HIV and bone health

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Abstract

Despite advances in HIV medicine people living with HIV (PLWH) continue to face many physical challenges. As the natural history of HIV infection evolves and with an ageing cohort, bone health and disease should be an important consideration for healthcare professionals working in this field. This continuing professional development (CPD) article will briefly describe bone health and the causes and symptoms of a range of bone diseases found both in the general and HIV-positive population. The article emphasises prevention strategies but treatment options are also detailed.

Given that reduction in bone density is associated with increased mortality, early detection and effective management of associated risk factors is imperative in order to enhance quality of life and limit overall disease burden. There is a clear role for nurses working in the field to collaborate with multidisciplinary colleagues in the provision of evidence-based screening and care for those at risk, in order to improve clinical outcomes and quality of life.

Key words: antiretroviral therapy, bone mineral density, HIV, prevention, treatment

A. Revalidation

This article has been prepared with continuing professional development (CPD) in mind and can be used to support your revalidation. It is estimated that 4 hours of CPD activity will be required for completion of the reading, 'time out' activities, the quiz, and writing a reflective account in relation to your learning and its applicability to your practice. You could test your knowledge by completing the self-assessment quiz before reading the article, returning to it afterwards to see how much you have learned.

B. Aims and intended learning outcomes

This article aims to increase knowledge and confidence. On completion of reading and undertaking the included activities and self-assessment quiz you should:

- Be able to outline how bone is formed across the human lifespan;
- Identify a range of risk factors for bone density loss;
- List a number of common bone disorders and related predisposing factors;
- Describe how bone density is assessed and classified;
- Evaluate the strengths and weaknesses of the FRAX tool and it's applicability in the HIV-positive cohort;
- Discuss a range of bone disease prevention strategies;
- Outline a range of interventions for the treatment of common bone diseases;
- Summarise current research findings in respect of bone disease in HIV-positive cohorts including the role of ART; and
- Discuss the basis for current recommendations for treatment for people living with HIV (PLWH) who are at risk of or have reduced bone mineral density.

C. Anatomy, physiology and bone formation

As well as providing structural support and movement the skeleton protects vital internal organs, provides mineral homeostasis and maintains acid–base balance and haematopoiesis within the bone marrow spaces. The adult human skeleton has in excess of 200 bones in four general categories, long bones, short bones, flat bones and irregular bones. Long bones include the humerus and femur and the short bones include the carpal and tarsal bones, and the patella. Flat bones include the skull and irregular bones include the vertebrae and sacrum. There are subtle differences in how these categories of bones are formed.

The adult human skeleton is composed of 80% cortical bone and 20% trabecular bone [1]. Different categories of bones have different ratios of these. Cortical bone is dense and solid, and surrounds the marrow space, whereas trabecular bone has the appearance of a honeycomb, in other words a network of plates and rods interspersed in the bone marrow space. In the absence of disease cortical bone and trabecular bone are normally formed in a pattern of fine, alternating layers. In good health, specialised cells called osteoblasts lay down collagen in this pattern and this has significant strength. A fibrous connective tissue sheath (the periosteum) surrounds the outer surface of bone, (except at joints where bone is lined by articular cartilage) and a membranous structure (endosteum) covers the inner surface, as illustrated in Figure 1.

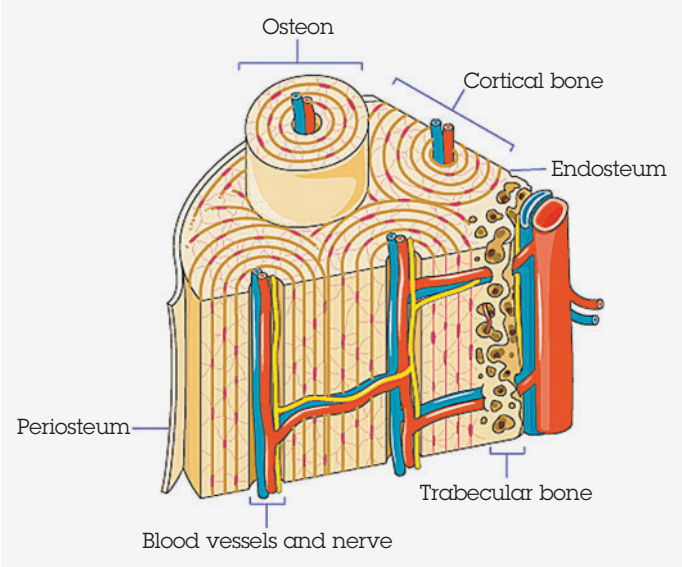

Figure 1: *Cross-section of bone structure [2]*

Longitudinal and radial growth occurs during childhood and adolescence. Modelling is the process by which bones adapt their overall shape in response to physiological influences or mechanical forces, slowly adjusting the skeleton to the forces that it encounters. This process tails off as adults age.

Remodelling occurs continually during life to ensure that the skeleton continues to adapt to changing biomechanical forces and that old, damaged bone is removed. Increased remodelling causes an increase in porosity and a decrease in bone mass. Healthy adults, as part of the normal ageing process, experience bone thinning and increased porosity. The remodelling cycle is composed of four phases: activation, resorption, reversal and finally formation. Bone formation takes approximately 4 to 6 months to complete. Simplified; osteoclasts are attracted to the areas needing repair where they remove damaged bone and osteoblasts are then responsible for filling the remaining gaps.

Key fact

In the first year of life almost 100% of the skeleton is replaced through remodelling. In adulthood this slows to approximately 10% per year [3].

D. Bone mineral density

Any imbalance between bone resorption and bone formation results in a decrease in bone mineral density (BMD). The structural integrity of bone is lost and the reduced load-bearing capacity increases the risk of fracture. A number of factors can disrupt the remodelling process, for example, hormone imbalances, vitamin D or calcium deficiency, some drug treatments, immune dysfunction and diseases such as parathyroid or Paget's disease. A number of modifiable factors are also considered influential, as listed in Box 1.

Box 1. Risk factors for bone mineral density loss

- Physical inactivity and a sedentary lifestyle
- Smoking
- Increasing age
- High alcohol intake
- Low body weight and weight loss *(body mass index of below 19 kg/m^2)*
- Young females who experience amenorrhea due to diet and over exercise
- White or Asian ethnic origin compared to Afro-Caribbean origin
- Post gender re-assignment, especially where hormone replacement therapy is discontinued
- Rheumatoid arthritis
- Low levels of oestrogen e.g. post menopause/early menopause
- Low levels of testosterone in men
- Hyperthyroidism
- Sarcoidosis
- Liver disease
- Parathyroid disease
- Conditions that affect nutrition absorption e.g. Crohn's or coeliac disease
- Medium- and long-term use of some prescribed drug treatments

Source: National Osteoporosis Society [4].

Time out activity 1

A number of pharmacological agents are associated with increased risk of reduced bone mineral density. Spend 10 minutes researching online and see if you can find at least five classes of drugs that have this potential side effect.

E. Bone disease in the general population

Worldwide, osteoporosis is the most significant bone-related disease [5]. The implications on mortality rates, quality of life, health and social care costs, and lost productivity are very significant. Osteoporosis will be discussed in more depth in section G.

Other bone diseases include Paget's disease where osteoblasts and osteoclasts are ineffective. This causes bone to become thickened and also brittle due to abnormal structural development. In the genetic disorder osteogenesis imperfecta, a defective gene affects collagen production. The resulting brittle bones fracture easily; hearing loss, teeth weakness and a curvature of the spine are also seen. Bone cancers include primary bone cancers such as leukemia, osteosarcoma, and Ewing sarcoma. Secondary bone cancers are commonly seen in malignant disease. The preventable bone disease, rickets, affects young children and is caused by a deficiency of vitamin D resulting in weak, brittle bones that fracture easily,

together with bone and muscle pain. Osteomalacia is caused by a defect in vitamin D metabolism resulting in weakened bones and abnormal bone formation. An excess of growth hormone production causes the condition known as acromegaly that is characterised by an overgrowth of bones in the face, hands and feet, the most common cause being a benign tumour in the pituitary gland. Osteomyelitis is a bacterial bone infection, which can either be acute or chronic. It most commonly affects the long bones and most cases are caused by the bacterium *Staphylococcus aureus* as a result of: a pre-existing systemic infection; injury, such as fracture or an animal bite; during or after surgery (such as a joint replacement); and in those with circulatory problems. Bone can become permanently damaged if not diagnosed and treated quickly. A 4–6-week course of antibiotics is usually required.

F. Assessing bone mineral density

The gold standard technique is an imaging technique called dual energy X-ray absorptiometry (DEXA) scan. This non-invasive procedure uses X-rays to measure calcium and other bone mineral depositions in different areas such as the hip and spine. The result is then compared with the bone density expected for a 30-year-old healthy adult. The difference is calculated as a standard deviation (SD) score and is referred to as a T-score. The result is also matched against the average BMD of individuals of the same sex, age, weight and ethnicity. This result is referred to as the Z-score.

Box 2. World Health Organization classification of BMD

WHO classifies T-scores as follows:

- Normal: between +1 and –1
- Osteopenia: between –1 and –2.5
- Osteoporosis: below –2.5

Z-score of below –2, indicates a BMD lower than it should be for someone with the same risk factors including age.

Source: NHS Choices [6].

T-scores alone may not be adequate to predict the risk for fragility fractures and diagnose osteoporosis because testing only partially explains the risk for these. A large part of resistance to fracture or bone strength is related to elements affecting the quality of the skeleton that DEXA cannot measure such as the microscopic architecture of the bone.

The World Health Organization (WHO) has validated a tool for assessing fracture risk. Devised in 2008 the FRAX Score [7] aims to predict risk of fracture in adults aged 40–90 years based on BMD and other risk factors such as sex and age. The result is given as a 10-year probability of a major fracture in the spine, hip, shoulder of forearm.

Time out activity 2

If you are not already familiar with this tool from your clinical practice take a few minutes now to consider what you would include in an assessment to determine fracture risk. Then look at Box 3 to see how your list compares to the questions asked by FRAX?

Box 3. Variables to consider in an assessment to consider fracture risk.

- Age
- Gender
- Weight
- Height
- Fracture history
- Alcohol intake: ≥3 units per day
- Current/recent smoker
- Glucocorticoid use for >3 months
- Biological parent with history of fractured hip
- Rheumatoid arthritis diagnosis
- Diagnosis of another condition linked to secondary osteoporosis
- Femoral neck bone mineral density measured by DEXA

The FRAX tool is available to download from 'www.sheffield.ac.uk/FRAX/' [7].

However, interestingly the National Institute for Health and Care Excellence (NICE) is not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX. The guidelines writing committee concluded that using a combination of T-score, age and a number of independent clinical risk factors for fracture is more appropriate for defining treatment recommendations [8].

There is a range of other possible techniques for assessing bone loss. Quantitative ultrasound appears to be one of the most widely used techniques. Use of conventional magnetic resonance imaging (MRI), which produces a negative image of the bone substance, for BMD calculations may also be beneficial although it has its limitations due to the low proton signals found in minerals such as bone. Biochemical markers can also be assessed to determine contributing factors associated with osteoporosis including serum total calcium, albumin, and phosphate to detect conditions associated with hypercalcemia or hypocalcemia. Assessment of renal function is also a valuable test in terms of screening for underlying risk factors for bone disease. Research continues into the relevance of a range of biochemical markers (such as collagens) in determining bone turnover rates.

G. Osteoporosis

The term osteoporosis originates from the Greek, meaning 'porous bone' as illustrated in Figure 2. WHO

describes this disorder as a 'decreased bone density and deterioration of the skeletal micro-architecture, resulting in bone fragility' [9]. The organisation defines osteoporosis as a bone mineral density T-score of less than –2.5. The condition's precursor, osteopenia, is defined as a BMD score between –1 and –2.5 SD.

Osteoporosis becomes more common with age and causes almost 9 million fractures annually [9]. More common in women, osteoporosis is estimated to affect approximately 10% of females aged 60 and 20% of those over 70 years of age, increasing incrementally thereafter. Worldwide, 1 in 3 women over the age of 50 (and 1 in 5 men) will experience fractures as a result [10]. In addition to advancing age an oestrogen deficiency in females (post menopause or oophorectomy) and a decrease in testosterone levels in males are also highly significant in terms of risk. Racial origin is also relevant with white and Asian people being at greater risk of the disease [11].

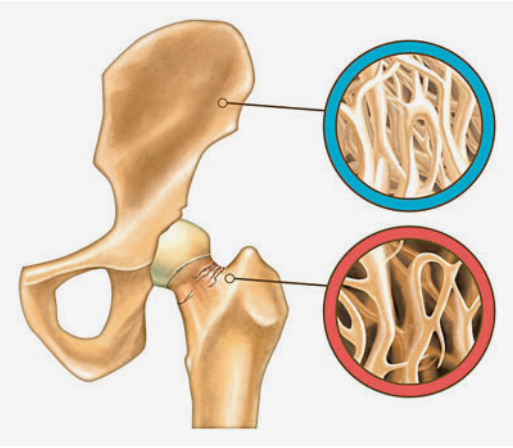

Figure 2: *The appearance of normal (blue circle) versus osteoporotic bone (red circle) [12]*

Osteoporosis may also occur as a secondary condition due to a range of comorbidities, examples of which are listed in Box 4.

Box 4. Comorbidities associated with osteoporosis

- Hyperthyroidism
- Parathyroid disease
- Kidney disease
- Diabetes
- Liver disease
- Cystic fibrosis
- Coeliac disease
- Cushing's syndrome
- Systemic lupus erythematosus
- Dementia
- Parkinson's disease
- Anorexia nervosa
- Alcoholism

H. Fragility fractures

These are a common outcome for those with osteoporosis and are often the first sign of the presence of disease. They are often referred to as a low-trauma fracture; that is a fracture sustained as the result of a force equivalent to that of a fall from a height equal to, or less than, that of an ordinary chair. Osteoporotic fragility fractures occur most commonly in the vertebrae, hip and wrist and can be extremely disabling. Hip fractures for example nearly always require hospitalisation and are fatal in 20% of cases with only 30% of patients recovering fully [8]. Enhanced risk of fracture can be assumed where one or both of the individual's parents have had a hip fracture, ≥4 units of alcohol a day are consumed and/or there is a concurrent diagnosis of rheumatoid arthritis.

Key fact

According to NICE direct medical costs from fragility fractures to the UK healthcare economy were estimated at £1.8 billion in 2000 [8], with the potential to increase to £2.2 billion by 2025. Most of these costs relate to hip fracture care. As average life expectancy increases across the population, incidence of osteoporosis and fragility fracture is also likely to increase.

I. Prevention of osteoporosis

I. Nutrition and bone health

Nutrition, especially in childhood, has an important and complex role in the building and maintenance of healthy bone. Box 5 summarises key dietary factors that can negatively influence bone health.

Box 5. Dietary factors that can negatively influence bone health

- Low dietary mineral intake such as calcium and/or phosphorus, magnesium, zinc, boron, iron, fluoride and copper*.
- Low intake of vitamins A, K, E and C*.
- Excess sodium intake*.
- Imbalance of omega-6 to omega-3 polyunsaturated fats*.
- Vitamin D insufficiency (this is associated with increased parathyroid hormone production, which in turn increases bone resorption, leading to bone loss)*.
- Over exposure to the metal cadmium (through ingestion or inhalation) is associated with an increased loss of bone mineral density. A diet high in shellfish and offal plus environmental factors such as air pollution and cigarette smoke increase risk of cadmium toxicity [13].
- Soft drinks, which contain phosphoric acid may increase risk of osteoporosis by blocking calcium re-absorption [14].

*Source: Cashman K [15].

The role of dietary protein has been disputed among nutritional experts. Protein intake has been identified as being both detrimental and beneficial to bone

health depending on a variety of factors, including the protein source, concurrent calcium intake and the acid–base balance of the diet as a whole. Calcium and protein intake interact constructively to enable bone development and maintenance. Despite concern that diets high in animal protein result in bone resorption, higher protein diets, when calcium intake is adequate, appear to be associated with greater bone mass and fewer fractures. The authors of one extensive literature review concluded that optimal protein intake for bone health is probably higher than the current recommended intake, particularly for older people [16].

II. Exercise and bone health

As already described bone is constantly being renewed. The process responds to increases in load and force so exercise increases bone strength as load increases. Generally peak bone mass is achieved around the age of 30. It then gradually begins to decline with age, often alongside a trend for a reduction in activity levels. For women, bone loss is usually most rapid during the first few years after menopause.

Not all forms of exercise stimulate bone. Low impact exercise such as swimming and cycling, for example, will not necessarily build bone density as weight bearing is minimised. Weight-bearing exercise is defined as any exercise in which the individual's body weight is supported through the legs or arms. Muscle-strengthening exercises through resistance are also useful as this works the tendons that attach muscle to bone, which in turn boosts bone strength. An important note to reinforce in patient education is that all forms of physical activity will help to reduce the risk of falls and fractures by helping to maintain good balance and posture, co-ordination, stamina and muscle tone, as well as confidence, especially in older people.

Box 6 gives The National Osteoporosis Society's recommendations for exercise based on Department of Health advice.

Box 6. Recommendations for exercise and bone health

- Children: 60 minutes of moderate-intensity physical activity each day.
- Adults: 30 minutes of moderate-intensity physical activity at least five days a week (or 150 minutes or more in total). They should also undertake physical activity to improve muscle strength on at least two days a week.
- Older adults (over the age of 65) who are at risk of falls should also incorporate specific exercises to improve balance and co-ordination for at least two days a week and reduce being sedentary for extended periods.

Source: National Osteoporosis Society [17].

Time out activity 2

Knowing what you do now about risk factors for poor bone health, try to list eight strategies for the prevention of osteoporosis, in particular with the aim of reducing fractures.

Compare your list with those provided later in this section

Strategies for the prevention of osteoporosis:

- Screening and early detection of bone disease using tools such as FRAX
- Effective medical management of the comorbidities associated with osteoporosis
- Avoiding long-term use of medications associated with BMD loss as far as possible
- Increasing weight-bearing exercise
- Smoking cessation
- Reducing alcohol intake
- Effective risk assessment and falls prevention strategies
- Nutritional advice and support especially in high-risk groups

J. Treatment of osteoporosis

There are many pharmacological interventions available, chiefly oestrogen or testosterone replacement, calcium and vitamin D supplementation and the use of bisphosphonates.

NICE makes recommendations on the prescribing of medication for osteoporosis, however, the guidance is currently being updated and a new publication date is awaited [8]. The existing guidance relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who already have a diagnosis of osteoporosis. In this instance osteoporosis is defined by a T-score of –2.5 or below, on DEXA scanning. NICE has summarised its guidance for two groups of people: primary prevention in postmenopausal women with osteoporosis who haven't had a fracture and secondary prevention, for those women with a new diagnosis made post fracture. The guidance assumes that those who receive bisphosphonates already have an adequate calcium intake and are not vitamin D deficient. If in doubt calcium and/or vitamin D supplementation should be offered first.

Key fact

The most accurate way to detect vitamin D deficiency is by performing a blood test to measure 25-hydroxy vitamin D, which is a form of vitamin D produced in the liver.

I. Bisphosphonates

Alendronate, etidronate and risedronate are inhibitors of bone resorption and increase BMD by altering osteoclast activation and function and are taken

orally. Gastrointestinal side effects are common and their administration is relatively complicated. Alendronate and risedronate, for example, must be taken with very specific amounts of water. Before and immediately after administration patients should not eat or drink and must remain upright after dosing for a set time period [18]. Adherence to treatment with oral bisphosphonates is challenging largely because of these inconvenient dosing regimens and restrictions mentioned here. There is now an alternative, zoledronic acid, given by intravenous infusion once yearly. This may be is a preferable option for many but has cost and resource implications at present. Treatment is currently usually limited to those at highest risk of fracture.

II. Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs), such as raloxifene are drugs with selective activity. They act as weak oestrogen receptor agonists in some organ systems and as oestrogen antagonists in others. The aim of treatment with SERMs is to maximise the beneficial effects of oestrogen on bone and to minimise the adverse effects, for example, on the breast and womb. Another agent, strontium ranelate, has properties similar to calcium. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. This treatment also has dose time and food-related restrictions [18]

III. Hormone replacement therapy

Hormone replacement therapy (HRT) is known to slow bone turnover and increases BMD in early and late postmenopausal women [19]. The anti-fracture efficacy of HRT has been assessed including in randomised controlled trials and in meta analysis. Overall, these analyses show that HRT decreases fragility fracture risk by 20–35% [20]. NICE suggests that physicians should consider prescribing HRT to women who have a premature menopause to reduce the risk of fragility fractures, alongside providing relief of menopausal symptoms [21]. However, for standard onset menopause HRT is regarded as an acceptable treatment only after all other treatment options have been considered. The potential for enhanced risk, for example, of breast cancer and venous thrombosis need to be weighed up on individual basis. It is also widely advised that women who decide to take HRT should use the lowest effective dose and for the shortest possible time and on the understanding that the benefits in terms of maintaining BMD appear not to persist in the long-term once HRT ceases.

K. Osteoarthritis

This common degenerative condition is the result of the breakdown of joint cartilage over time. The main symptom is pain, causing stiffness and loss of mobility of the affected joint. Stiffness is most common in the morning and after periods of inactivity. Crepitus on movement of the joint can also be a sign. In smaller joints, such as in the fingers, hard prominent boney growths Heberden's nodes and Bouchard's nodes (Figure 3) may form and limit movement further.

The most commonly involved joints are those near the ends of the fingers, the base of the thumb, the neck and knee and hip joints. Apart from increasing age other causes include previous injury to the joint, employment involving heavy manual labour and genetic factors. Obesity also enhances risk significantly due to the additional impact through weight-bearing joints in particular. The mechanical stress on the joint causes low-grade inflammatory changes, cartilage is lost and eventually the underlying bone becomes affected. The cartilage covering the ends of the bones gradually thins, becomes rough and the bone

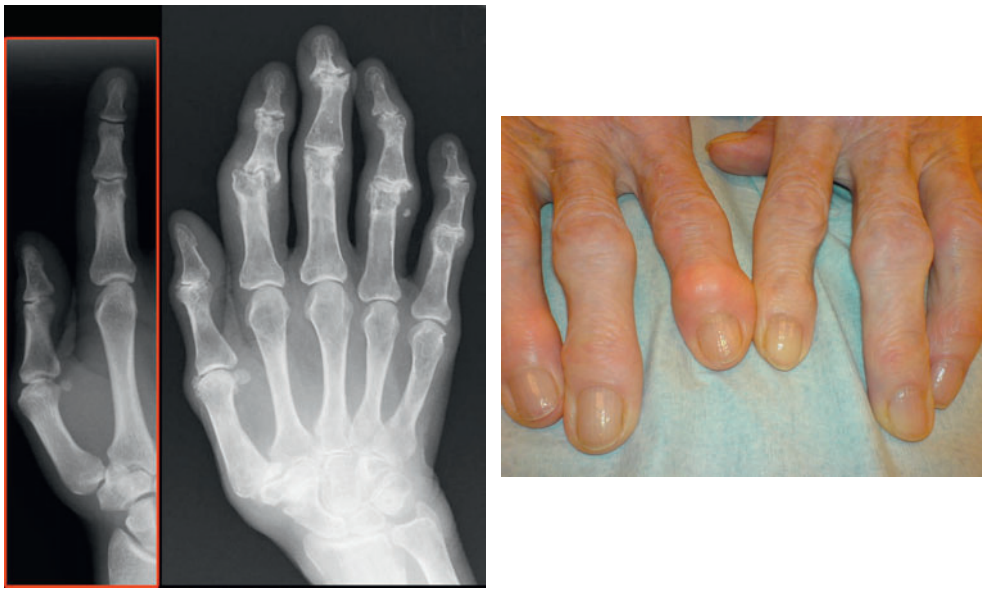

Figure 3: *X-ray showing bone growth at end joints called Heberden's nodes, growth at middle joints called Bouchard's nodes. Left X-ray in red box shows normal bone structure*

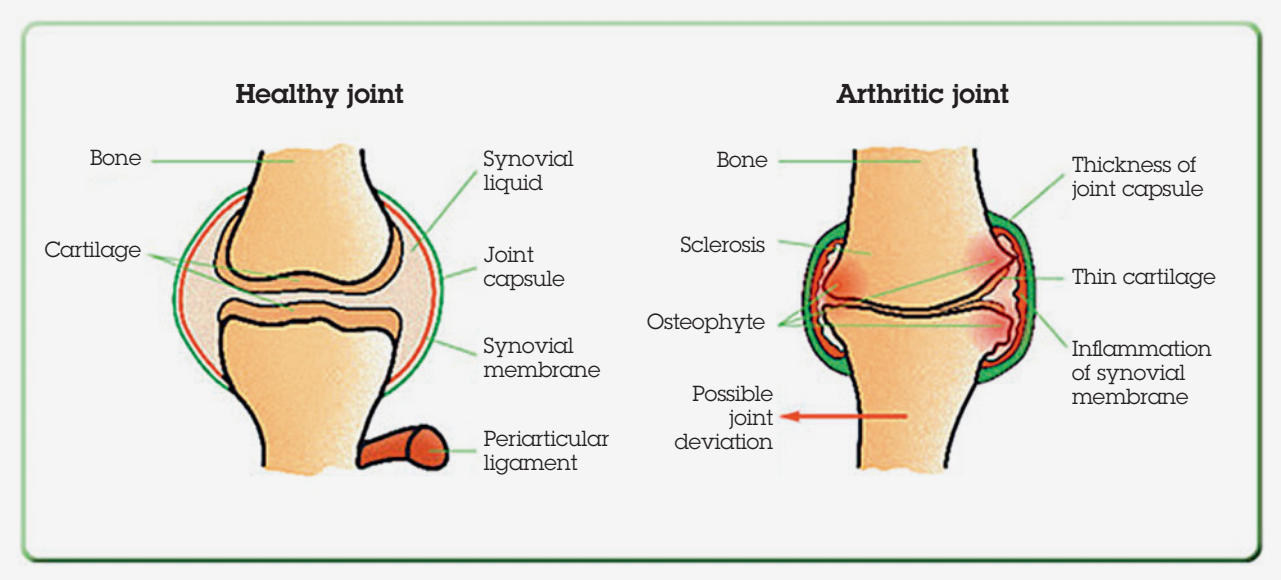

Figure 4: *Illustration of a normal healthy knee compared to one affected by osteoarthritis*

underneath thickens. Boney spurs called osteophytes form and the synovium thickens, usually causing swelling (Figure 4).

Diagnosis is typically based on signs and symptoms and X-rays. MRI scanning can be useful where the knee is affected and blood tests are used to rule out other systemic inflammatory conditions. Treatment of osteoarthritis (OA) includes pain relief (typically with non-steroidal anti-inflammatory agents) and exercise to decrease joint stress and build muscle strength to support the affected joint. Weight loss is advised for those who are overweight. Where pain persists in interfering with normal activities and/or employment then joint replacement surgery is commonly offered.

L. HIV and bone disease

A range of cohort studies including randomised controlled studies and meta analysis have been carried out over the past ten years and have described a significantly higher prevalence of bone disease in PLWH when compared to age, race and sex-matched HIV-negative individuals. The prevalence of reduced BMD has been found in up to 80% of PLWH in some studies and the prevalence of osteopenia is also significant [22].

In recent years it has become evident that the immune and skeletal systems are interlinked, and that changes in the immune system potently affect skeletal metabolism [23]. Bone loss may result from interactions between T cells, osteoclasts and osteoblasts, fuelled by elements of both HIV infection and antiretroviral therapy (ART). We also know that certain lifestyle-related risk factors are also more prevalent among PLWH. In addition there are relevant nutritional and hormonal changes commonly associated with HIV infection, such as muscle wasting, gastrointestinal disturbance causing nutrient malabsorption and low testosterone levels. Cigarette smoking, alcohol and opiate use are also more prevalent in this cohort [22].

Given all this information it can be concluded that the causes of excess bone loss associated with HIV are complex and multifactorial. The large number of variables and the inter-related nature of the risk factors, alongside the prescribing of complex ART combinations, mean that, to date, there remains a lack of consensus on the exact causes and appropriate interventions for bone disease in HIV.

Osteoarthritis is also associated with HIV infection. A poster presentation by Tomi *et al.* at CROI in 2014 reported that PLWH have a higher risk of hand osteoarthritis than the general population of the same age [24]. The authors state that PLWH, particularly those with metabolic syndrome, are at risk of more severe osteoarthritis.

The relationship between osteonecrosis or avascular necrosis and HIV is also disputed. One study [25] from 2007 concluded that PLWH had a dramatically increased risk of developing osteonecrosis than the general population but the researchers found that corticosteroid use in this cohort was one of the most important risk factors. Use of lipid lowering medications, heavy alcohol intake and testosterone supplementation also appeared to play a part, however, the researchers could not ascertain the role of HIV infection itself nor the relevance of ART in this condition.

M. Bone loss and antiretroviral therapy

ART has long been suspected of influencing both bone turnover and bone loss but until recently evidence has been far from conclusive. Eight years ago meta-analysis concluded that it was conventional risk factors for osteoporotic fractures, plus HIV-related muscle wasting, low testosterone and disorders in calcium and phosphate metabolism that accounted for bone loss in PLWH and reported no consensus of a

treatment-related contribution [26]. But some studies have reported that those receiving protease inhibitors (PIs) had a higher prevalence of increased rates of BMD loss and osteoporosis compared to those receiving non PI-based regimens [27,28]. Today it is accepted that initiation of ART is associated with decrease in BMD over the first year or so of therapy for commonly prescribed treatment regimens.

Time out activity 3

Take a few minutes to consider what factors, alongside the more obvious and modifiable lifestyle ones, might confound the interpretation of such studies?

Compare your list to that provided later in this section.

Factors that might confound the interpretation of studies on bone loss and ART:

- The diversity of treatment regimens used in clinical practice
- Previously prescribed regimens/treatment history
- Inadequate controlling for traditional osteoporosis risk factors
- Variability in the anatomical sites used in BMD analysis
- The presence of other comorbidities
- Duration of treatment
- Stage of immune dysfunction or reconstitution
- Hormonal function
- Body composition
- Genetic factors

The familiar and far-reaching START trial was designed to address the long-standing controversy over the optimal timing of HIV treatment, especially for people with high CD4 counts. A substudy used DEXA scans and compared Z-scores and T-scores across age bands and ethnic groups and also took into account a range of other risk factors such as cigarette smoking [29]. Although immediate treatment was found to be beneficial overall, participants who started ART soon after HIV diagnosis showed a greater decrease in bone density at the hip and spine compared to those who deferred starting treatment. However there was no evidence of difference in the development of osteoporosis or an increased risk of fractures.

In recent years the widely used and generally well tolerated nucleoside reverse transcriptase inhibitor, tenofovir disoproxil fumarate (TDF), has been strongly associated with an acute decrease in BMD commencing soon after starting treatment. However, the older formulation can now be replaced by tenofovir alafenamide (TAF) and, as reported by researchers at CROI 2017 [30], this is associated with improved bone health, including a reduction in osteoporosis. The interim update from BHIVA (2016) recommends TDF may be best avoided in patients with osteoporosis and those at an increased risk of fracture [31].

One increasingly relevant concern is the impact of pre-exposure prophylaxis (PrEP) on BMD, especially in adolescents where bone growth is still occurring. A year-long study of young men aged <20 years explored this: all participants received daily PrEP and monitoring included DEXA scans at baseline and weeks 24 and 48. Participants who either lost or failed to gain bone entered an extension phase with further DEXA scans after stopping PrEP. BMD was measured at a number of body sites and found to drop significantly when on PrEP but this subsequently returned (in all sites other than the spine, to pre-ART/PrEP levels) [32]. Obviously in the short-term, the protection from HIV in this very high-risk group, is a priority and the benefits probably outweigh the risk of this finding, however, further research is needed to explore alternative options for PrEP with minimal side-effect profiles.

Current consensus appears to be that initiation of most, if not all ART regimens is associated with non-progressive bone loss in the majority of individuals. The mechanism of this bone loss is as yet unclear but it is thought that it may be secondary to the differential impact of immune reconstitution on osteoclasts versus osteoblasts and, in the case of tenofovir-DF, secondary to renal phosphate loss. The clinical significance of small amounts of bone loss in otherwise healthy individuals also remains uncertain at the moment, but ongoing vigilance and continued research is obviously important.

N. Other HIV-related factors enhancing risk

Aside from ART use a range of other factors disproportionately apply to the HIV-positive cohort. Low vitamin D status for example, is common in PLWH in the northern Europe in particular. One Dutch study found that of participants not taking ART, 25% had vitamin D deficiency compared to 30% of individuals taking treatment [33]. Sunlight is the main source of Vitamin D. Between late March/early April to the end of September in the UK, most people obtain all the vitamin D they need through exposure to daylight on the skin and from a balanced diet. However, during autumn and winter and for those exposed to little daylight the Department of Health recommends a daily supplement containing 10 mcg of vitamin D [34]. People with darker skin tones from African, Afro-Caribbean and South Asian backgrounds may not get enough vitamin D from sunlight even during the summer months and should consider taking a daily supplement throughout the year.

Box 7 lists other possible risk factors disproportionately affecting the HIV-positive population that have an impact on bone health.

Box 7. Possible risk factors disproportionately affecting the HIV-positive population

- Hypogonadism causing low testosterone levels
- Increased alcohol intake
- Tobacco and opiate use
- Low body weight and/or muscle wasting e.g. in lipoatrophy
- Other metabolic HIV-related conditions
- Renal dysfunction
- Co-infection with hepatitis C

O. Monitoring and screening

Optimisation of bone health and treatment of bone disease constitute part of the overall management of PLWH, together with treatment of other comorbidities. This is obviously particularly important in view of the ageing HIV-positive cohort. Advice is based on a number of robust studies that have found that the incidence of fractures affects HIV-positive men at a significantly younger age compared to their HIV-negative peers. Analysis by age group showed that fracture incidence among men in their 50s was double that observed in HIV-negative men in the same age range (the control group) [35].

Guidelines from BHIVA (as per European and US guidelines) recommend that PLWH over the age of 50 years, and all women who have gone through the menopause, should be assessed every three years for fracture risk [36]. If additional major risk factors exist then those in the 40–50 years age group should also be assessed. The organisation suggests that although FRAX is not specifically validated for the HIV-positive population it is an appropriate tool to use. Note that the FRAX algorithm may underestimate fracture risk in this population because some HIV-specific risk factors are partially independent of BMD.

Subsequently, only people identified as at increased risk should have their BMD measured by DEXA. A history of falls should also be taken. In addition vitamin D/parathyroid hormone status in these 'at-risk' individuals should be assessed and optimised, and their use of medication, including antiretroviral therapy, adjusted if necessary. Box 8 summarises BHIVA's current recommendations.

Box 8. Summary of recommendations for investigation and monitoring of PLWH in relation to BMD loss

- 10% risk on FRAX – reassure patient and repeat FRAX after 3 years.
- 10–20% risk identified – consider DEXA scan to refine risk estimate
- >10% fracture risk – provide lifestyle advice and optimise risk factors including vitamin D deficiency
- >20% risk – optimise risk factors, review ART (especially use of TDF) and lifestyle factors, and refer for osteoporosis treatment

Source: BHIVA [36].

P. Treatment options

As with all people at risk of reduced bone density it is first important to focus on modifiable lifestyle factors contributing to bone health, including exercise, smoking cessation and good nutrition (in particular sufficient calcium and vitamin D intake). Low vitamin D levels are common in PLWH as mentioned in Section N. Whereas calcium and vitamin D supplementation have been found to protect against BMD reductions associated with tenofovir initiation, vitamin D supplements alone had no effect on BMD in clinically stable patients who were already established on ART [22] but supplements are widely recommended for patients with low vitamin D levels (below 10 ng/ml). To date, current guidelines do not make firm recommendations as to the benefit of a universal vitamin D deficiency 'test and treat' strategy.

In relation to decision-making around commencing ART, BHIVA make a number of recommendations [36]. In those aged >40 years with osteoporosis, a history of fragility fracture, or a FRAX score determining 'high risk' they advise against the use of TDF, and TAF may, therefore, be used in these cases. In those already established on ART and later diagnosed with osteoporosis, a fragility fracture or a FRAX score of >20%, switching to an alternative ART regimen is advised. PLWH who are diagnosed with a vertebral or hip fracture and/or a DEXA score of less than 2.5 at femoral neck/spine should be treated pharmacologically. The consensus at present is that anti-osteoporosis treatment should be initiated on the basis of the same criteria as those used in the general population but with closer and earlier monitoring as mentioned previously.

The ability of bisphosphonates to increase BMD has been demonstrated in PLWH. A study using alendronate for example showed similar efficacy and outcomes to an HIV-negative cohort [37], and data were backed up by the results of a large randomised controlled trial that compared bisphosphonate use with a placebo [38]. As in the general population, treatment duration should be individualised and the challenges related to adherence (as described in Section J) also apply for PLWH and their healthcare team, referral to a rheumatologist is appropriate.

The effects of the aforementioned intravenous zoledronic acid on BMD has also been studied in PLWH. In a 2-year randomised controlled trial the benefit of two doses (given intravenously one year apart) on BMD and bone turnover markers was demonstrated to persist for at least 5 years [39]. Of note, calcium and vitamin D supplements were given to both the treatment and placebo groups. A further, perhaps obvious question also arises – how can we protect against BMD loss in the first place? There is also some evidence that calcium and vitamin D supplementation alone may protect against bone loss associated with initiation of ART. In a large

randomised controlled trial treatment-naive PLWH showed significantly less bone loss when given vitamin D_3 and calcium supplements daily, compared to those receiving a placebo [39]. It is also possible to gain protection with a single infusion of zoledronic acid. If given at the time ART is commenced, a study presented at CROI 2016 suggested it can be used as a prophylaxis against bone mineral loss during the first year of ART [40], however, further research on this and other interventions is needed.

Q. Conclusions and the nurse's role

Life expectancy has been dramatically prolonged for PLWH but several comorbidities have emerged in the ageing HIV-positive population, including osteoporosis and an increased risk of fracture. At the moment, the aetiology of bone disease in PLWH is not completely understood. The causes appear to be multifactorial and probably represent a complex interaction between HIV infection, traditional risk factors exacerbated by consequences of chronic HIV infection (e.g. poor nutrition and low body weight), low vitamin D levels and ART-related factors. Further research is needed to clarify the correlation between BMD, HIV and ART.

Nurses have participated in the successful treatment of PLWH with ART and will need to continue to respond proactively to meet the changing requirements of PLWH in their care. There are a range of interventions available, many of which can be delivered effectively by nurses, the interventions can screen for, minimise risk and prevent deterioration in bone health in this population. Facilitating a change in modifiable lifestyle risk factors such as smoking cessation, maintaining a healthy BMI, reducing alcohol consumption and undertaking weight-bearing exercise can play a vital role in the prevention and management of bone disease. Guidelines are available to assist healthcare professionals to optimise prevention and treatment strategies. Nurses need to ensure that they, and any locally determined policies and practices, are regularly updated as new research evidence emerges.

R. Useful resources

The WHO Assessment of Osteoporosis at Primary Healthcare level Report. Available at: www.who.int/chp/topics/Osteoporosis.pdf?ua=1

The National Osteoporosis Society. Available at: www.nos.org.uk

Kruger M and Nell T. Bone mineral density in people living with HIV: a narrative review of the literature. *AIDS Res Ther* 2017; 14: 35.

The National Osteoporosis Society Review. Available at: nos.org.uk/for-health-professionals/membership/osteoporosis-review/

Patient education. Available at: nos.org.uk/about-osteoporosis/prevention-are-you-at-risk/factsheets/exercise-and-osteoporosis/

S. References

1. Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol* 2008; **3** Suppl 3: S131–139.
2. Servier Medical Art. *Cross-section of bone*. Available at: smart.servier.com/ (accessed November 2017).
3. Allen AR and Burr D. Bone modeling and remodeling. In: *Basic ans applied bone biology*: Elsevier Inc., 2013. pp. 75–90.
4. National Osteoporosis Society. *Finding people at risk*. 2016. Available at: nos.org.uk/about-osteoporosis/diagnosing-osteoporosis/finding-people-at-risk/ (accessed November 2017).
5. Johnell O and Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17**: 1726–1733.
6. NHS choices. *DEXA (DXA) scan*. Available at: www.nhs.uk/conditions/dexa-scan/what-happens/ (accessed November 2017).
7. Kanis JA. *FRAX: fracture risk assessment tool*. University of Sheffield. Sheffield. Available at: www.sheffield.ac.uk/FRAX/ (accessed November 2017).
8. National Instutute for Health and Care Excellence. *Osteoprosis: asssessing the risk of fragility fracture NICE*, 2017. Available at: www.nice.org.uk/guidance/cg146 (accessed November 2017).
9. WHO. *WHO scienitic group on the assessment of osteoporosis at primary health care level: summary meeting report*. Brussels, Belgium: Available at: www.who.int/chp/topics/Osteoporosis.pdf?ua=1 (accessed November 2017).
10. International Osteoporosis Foundation. *Facts and Statistics. IOF*. Available at: www.iofbonehealth.org/facts-statistics (accessed November 2017).
11. Barrett-Connor E, Siris ES, Wehren LE *et al*. Osteoporosis and fracture risk in women of different ethnic groups. *J Bone Miner Res* 2005; **20**: 185–194.
12. Andrea Danti. *Skeleton close-up showing normal bone and osteoporosis*. Available at: Andreus / 123RF Stock Photo (accessed November 2017).
13. Staessen JA, Roels HA, Emelianov D *et al*. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. *Lancet* 1999; **353**: 1140–1144.
14. Tucker KL, Morita K, Qiao N *et al*. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study. *Am J Clin Nutr* 2006; **84**: 936–942.
15. Cashman KD. Diet, nutrition, and bone health. *J Nutr* 2007; **137**: 2507S–2512S.
16. Heaney RP and Layman DK. Amount and type of protein influences bone health. *Am J Clin Nutr* 2008; **87**: 1567S–1570S.
17. National Osteoporosis Society. *Exercise and osteoporosis: how can exercise help with bone health, fragile bones and fractures*. UK. Available at: nos.or.uk/about-osteoporosis/prevention-are-you-at-risk/factsheets/exercise-and-osteopprosis/ (acessed November 2017)
18. Joint Formulary Committee. *BNF* 73rd edn. Pharmaceutical Press, 2017.
19. Gambacciani M, Cappagli B, Ciaponi M *et al*. Ultra low-dose hormone replacement therapy and bone protection in postmenopausal women. *Maturitas* 2008; **59**: 2–6.
20. Cauley JA, Robbins J, Chen Z *et al*. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003; **290**: 1729–1738.
21. NICE. *Clinical Knowledge Summaries: osteoporosis – prevention of fragility fractures*. Available at: cks.nice.org.uk/osteoporosis-prevention-of-fragility-fractures#!scenario:1 (accessed November 2017).
22. Saccomanno MF and Ammassari A. Bone disease in HIV infection. *Clin Cases Miner Bone Metab* 2011; **8**: 33–36.
23. Ofotokun I, Titanji K, Vunnavu A *et al*. A single dose of zoledronic acid prevents antiretroviral-induced bone loss. *Conference on Retroviruses and Opportunisic Infections*, 2016, Boston, Massachusetts. Abstract 47.

24. Tomi AL, Sellam J, Lacombe K *et al*. Increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study. *Ann Rheum Dis* 2016; **75**: 2101–2107.
25. Morse CG, Mican JM, Jones EC *et al*. The incidence and natural history of osteonecrosis in HIV-infected adults. *Clin Infect Dis* 2007; **44**: 739–748.
26. Paccou J, Viget N, Legrout-Gerot I *et al*. Bone loss in patients with HIV infection. *Joint Bone Spine* 2009; **76**: 637–641.
27. Tebas P, Powderly WG, Claxton S *et al*. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000; **14**: F63–67.
28. Brown TT and Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; **20**: 2165–2174.
29. Hoy JF, Grund B, Roediger M *et al*. Effects of immediate versus deferred initiation of antiretroviral therapy on bone mineral density: a substudyof the INSIGHT Strategic Timing of Antiretroviral Therapy (START) study. *15th European AIDS Conference*, 2015; Barcelona, Spain. Abstract ADRLH-62.
30. Arribas JR, Thompson M, Sax PE *et al*. Significant efficacy and long-term safety difference with TAF-based STR in naive adults. *Conference on Retroviruses and Opportunistic Infections*, 2017, Seattle Washington. Abstract 453.
31. British HIV Association. *BHIVA guidelines for the treatment of HIV-1-positive adults 2015 (2016 interim update)*. London: BHIVA, Available at: www.bhiva.org/HIV-1-treatment-guidelines.aspx (accessed November 2017).
32. Mulligan K *et al*. Changes in bone mass after discontinuation of pre-exposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine in young msm who lost bone while using PrEP. *18th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV*, 2016, New York, USA. Abstract 001.
33. Van Den Bout-Van Den Beukel CJ, Fievez L, Michels M *et al*. Vitamin D deficiency among HIV type 1-infected individuals in the Netherlands: effects of antiretroviral therapy. *AIDS Res Hum Retroviruses* 2008; **24**: 1375–1382.
34. Association of UK Dietitians. *Food fact sheet: vitamin D*. 2016. BDA. Available at: www.bda.uk.com/foodfacts/home (accessed November 2017).
35. Gonciulea A, Wang R, Althoff KN *et al*. An increased rate of fracture occurs a decade earlier in HIV+ compared with HIV- men. *AIDS* 2017; **31**: 1435–1443.
36. *British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016*. London: BHIVA, Available at: www.bhiva.org/guidelines.aspx (accessed November 2017).
37. Guaraldi G, Orlando G, Madeddu G *et al*. Alendronate reduces bone resorption in HIV-associated osteopenia/osteoporosis. *HIV Clin Trials* 2004; **5**: 269–277.
38. McComsey GA, Kendall MA, Tebas P *et al*. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. *AIDS* 2007; **21**: 2473–2482.
39. Compston J. HIV infection and bone disease. *J Intern Med* 2016; **280**: 350–358.
40. Ofotokun I and Weitzmann MN. HIV-1 infection and antiretroviral therapies: risk factors for osteoporosis and bone fracture. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 523–529.

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