 11:263–270. [PubMed: 24962286]
111. Bolland MJ, Grey A, Gamble GD, Reid IR. Vitamin D supplementation and falls: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol*. 2014; 2:573–580. [PubMed: 24768505]
112. Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. *J Clin Endocrinol Metab*. 2013; 98:3821–3828. [PubMed: 23788685]

113. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010; 303:1815–1822. [PubMed: 20460620]
114. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. *JAMA Intern Med*. 2016:1–10.
115. Overton ET, Chan ES, Brown TT, Tebas P, McComsey GA, Melbourne KM, et al. Vitamin D and Calcium Attenuate Bone Loss With Antiretroviral Therapy Initiation. *Ann Intern Med*. 2015; 162:815–824. [PubMed: 26075752]

Bullet Points

- The interaction between falls and fracture risks is an area of increasing clinical relevance, however little is known about the issues unique to HIV-infected adults.
- The combination of increased fall risk and lower bone mineral density highlights the importance of evaluating, monitoring, and modifying risks for both falls and fracture.
- Considering falls as a geriatric syndrome allows for a broader, multifactorial approach to prevention and treatment.
- Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

Figure. The interrelated factors contributing to falls and fractures

Falls are multifactorial, and affected by adiposity, sarcopenia, physical function impairment, and low physical activity; a fall can also result in many of these same factors, leading to further physical function impairment, fear of falling, and subsequent fracture.