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## How to monitor bone disease in HIV infection

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HIV-infected subjects show several bone lesions that are especially correlated with the development of osteopenia and osteoporosis. Since from early times after the HIV isolation and clinical characterization, several reports indicated some bone abnormalities during the development of HIV disease. Osteopenia and osteoporosis are the common bone lesions detectable in HIV positive patients.

The classic risk factors for osteoporosis include: hypogonadism, family history of fractures, BMI <19 kg/m<sup>2</sup>, hypovitaminosis D, smoking, sedentary lifestyle, low impact fractures, advanced age, female gender, menopause and/or amenorrhea, habitual alcohol consumption of >3 units/day, steroids exposure for >3 months.

National Osteoporosis Foundation recommends a comprehensive approach to the management of osteoporosis: all subjects, naïve or experienced, with osteopenia/osteoporosis must be monitored before and during ARV treatment (*National Osteoporosis Foundation, 2010; Dickinson et al. 2012*).

A detailed history and physical examination together with bone mineral density (BMD) assessment and, where appropriate, the WHO 10-year estimated fracture probability, are utilized to establish the individual patient's fracture risk (*National Osteoporosis Foundation GL, 2010*).

### Dual-energy x-ray absorptiometry

BMD testing is a vital component in the diagnosis and management of osteoporosis. BMD has been shown to correlate with bone strength and is an excellent predictor of future fracture risk. Instead of a specific threshold, fracture risk increases exponentially as BMD decreases.

Dual-energy x-ray absorptiometry (DXA) measurement of the hip and spine is the method of choice

to establish or confirm diagnosis of osteopenia/osteoporosis and to predict future fracture risk (*Riggs et al, 2012; Negredo et al, 2012; Aberg et al, 2009; McComsey et al, 2010, Calmy et al, 2012, Lorente Ramos et al, 2012; Mary-Krause et al, 2012*).

DXA measurement of the hip and spine is the technology now used to establish or confirm a diagnosis of osteoporosis, predict future fracture risk and monitor patients by performing serial assessments (*NOF GL 2010*).

Most experts agree that DXA is the diagnostic modality of choice for HIV patients, especially those patients with traditional risk factors for bone loss. (*Negredo et al, 2012*).

Serial central DXA BMD testing is an important component of osteoporosis management. Measurements for monitoring patients should be performed in accordance with medical necessity, expected response and in consideration of local regulatory requirements (*NOF GL 2010*).

Baseline bone densitometry should be performed in postmenopausal women aged >65 years and in younger postmenopausal women with >1 additional risk factor(s) (other than being female and postmenopausal) for premature bone loss. Baseline bone densitometry should be considered in HIV-infected persons aged >50 years, especially if they have >1 risk factor(s) for premature bone loss. (*Aberg et al, 2009*).

Recently published guidelines for the management of low BMD in the general US population recommend a DXA for persons of any age with a fragility fracture, women >65 years of age, and men >70 years of age (*NOF*). For those with an additional risk factor, the recommendation is to perform a DXA in younger post-menopausal women and men >50 years of age. Although HIV infection is not listed as a condition that is associated with low BMD, current evidence supports the inclusion of HIV-infection among other

risk factors. Thus, it is possible to consider a DXA scan for all HIV infected post-menopausal women and men >50 years.

DXA scans in younger HIV-infected persons are probably not indicated, because the risk for fracture is low. (McComsey et al, 2010).

NOF recommends that repeat BMD assessments generally agree with Medicare guidelines of every two years, but recognizes that testing more frequently may be warranted in certain clinical situations. (NOF GL 2010).

If the results of the test do not warrant medical treatment, the test should be repeated every 2–5 years, depending on the proximity to thresholds for therapy.

One of the most powerful predictors of future fragility fractures in the general population is a history of fragility fracture. Patients who have a history of fragility fracture should be evaluated by DXA regardless of age or sex, which is a diagnostic modality clearly underutilized in this population. (McComsey et al, 2010).

In a recent published study, among chronically HIV-infected patients, osteopenia progressed to osteoporosis in a quarter of patients. Although time of progression was more than 8 years, for patients with a minimum baseline T score <-2 SD (lower tertile) it was 3 years. Authors observed that baseline T score, divided into tertiles, enabled them to establish time of progression of bone loss more accurately than the simple classification according to the WHO criteria. The time of progression to osteoporosis varied widely among patients with osteopenia in the first DXA scan according to the tertile: 8 years for those whose minimum T score was in the higher tertile (between -1.1 and -1.6 SD), but only 3 years for those whose minimum T score was in the lowest tertile (from -2 to -2.4 SD). These results are consistent with recent published data in older HIV-negative women. In this analysis of data from 4,957 women, baseline T score was the most determinant of a BMD testing interval; osteoporosis developed in 15 years for women with mild osteopenia (T score, greater than -1.5), 5 years for women with moderate osteopenia (T score from -1.5 to -1.99) and 1 year for women with advanced osteopenia (T score from -2.0 to -2.49) (Gourlay, 2012).

According to this data, a reasonable proposal would be to set the frequency of DXA according to the tertile: patients in the lowest T score tertiles (defined as a T score from -2 to -2.4 among those with osteopenia) should undergo another DXA scan more frequently than those in the other 2 tertiles. A subsequent DXA scan should be recommended as soon as 1–2 years later for those in the lower tertiles; this frequency will help to diagnose early changes in BMD status (from osteopenia to osteoporosis) and, in the case of progression, enable appropriate measures to be taken.

Patients in the other 2 tertiles (T score from -1.1 to -2 among patients with osteopenia) could be assessed by a DXA scan after at least 6–7 years. Since it is unlikely that a patient would progress in less than 7–8 years, more frequent DXA scanning would not affect management, although it would increase costs and inconvenience to patients (Negredo, 2012).

DXA can be repeated every 2 years (Gourlay et al, 2012), but in osteopenic subjects in the highest T-score tertile (from -1.1 to -1.6 SD) can be repeated less frequently, e.g. after 6 years (Negredo et al, 2012).

## Bone Turnover Markers

Correct assessment of the bone structure cannot be separated from a study mineral metabolism.

Bone turnover markers (BTM) may be utilized to predict rate of bone loss and fracture risk, especially in aging patients with osteopenia/osteoporosis (Brown et al, 2009; SIBOMM, 2009; Singapore Ministry of Health, 2008; National Osteoporosis Guideline Group, 2008; Vasikaran et al, 2010; Dawson-Hughes et al, 2008; Martín-Morales et al, 2012).

BTM are most commonly measured before and 3–6 months after initiation of treatment with antiresorptive therapies to estimate fracture risk reduction, but much of the early work on the clinical utility of BTMs focused on the prediction of bone loss (Terreni et al, 2012; Garnero et al, 2008; Lee et al, 2012; Bergmann et al, 2008, Haskelberg, 2012).

Bone remodelling (or turnover) occurs throughout life to repair fatigue damage and microfractures in bone. Biochemical markers of bone remodelling [e.g., resorption markers—serum C-telopeptide (CTX) and urinary N-telopeptide (NTX) and formation markers—serum bone specific alkaline phosphatase (BSAP) and osteocalcin] can be measured in the serum and urine in untreated patients to assess risk of fracture. They may predict bone loss (NOF GL 2010).

Potential clinical uses of BTMs include prediction of bone loss and fracture in untreated postmenopausal women (Brown JP et al, 2009).

These markers are not useful to make the diagnosis, but they are useful to orient physicians about the dynamics of bone turnover in a particular patient. This will help physicians to identify patients with a higher fracture risk. (Sociedad Iberoamericana de Osteología y Metabolismo Mineral –SIBOMM - Ibero-American consensus on osteoporosis, 2009) www.aaomm.org.ar.

Bone turnover markers do aid in fracture risk assessment, the prediction of rates of bone loss (Singapore Ministry of Health. Clinical practice guidelines for osteoporosis. Ministry of Health, Singapore, 2008) www.moh.gov.sg/cpg.

BTMs have the potential of aiding risk assessment as well as for monitoring therapy (level Ib) (National Osteoporosis Guideline Group. Osteoporosis - clinical guide-

line for prevention and treatment—executive summary, 2008) [www.shef.ac.uk/NOGG](http://www.shef.ac.uk/NOGG).

Bone turnover markers in fracture risk prediction: oestrogen deficiency, associated with menopause, results in a generalised increase in bone remodelling and an imbalance between bone formation and resorption. This increase is maintained for several decades after the menopause and is associated with accelerated bone loss. An increased rate of bone loss from the forearm and hip is associated with an increase in the risk of vertebral fracture, an effect independent of final BMD. Thus, it is logical to consider that high bone turnover might predict fracture. The mechanism by which sustained high bone turnover might be associated with increased fracture risk could be related simply to the bone loss resulting in a low BMD. In addition, there are other mechanisms whereby increased bone turnover might be associated with an increased fracture risk independent of BMD. Deterioration of bone architecture may contribute to skeletal fragility over and above that provided by the decrease in bone mass. For example, resorption cavities on either side of a trabeculum give rise to stress concentrators that result in the local weakening of the trabeculum that is disproportionate to the small amount of bone lost. In addition, increased bone turnover increases the proportion of recently synthesised bone which is less well mineralised than mature bone with fewer enzymatic post-translational modifications of bone collagen (cross-linking and -isomerisation). It is possible that these features impair the structural properties of bone (*Vasikaran et al, 2010*).

BTMs in prediction of rate of bone loss: much of the early work on the clinical utility of BTMs focused on the prediction of bone loss in women at the time of the menopause. It was considered that a low BMD along with a high rate of bone loss might help identify those who would benefit most from hormone replacement therapy (HRT). This approach had assumed that there would be a subpopulation of 'fast losers' but bone loss is normally distributed. Also, the use of HRT for the prevention of osteoporosis is an approach no longer widely adopted. BTMs, together with demographic variables, predict 30–40% of the variance in bone loss in untreated postmenopausal women. There are consistent associations between BTMs and bone loss at the distal forearm and the calcaneus, a modest relationship with bone loss at the hip and only a weak relationship with bone loss at the spine; the latter may be related to BMD measurement artefacts due to the high prevalence of spinal osteoarthritis in the elderly. Increased BTMs in early menopause have an 80% sensitivity for detecting fast bone losers (bone loss >3%/year) at the forearm in the next 2–12 years, but they have not been shown to be sufficiently predictive of bone loss at the hip or spine in individual patients. Some physicians might

use a high BTM to indicate that rapid bone loss is quite likely and so review the patient earlier for BMD monitoring, but BTM thresholds for intervention to prevent bone loss in menopausal and elderly subjects have not been defined (*Vasikaran et al, 2010*).

BTM may predict bone loss and, when repeated after 3–6 months of treatment with FDA approved antiresorptive therapies, may be predictive of fracture risk reduction (*NOF GL 2010*).

Suppression of biochemical markers of bone turnover after 3–6 months of specific antiresorptive osteoporosis therapies, and biochemical marker increases after 1–3 months of specific anabolic therapies, have been predictive of greater BMD responses in studies evaluating large groups of patients. Because of the high degree of biological and analytical variability in measurement of biochemical markers, changes in individuals must be large in order to be clinically meaningful. It is critical to appreciate the LSC associated with the biomarker being utilized, which is calculated by multiplying the "precision error" of the specific biochemical marker (laboratory provided) by 2.77 (95% confidence level). Biological variability can be reduced by obtaining samples in the early morning after an overnight fast. Serial measurements should be made at the same time of day and preferably during the same season of the year (*NOF GL 2010*).

Possible algorithm: measure at baseline s-CTX (antiresorptive therapy) and Total s-PINP (anabolic therapy), other when available. Remeasure at 3–6 months. Significant change is measured by absolute percentages, >40% for bone formation markers, and 35–55% change in bone resorption markers (*Brown JP et al, 2009*).

Biochemical markers of bone remodelling (resorption and formation) can be measured in the serum and urine in untreated patients to assess risk of fracture. They may predict bone loss and, when repeated after 3–6 months of treatment with FDA approved antiresorptive therapies, may be predictive of fracture risk reduction (*Dawson-Hughes B et al, 2008*) [www.nof.org](http://www.nof.org).

## Height

Height should be assessed in all patients with osteopenia/osteoporosis, and is to be assessed every 2 years.

A height loss of more than 3 cm suggests a diagnosis of vertebral fracture.

## Vertebral fracture assessment

Vertebral Fracture Assessment (VFA) performed in patients with osteopenia/osteoporosis and historical height loss of 2 to 6 cm or self-reported osteoporotic fracture, may confirm vertebral fractures and is a

strong predictor of new other fractures (*National Osteoporosis Foundation, 2010; ISCD Official Positions, Updated 2007; Walker Harris et al, 2012; Torti et al, 2011; Triant et al, 2008; Young et al, 2011*).

VFA could be performed when there is evidence of a decrease in height (*EACS Guidelines, 2011*).

VFA is the correct term to denote densitometric spine imaging performed for the purpose of detecting vertebral fractures. Independent of BMD, age and other clinical risk factors, radiographically confirmed vertebral fractures are a strong predictor of new vertebral fractures, and they also predict other fractures. VFA imaging of the thoracic and lumbar spine using central DXA scanners should be considered at the time of BMD assessment when the presence of a vertebral fracture not previously identified may influence clinical management of the patient. International Society for Clinical Densitometry indications for VFA in postmenopausal women and men are available at [www.iscd.org.14](http://www.iscd.org.14) (*NOF GL 2010*).

Consider VFA when the results may influence clinical management.

- Postmenopausal women with low bone mass (osteopenia) by BMD criteria, PLUS any one of the following:
  - Age greater than or equal to 70 years
  - Historical height loss greater than 4 cm (1.6 in.)
  - Prospective height loss greater than 2 cm (0.8 in.)
  - Self-reported vertebral fracture (not previously documented)
  - Two or more of the following;
    - Age 60 to 69 years
    - Self-reported prior non-vertebral fracture
    - Historical height loss of 2 to 4 cm
    - Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)
- Men with low bone mass (osteopenia) by BMD criteria, PLUS any one of the following:
  - Age 80 years or older
  - Historical height loss greater than 6 cm (2.4 in.)
  - Prospective height loss greater than 3 cm (1.2 in.)
  - Self-reported vertebral fracture (not previously documented)
    - Two or more of the following;
      - Age 70 to 79 years
      - Self-reported prior non-vertebral fracture
      - Historical height loss of 3 to 6 cm
      - On pharmacologic androgen deprivation therapy or following orchiectomy
      - Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)
- Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for

three (3) months or longer).

- Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management.

The methodology utilized for vertebral fracture identification should be similar to standard radiological approaches and be provided in the report.

Fracture diagnosis should be based on visual evaluation and include assessment of grade/severity. Morphometry alone is not recommended because it is unreliable for diagnosis.

The Genant visual semi-quantitative method is the current clinical technique of choice for diagnosing vertebral fracture with VFA.

Severity of deformity may be confirmed by morphometric measurement if desired (*ISCD Official Positions - Updated 2007*).

The decision to perform additional imaging must be based on each patient's overall clinical picture, including the VFA result.

Indications for follow-up imaging studies include:

Two or more mild (grade 1) deformities without any moderate or severe (grade 2 or 3) deformities.

Lesions in vertebrae that cannot be attributed to benign causes.

Vertebral deformities in a patient with a known history of a relevant malignancy.

Equivocal fractures.

Unidentifiable vertebrae between T7-L4.

Sclerotic or lytic changes, or findings suggestive of conditions other than osteoporosis. (*ISCD Official Positions - Updated 2007*).

## FRAX

FRAX® can calculate the 10-year probability of a fracture in patients with osteopenia/osteoporosis age 50 and older, is most useful in patients with low hip BMD, but there are insufficient data to validate its utility in HIV infected patients. (*ISCD Official Position, 2010; Gazzola et al, 2010*).

FRAX® can be repeated every 2 years, or for new risk factors upcoming.

FRAX® with BMD predicts fracture risk better than clinical risk factors or BMD alone: use of FRAX® without BMD is appropriate when BMD is not readily available or to identify individuals who may benefit from a BMD measurement. HIV infection is a secondary cause of osteoporosis, and fracture risk is mediated primarily through impact on BMD: for this reason, when T-scores are inserted into FRAX®, the secondary osteoporosis button is automatically inactivated (*ISCD Official Position, 2010*).

FRAX® was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as clinical vertebral, hip, forearm or proximal humerus

fracture) taking into account femoral neck BMD and the clinical risk factors. The FRAX® algorithm is available at [www.nof.org](http://www.nof.org) and at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX); it should soon be available on newer DXA scanners.

FRAX® is most useful in patients with low hip BMD. Utilizing FRAX® in patients with low BMD at the spine but a relatively normal BMD at the hip requires special consideration. Specifically, the WHO algorithm has not been validated for the use of spine BMD. As such, clinicians will need to use clinical judgment in this situation, since FRAX® may underestimate fracture risk in these individuals based on the exclusive use of femoral neck BMD.

FRAX® is intended for postmenopausal women and men age 40 and older; it is not intended for use in younger adults or children.

The FRAX® tool has not been validated in patients currently or previously treated with pharmacotherapy for osteoporosis. In such patients, clinical judgment must be exercised in interpreting FRAX® scores.

In the absence of femoral neck BMD, total hip BMD may be substituted; however, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated.

The WHO determined that for many secondary causes of osteoporosis, fracture risk was mediated primarily through impact on BMD. For this reason, when T-scores are inserted into FRAX®, the secondary osteoporosis button is automatically inactivated. The therapeutic thresholds proposed in this Guide are for clinical guidance only and are not rules. All treatment decisions require clinical judgment and consideration of individual patient factors, including patient preferences, comorbidities, risk factors not captured in the FRAX model (e.g., frailty, falls), recent decline in bone density and other sources of possible under- or over-estimation of fracture risk by FRAX®. The therapeutic thresholds do not preclude clinicians or patients from considering intervention strategies for those who do not have osteoporosis by BMD (WHO diagnostic criterion of T-score  $\leq$  -2.5), do not meet the cut points after FRAX®, or are not at high enough risk of fracture despite low BMD. Conversely, these recommendations should not mandate treatment, particularly in patients with osteopenia. Decisions to treat must still be made on a case-by-case basis (NOF GL 2010).

### Calcium intake

Adequate intake of dietary daily calcium (at least 1,000-1,200 mg per day) is a safe and inexpensive way to help reduce fracture risk in patients with osteopenia/osteoporosis. If necessary, increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary

intake cannot be achieved (Li Vecchi et al, 2012; Leite et al, 2010). Review intake of dietary calcium annually.

Providing adequate daily calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk. Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture.

Advise all individuals to obtain an adequate intake of dietary calcium (at least 1,200 mg per day, including supplements if necessary). Lifelong adequate calcium intake is necessary for the acquisition of peak bone mass and subsequent maintenance of bone health. The skeleton contains 99 percent of the body's calcium stores; when the exogenous supply is inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level. NOF supports the National Academy of Sciences (NAS) recommendation that women older than age 50 consume at least 1,200 mg per day of elemental calcium. Intakes in excess of 1,200 to 1,500 mg per day have limited potential for benefit and may increase the risk of developing kidney stones or cardiovascular disease. Men and women age 50 and older typically consume only about 600 to 700 mg per day of calcium in their diets. Increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary intake cannot be achieved.

### 25(OH)Vitamin D

Serum 25(OH)D levels should be measured in patients with osteopenia/osteoporosis, and vitamin D supplemented in amounts sufficient to bring the serum 25(OH)D level to 30 ng/ml (75 nmol/L) or higher (Bang et al, 2012; Banon et al, 2012; Viganò et al, 2012, Bech et al 2012, Foissac et al, 2012).

Review vitamin D supplementation annually, in winter or spring.

Considering that in some individuals (especially those with very low 25-OH vitamin D plasma levels) regular nutritional supplementation may not be able to obtain optimal level, retesting plasma levels after 6 months from nutritional supplementation is advisable.

In the case of hypovitaminosis, testing of plasma calcium, phosphate, alkaline phosphatase and PTH levels is indicated.

Vitamin D plays a major role in calcium absorption, bone health, muscle performance, balance and risk of falling. NOF recommends an intake of 800 to 1,000 international units (IU) of vitamin D per day for adults age 50 and older. This intake will bring the average adult's serum 25(OH)D concentration to the desired level of 30 ng/ml (75 nmol/L) or higher. Chief dietary sources of vitamin D include vitamin D-fortified milk (400 IU per quart, although certain

products such as soy milk are not supplemented with vitamin D) and cereals (40 to 50 IU per serving), egg yolks, salt-water fish and liver. Some calcium supplements and most multivitamin tablets also contain vitamin D. Many elderly patients are at high risk for vitamin D deficiency, including patients with malabsorption (e.g., celiac disease) and chronic renal insufficiency, housebound patients, chronically ill patients and others with limited sun exposure. Serum 25(OH)D levels should be measured in patients at risk of deficiency and vitamin D supplemented in amounts sufficient to bring the serum 25(OH)D level to 30 ng/ml (75 nmol/L) or higher. Many patients, including those with malabsorption, will need more. The safe upper limit for vitamin D intake for the general adult population was set at 2,000 IU per day in 1997; recent evidence indicates that higher intakes are safe and that some elderly patients will need at least this amount to maintain optimal 25(OH)D levels (*NOF GL 2010*).

Vitamin D supplementation in 181 patients produced a significant decrease in serum PTH (57.2 if not treated vs 50.5 pg/ml,  $p=0.02$ , 23% continues with SH) and the only factor associated with lack of response was persistent vitamin D deficiency (*Banon et al, 2012*).

Cholecalciferol supplementation produced an early decrease in PTH levels (3 months) and a later concomitant increase in 25(OH)D and 1,25(OH)<sub>2</sub>D levels (6 months), both persisting up to 12 months (*Viganò et al, 2012*).

In a recent open-label study, one-year treatment improved vitamin D levels, decreased serum parathyroid hormone (PTH), and improved calcium balance and bone mineral density (*Bech et al, 2012*).

### Life-style

Patients with osteopenia/osteoporosis should be reminded of the health benefits of regular weight-bearing and muscle-strengthening exercise, fall prevention, avoidance of tobacco use and excessive alcohol intake (*Aberg et al, 2009*).

Reminder of these issues can be repeated every medical visit.

Patients should be reminded of the health benefits of regular exercise and adequate calcium and vitamin D intake. They should also be counseled about the risks of cigarette smoking and excessive alcohol consumption. Secondary causes of decreased bone density, such as hypogonadism and vitamin D deficiency, should be investigated and treated accordingly (*Aberg et al, 2009*).

### Regular weight-bearing exercise

Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures. Among its many health benefits, weight-

bearing and muscle-strengthening exercise can improve agility, strength, posture and balance, which may reduce the risk of falls. In addition, exercise may modestly increase bone density. NOF strongly endorses lifelong physical activity at all ages, both for osteoporosis prevention and overall health, as benefits are lost when the person stops exercising. Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body's weight) includes walking, jogging, Tai-Chi, stair climbing, dancing and tennis. Muscle-strengthening exercise includes weight training and other resistive exercises. Before an individual with osteoporosis initiates a new vigorous exercise program, such as running or heavy weight-lifting, a clinician's evaluation is appropriate.

### Fall prevention

In addition to maintaining adequate vitamin D levels and physical activity, as described above, strategies to reduce falls include, but are not limited to, checking and correcting vision and hearing, evaluating any neurological problems, reviewing prescription medications for side effects that may affect balance and providing a checklist for improving safety at home. Wearing undergarments with hip pad protectors may protect an individual from injuring the hip in the event of a fall. Hip protectors may be considered for patients who have significant risk factors for falling or for patients who have previously fractured a hip.

### Avoidance of tobacco use and excessive alcohol intake

Advise patients to avoid tobacco smoking. The use of tobacco products is detrimental to the skeleton as well as to overall health. NOF strongly encourages a smoking cessation program as an osteoporosis intervention.

Recognize and treat patients with excessive alcohol intake. Moderate alcohol intake has no known negative effect on bone and may even be associated with slightly higher bone density and lower risk of fracture in postmenopausal women. However, alcohol intake of three or more drinks per day is detrimental to bone health, increases the risk of falling and requires treatment when identified (*NOF GL 2010*).

### CT-based absorptiometry and Quantitative ultrasound densitometry

CT-based absorptiometry has been shown to predict fractures in postmenopausal women and Quantitative ultrasound densitometry has been shown to predict fractures in postmenopausal women and in aging men, but there is lack of evidence in HIV infected patients (*Danielson et al, 2012*).

Quantitative computed tomography (QCT) measures volumetric trabecular and cortical bone den-

sity at the spine and hip, whereas peripheral QCT (pQCT) measures the same at the forearm or tibia. In postmenopausal women, QCT measurement of spine trabecular BMD can predict vertebral fractures whereas pQCT of the forearm at the ultra distal radius predicts hip, but not vertebral fractures. There is lack of sufficient evidence for fracture prediction in men. QCT and pQCT are associated with greater amounts of radiation exposure than central DXA or pDXA (*NOF GL 2010*).

Quantitative ultrasound densitometry (QUS) does not measure BMD directly but rather speed of sound (SOS) and/or broadband ultrasound attenuation (BUA) at the heel, tibia, patella and other peripheral skeletal sites. A composite parameter using SOS and BUA may be used clinically. Validated heel QUS devices predict fractures in postmenopausal women (vertebral, hip and overall fracture risk) and in men 65 and older (hip and non-vertebral fractures). QUS is not associated with any

radiation exposure (*NOF GL 2010*).

In conclusion, concerning to osteopenic subjects, median progression time to osteoporosis is more accelerated in subjects in “high-risk” tertile (T score from -2.0 to -2.4 SD), so the lowest T-score tertile may indicate the recommendation of a subsequent DXA scan every 2 years (*Negredo et al, 2012*).

In this setting, adequate intake of dietary daily calcium, optimal serum 25(OH)D levels, regular weight-bearing and muscle-strengthening exercise, fall prevention, avoidance of tobacco use and excessive alcohol intake are very important issues (*Li Vecchi et al, 2012; Leite et al, 2010, Bang et al, 2012; Banon et al, 2012; Viganò et al, 2012, Bech et al 2012, Foissac et al, 2012, Aberg et al, 2009*).

If osteopenia status is progressing, evaluate and treat potential secondary causes of osteopenia, life style advice and calculate FRAX® score (*Aberg et al, 2009, McComsey et al, 2010, ISCD Official Position, 2010; Gazzola et al, 2010*).

## References

- Judith A. Aberg, Jonathan E. Kaplan, Howard Libman, Patricia Emmanuel, Jean R. Anderson, Valerie E. Stone, James M. Oleske, Judith S. Currier, and Joel E. Gallant  
Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: 2009 Update by the HIV Medicine Association of the Infectious Diseases Society of America  
*Clinical Infectious Diseases* 2009; 49:651–81
- Ulrich Christian Bang, Lilian Kolte, Mette Hitz, Louise Lind Schierbeck, Susanne Dam Nielsen, Thomas Benfield, Jens-Erik Beck Jensen  
The effect of cholecalciferol and calcitriol on biochemical bone markers in HIV-1 infected males: results of a clinical trial.  
*AIDS Research and Human Retroviruses* (doi: 10.1089/AID.2012.0263)
- Bañon S, Del Palacio M, Pérez Elías M, Moreno A, Moreno S, Dronda F, Casado J.  
Secondary hyperparathyroidism in HIV-infected patients: relationship with bone remodeling and response to vitamin D supplementation.  
*J Int AIDS Soc.* 2012 Nov 11;15(6):18319.
- Bech A, Van Bentum P, Telting D, Gisolf J, Richter C, De Boer H.  
Treatment of calcium and vitamin D deficiency in HIV-positive men on tenofovir-containing antiretroviral therapy.  
*HIV Clin Trials.* 2012 Nov-Dec;13(6):350-6.
- P. Bergmann, J.-J. Body, S. Boonen, Y. Boutsen, J.-P. Devogelaer, S. Goemaere, J.-M. Kaufman, J.-Y. Reginster, V. Gangji, Members of the Advisory Board on Bone Markers  
Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club  
*Int J Clin Pract.* January 2009, 63, 1, 19–26
- Calmy A, Chevalley T, Delhumeau C, Toutous-Trellu L, Spycher-Elbes R, Ratib O, Zawadzynski S, Rizzoli R.  
Long-term HIV infection and antiretroviral therapy are associated with bone microstructure alterations in premenopausal women.  
*Osteoporos Int.* 2012 Nov 9.
- Danielson ME, Beck TJ, Karlamangla AS, Greendale GA, Atkinson EJ, Lian Y, Khaled AS, Keaveny TM, Kopperdahl D, Ruppert K, Greenspan S, Vuga M, Cauley JA.  
A comparison of DXA and CT based methods for estimating the strength of the femoral neck in post-menopausal women.  
*Osteoporos Int.* 2012 Jul 19.
- Dickinson SA, Fantry LE.  
Use of Dual-Energy X-Ray Absorptiometry (DXA) Scans in HIV-Infected Patients.  
*J Int Assoc Physicians AIDS Care (Chic).* 2012 Jul-Aug; 11(4):239-44
- Frantz Foissac, Jean-Marc Tréluyer, Jean-Claude Souberbielle, Hafeda Rostane, Saïk Urien and Jean-Paul Viard  
Vitamin D3 supplementation scheme in HIV-infected patients 1 based upon a pharmacokinetic modelling of 25-hydroxycholecalciferol  
*British Journal of Clinical Pharmacology* © 2012
- L. Gazzola, L. Comi, A. Savoldi, L. Tagliabue, A. Del Sole, L. Pietrogrande, T. Bini, A. d’Arminio Monforte, and G. Marchetti  
Use of the FRAX Equation as First-Line Screening of Bone Metabolism Alteration in the HIV-Infected Population  
*The Journal of Infectious Diseases* 2010;202(2):330–331
- Margaret L. Gourlay, M.D., M.P.H., Jason P. Fine, Sc.D., John S. Preisser, Ph.D., Ryan C. May, Ph.D., Chenxi Li, Ph.D., Li-Yung Lui, M.S., David F. Ransohoff, M.D., Jane A. Cauley, Dr.P.H., and Kristine E. Ensrud, M.D., M.P.H. for the Study of Osteoporotic Fractures Research Group  
Bone-Density Testing Interval and Transition to Osteoporosis in Older Women  
*N Engl J Med.* 2012 January 19; 366(3): 225–233.
- Hila Haskelberg, Jennifer F. Hoy, Janaki Amin, Peter R. Ebeling, Sean Emery, Andrew Carr, STEAL Study Group  
Changes in Bone Turnover and Bone Loss in HIV-Infected Patients Changing Treatment to Tenofovir-Emtricitabine or Abacavir-Lamivudine

- PLoS ONE 7(6): e38377. doi:10.1371/journal.pone.0038377
- Jehoon Lee, M.D., and Samuel Vasikaran, M.D.  
Current Recommendations for Laboratory Testing and Use of Bone Turnover Markers in Management of Osteoporosis  
*Ann Lab Med* 2012;32:105-112
  - Leite LH, Sampaio AB  
Dietary calcium, dairy food intake and metabolic abnormalities in HIV-infected individuals.  
*J Hum Nutr Diet.* 2010 Oct;23(5):535-43
  - Valentina Li Vecchi, Maurizio Soresi, Lydia Giannitrapani, Giovanni Mazzola, Sara La Sala, Fabio Tramuto, Giuseppe Caruso, Claudia Colomba, Pasquale Mansueto, Simona Madonna, Giuseppe Montalto and Paola Di Carlo  
Dairy calcium intake and lifestyle risk factors for bone loss in hiv-infected and uninfected mediterranean subjects  
*BMC Infectious Diseases* 2012, 12:192
  - Lorente Ramos RM, Azpeitia Armán J, Arévalo Galeano N, Muñoz Hernández A, García Gómez JM, Gredilla Molinero J.  
Dual energy X-ray absorptimetry: fundamentals, methodology, and clinical applications.  
*Radiologia.* 2012 Sep-Oct;54(5):410-23.
  - Martín-Morales R, Ruiz J, Nuño E, Márquez M, Santos J, Palacios R.  
Bone turnover markers in HIV-infected patients before starting antiretroviral therapy.  
*J Int AIDS Soc.* 2012 Nov 11;15(6):18321
  - Mary-Krause M, Viard JP, Ename-Mkoumazok B, Bentata M, Valantin MA, Missy P, Darasteanu I, Roux C, Kolta S, Costagliola D, Rozenberg S.  
Prevalence of low bone mineral density in men and women infected with human immunodeficiency virus 1 and a proposal for screening strategy.  
*J Clin Densitom.* 2012 Oct-Dec;15(4):422-33
  - Grace A. McComsey, Pablo Tebas, Elizabeth Shane, Michael T. Yin, E. Turner Overton, Jeannie S. Huang, Grace M. Aldrovandi, Sandra W. Cardoso, Jorge L. Santana, and Todd T. Brown  
Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers  
*Clinical Infectious Diseases* 2010; 51(8):937–946
  - Eugenia Negredo, Anna Bonjoch, Moises Gomez-Mateu, Carla Estany, Jordi Puig, Nuria Perez-Alvarez, Joaquin Rosales, Silvana di Gregorio, Luis del Rio, Guadalupe Gomez, Bonaventura Clotet  
Time of Progression to Osteopenia/Osteoporosis in Chronically HIV-Infected Patients: Screening DXA Scan  
*PLoS ONE* 7(10): e46031. doi:10.1371/journal.pone.0046031
  - B. Lawrence Riggs, Sundeep Khosla, and L. Joseph Melton III  
Better tools for assessing osteoporosis  
*J Clin Invest.* 2012; 122(12):4323–4324.
  - Alessandro Terreni, Paola Pezzati  
Biochemical markers in the follow-up of the osteoporotic patients  
*Clinical Cases in Mineral and Bone Metabolism* 2012; 9(2): 80-84
  - Carlo Torti, Gherardo Mazziotti, Pier Antonio Soldini, Emanuele Foca, Roberto Maroldi, Daria Gotti, Giampiero Carosi, Andrea Giustina  
High prevalence of radiological vertebral fractures in HIV-infected males  
*Endocrine* (2012) 41:512–517
  - Virginia A. Triant, Todd T. Brown, Hang Lee, and Steven K. Grinspoon  
Fracture Prevalence among Human Immunodeficiency Virus (HIV)-Infected Versus Non-HIV-Infected Patients in a Large U.S. Healthcare System  
*J Clin Endocrinol Metab.* September 2008, 93(9):3499–3504
  - S. Vasikaran, R. Eastell, O. Bruyère, A. J. Foldes, P. Garnero, A. Griesmacher, M. McClung, H. A. Morris, S. Silverman, T. Trenti, D. A. Wahl, C. Cooper, J. A. Kanis, for the IOF-IFCC Bone Marker Standards Working Group  
Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards  
*Osteoporos Int* (2011) 22:391–420
  - Viganò A, Giacomet V, Manfredini V, Bedogni G, Mora S, Cerini C, Borelli M, Trabattini D, Zuccotti G.  
Cholecalciferol supplementation, vitamin D status and T-cell immune phenotype in HIV-infected children: a randomised controlled trial.  
*J Int AIDS Soc.* 2012 Nov 11;15(6):18231
  - V. Walker Harris, T. T. Brown  
Osteopenia, Osteoporosis, and Fractures in HIV-Infected Patients: Extent of the Problem  
*Clinic Rev Bone Miner Metab* DOI 10.1007/s12018-012-9132-z
  - Benjamin Young, Christine N. Dao, Kate Buchacz, Rose Baker, John T. Brooks, and the HIV Outpatient Study (HOPS) Investigators  
Increased Rates of Bone Fracture Among HIV-Infected Persons in the HIV Outpatient Study (HOPS) Compared With the US General Population, 2000–2006  
*Clinical Infectious Diseases* 2011;52(8):1061–1068