INTERACTION BETWEEN BONE QUALITY, HIV AND ART

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Bone disease in HIV

- ✓ The transformation of HIV infection into a manageable chronic condition, as a result of effective antiretroviral therapy (ART), represents a significant modern medical achievement. However, this advancement has unveiled new clinical challenges in the form of advanced age disease in people with HIV (PWH), with bone disease being at the forefront of scientific discussion and research in the field

- ✓ The compelling nature of this subject stems from the multifaceted risk factors for bone disease in HIV, which involve a combination of traditional risk factors and those uniquely associated with HIV infection and its treatment

Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review

Todd T. Brown[a] and Roula B. Qaqish[b]

AIDS 2006, **20**:2165–2174

Methods: We conducted a meta-analytical review of cross-sectional studies published in English to determine the pooled odds ratios (OR) of reduced BMD and osteoporosis in the following groups: HIV-positive versus HIV-negative; ART-treated versus ART-naive; protease inhibitor (PI)-treated versus PI-untreated. We searched the MEDLINE, PubMed, and EMBASE databases for eligible references between January 1966 and November 2005. Random effects models were used to generate pooled OR estimates and confidence intervals.

Results: Of 37 articles identified, 20 met the inclusion criteria. Of the 884 HIV-infected patients, 67% had reduced BMD, of whom 15% had osteoporosis, yielding a pooled OR of 6.4 and 3.7, respectively, compared with HIV-uninfected controls ($n = 654$) using 11 studies with available data. Compared with ART-naive patients ($n = 202$, 10 studies), ART-treated individuals ($n = 824$) had a 2.5-fold increased odds of prevalent reduced BMD. The risk of prevalent osteoporosis (seven studies) was similarly elevated in ART-treated individuals. Compared with non-PI-treated HIV patients ($n = 410$, 14 studies), PI-treated patients ($n = 791$) had increased odds of reduced BMD and osteoporosis (12 studies). Few studies adjusted for important covariates such as HIV disease severity or treatment duration.

Conclusion: The prevalence of osteoporosis in HIV-infected individuals is more than three times greater compared with HIV-uninfected controls. ART-exposed and PI-exposed individuals had a higher prevalence of reduced BMD and osteoporosis compared with their respective controls. The influence of other disease and treatment variables on these estimates could not be determined.

Prevalence and Risk Factors of Low Bone Mineral Density in HIV/AIDS Patients: A Chinese Cross-Sectional Study

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Results: A total of 1143 patients were included. In the ART-naive group, low BMD was diagnosed in 19.2% (117/608), including osteoporosis in 1.0% (6/608) and osteopenia in 18.3% (111/608). In the ART group, low BMD was diagnosed in 32.2% (231/717), including osteoporosis in 2.4% (17/717) and osteopenia in 29.8% (214/717). Using multivariate analysis, we identified age older than 50 years, body mass index < 18.5 kg/m^2, and treatment based on tenofovir disoproxil fumarate as independent risk factors for low BMD. Low high-density lipoprotein cholesterol was a protective factor for low BMD. Among low BMD participants, the most common number of low BMD sites for a patient to have was 4 (33.6%, 117/348).

Conclusion: We confirmed a high prevalence of low BMD and osteoporosis in HIV/AIDS patients, and we identified age older than 50 years, low body mass index, and a treatment based on tenofovir disoproxil fumarate as risk factors for low BMD. Low high-density lipoprotein cholesterol had a protective effect against low BMD. Among low BMD patients, patients most commonly had 4 sites with low BMD, which has been associated with fracture risk. In addition, bone changes to L1 can present before low BMD diagnosis and may be a potentially useful indicator that low BMD is developing.

Key Words: human immunodeficiency, prevalence, bone mineral density, risk factors, TDF, HDL-C

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Incident bone fracture and mortality in a large HIV cohort outpatient study, 2000–2017, USA

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Abstract

Summary We evaluated the association of bone fracture with mortality among persons with HIV, controlling for sociodemographic, behavioral, and clinical factors. Incident fracture was associated with 48% greater risk of all-cause mortality, underscoring the need for bone mineral density screening and fracture prevention.

Purpose/Introduction Low bone mineral density (BMD) and fracture are more common among persons with HIV (PWH) than those without HIV infection. We evaluated the association of bone fracture with mortality among PWH, controlling for sociodemographic, behavioral, and clinical factors.

Methods We analyzed data from HIV Outpatient Study (HOPS) participants seen at nine US HIV clinics during January 1, 2000, through September 30, 2017. Incident fracture rates and post-fracture mortality were compared across four calendar periods. Cox proportional hazards analyses determined factors associated with all-cause mortality among all participants and those with incident fracture.

Results Among 6763 HOPS participants, 504 (7.5%) had incident fracture (median age = 47 years) and 719 (10.6%) died. Of fractures, 135 (26.8%) were major osteoporotic (hip/pelvis, wrist, spine, arm/shoulder). During observation, 27 participants with major osteoporotic fractures died (crude mortality 2.97/100 person-years [PY]), and 48 with other site fractures died (crude mortality 2.51/100 PY). Post-fracture, age- and sex-adjusted all-cause mortality rates per 100 PY decreased from 8.5 during 2000–2004 to 1.9 during 2013–2017 ($P<0.001$ for trend). In multivariable analysis, incident fracture was significantly associated with all-cause mortality (Hazard Ratio 1.48, 95% confidence interval 1.15–1.91). Among 504 participants followed post-fracture, pulmonary, kidney, and cardiovascular disease, hepatitis C virus co-infection, and non-AIDS cancer, remained independently associated with all-cause mortality.

Conclusions Incident fracture was associated with 48% greater risk of all-cause mortality among US PWH in care, underscoring the need for BMD screening and fracture prevention. Although fracture rates among PWH increased during follow-up, post-fracture death rates decreased, likely reflecting advances in HIV care.

Figure 2. Different factors that may lead to low BMD in PLWHIV.

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Bone quality in relation to HIV and antiretroviral drugs

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- ✓ The skeleton undergoes continuous self-renewal through a process known as bone remodeling. Bone remodeling is defined by the coordinated actions of bone resorbing osteoclasts and bone forming osteoblasts

- ✓ Due to the complexity of bone remodeling and the yet fully defined coupling factors linking osteoclasts with osteoblasts, it is common practice to investigate the effects of outside stimuli directly on primary osteoclasts and osteoblasts separately in vitro

HIV effects on Osteoclasts

Osteoclasts themselves are also targets for HIV infection.
Raynaud-Messina et al. confirmed the presence of HIV-infected osteoclasts in bones derived from HIV-1–infected BLT-humanized mice and in human synovial explant tissues

Osteoclast survival, proliferation, differentiation, and activation are driven by interactions between soluble receptor activator of nuclear factor-κB ligand (RANKL) and its receptor, the receptor activator of nuclear factor κB (RANK)

Osteoprotegerin (OPG) is a soluble antagonist to RANKL and the OPG/RANKL ratio is significantly lower in cART naïve with low BMD and RANKL levels are positively associated with HIV viral load

ARV effects on Osteoclasts

Immune reconstitution is also associated with an increased release of pro-inflammatory cytokines which may contribute to bone loss. For example, immune reconstitution following cART initiation is associated with an increase in circulating RANKL and TNFα , which promote osteoclastogenesis

Ofotokun et al. reported that the degree of bone loss in PLWH is positively associated with the magnitude of immune reconstition: PLWH with the greatest increase in CD4+ cell count following cART initaition experience the greatest BMD loss

ARVs can also directly influence osteoclast activity. While one study found that an association between tenofovir disoproxil fumarate (TDF) exposure and increased circulating RANKL levels after cART initiation

Three studies have primarily focused on protease inhibitors (PI), which are no longer used in the management, and noted that osteoclast activity is elevated in response to treatment with nelfinavir (NFV), indinavir (IDV), saquinavir (SQV), or ritonavir (RTV)

The increased osteoclast activity following PI exposure was confirmed by Yin et al. who demonstrated greater osteoclast differentiation potential of PBMCs isolated from PLWH treated with RTV when compared to other ARVs

HIV effects on Osteoblasts

Bone matrix is formed by osteoblasts, which differentiate from mesenchymal stem cells (MSCs). After synthesizing the new bone matrix, a small fraction of osteoblasts become trapped within the bone and terminally differentiate into osteocytes , a long-lived cell responsible for mediating the skeletal response to mechanical loading and producing bone-derived hormones

Despite detectable mRNA expression of HIV binding receptors CD4 and CCR5 neither cultured osteoblasts nor osteoblasts isolated from PLWH show evidence of HIV infection

However, viral products, including gp120 , gag p55, Tat and Nef all of which continue to circulate even in well controlled PLWH have all been reported to impair osteoblast differentiation or function in vitro

ARV effects on Osteoblasts (I)

In vitro treatment of cultured MSCs with PIs, atazanavir (ATV) or lopinavir (LPV), induced cell senesence and inhibited osteoblast differentiation and also inhibited the function of mature osteoblasts.

Cazzaniga et al. investigated the terminal differentiation of osteoblasts and noted that ATV but not darunavir (DRV) inhibited osteocyte-related gene expression

In addition to inhibiting differentiation and matrix production, NFV and RTV are also reported to promote the osteoblast expression of pro-inflammatory cytokines, such as monocyte chemoattractant protein 1 (MCP)-1 and interleukin-8 (IL-8) , both of which are associated with increased osteoclastogenesis and subsequent bone resorption

ARV effects on Osteoblasts (II)

Little is known about the effects of non-PI ARVs on osteoblast function. Despite the well-described bone loss associated with TDF , only one study has investigated its effects on osteoblast function and found that TDF inhibited matrix formation

Only one study has investigated the effects of INSTIs on osteoblasts, reporting that dolutegravir (DTG), inhibits both the differentiation of osteoblasts from MSCs and the terminal differentiation of osteoblasts into osteocytes, as evidenced from impaired expression of sclerostin and DMP1

Bone remodeling

Serrano et al. evaluated bone tissue biopsies taken from cART naïve PLWH and compared histological measures of bone remodeling according to HIV-uninfected controls : bone samples from PLWH had decreased osteoblast and osteoclast surfaces, bone formation rate, and activation frequency when compared to tissues from uninfected patients and the all parameters were further reduced in those with the most severe disease

Ramalho et al. evaluated bone tissue biopsies taken from men with HIV prior to and 12-months after initiating a fixed dose cART regimen of TDF/3TC/EFV : prior to cART initiation, PLWH have an elevated number of osteoclasts and increased eroded surface, a measure of osteoclast activity. After cART initiation, osteoid volume, osteoblast surface, and osteoclast surface indices all increased

Bone turnover markers (BTMs) I

In cART naïve PLWH, serum calcium, phosphate, osteocalcin, procollagen and 25-hydroxy vitamin D are all reduced when compared to HIV-uninfected individuals, as are BTMs commonly associated with bone formation, including. In contrast, BTMs released during bone resorption, such as C-terminal telopeptide of collagen (CTX), are elevated when compared to HIV uninfected individuals

Changes in both bone resorption (CTX) and bone formation (P1NP and bone specific alkaline phosphatase) were reported to be greater in PLWH initiating TDF/FTC when compared to abacavir . Those receiving either raltegravir (RAL) or DTG-based treatment exhibit smaller changes in BTM levels

Bone turnover markers (BTMs) II

Parathyroid hormone (PTH) is another regulator of bone remodeling that is reported to be elevated in both cART naïve PLWH and following cART initiation. The extent of PTH increase following cART is greater in PLWH receiving TDF-containing cART , which may be due to low circulating vitamin D levels or TDF-induced alterations the PTH

The circulating levels of pro-inflammatory cytokines have also been evaluated as a potential mechanism of bone loss. Higher baseline levels of pro-inflammatory cytokines known to affect bone cell function including IL-6 are associated with greater BMD loss after cART initiation.
Soluble CD14 levels, a marker of immune activation, found on the surface of monocytes and macrophages, are also associated with greater BMD loss , confirming that immune reconstitution contributes to HIV and ARV-induced bone loss

Bone Architecture

Osteoporosis is also characterized by a deterioration of bone architecture, which can negatively affect bone strength and fracture resistance independently of BMD

The increasing availability of high resolution peripheral quantitative computed tomography (HRpQCT) has made it possible to perform high resolution imaging of bone architecture in PLWH. Biver et al. reported that HIV-serostatus negatively affects bone architecture independently of classical clinical risk factors, such as age, BMI, and low vitamin D levels

In addition to HIV infection-induced impairment of bone architecture , cART use, particularly TDF, negatively affects bone architecture . Additional risk factors, such as poor nutrition and low physical activity have been reported to negatively affect bone architecture in PLWH

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Bone Disease in HIV: Need for Early Diagnosis and Prevention

Georgios Schinas [1], Ioannis Schinas [2], Georgios Ntampanlis [1], Eleni Polyzou [1], Charalambos Gog [1] and Karolina Akinosoglou [1,3,*]

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Short-Term Effects of ART on Bone

Upon the initiation of ART, a notable decrease in BMD is frequently observed, with reductions typically ranging from 2% to 6% within the first two years of treatment. This period of initial bone loss is often followed by a phase of stabilization or potential increase in BMD

A study by the AIDS Clinical Trials Group, involving 4640 participants across 26 randomized ART studies with a median follow-up of 5 years, found an initial increase in fracture rates to 0.53 per 100 person-years in the first 2 years after ART initiation, which subsequently decreased to 0.30 per 100 person-years

The exact mechanisms underlying these early changes are not entirely understood but may involve processes such as T-cell repopulation and immune reconstitution inflammatory syndrome (IRIS). The extent of immune reconstitution in terms of CD4+ count, has been associated with improvements in bone resorption markers in humans, as observed in a study over a 24-week period following ART initiation

The START Bone Mineral Density Substudy demonstrated that immediate ART initiation (with CD4 > 500 cells/μL) resulted in greater BMD declines at both the hip and spine over 2.2 years of follow-up, compared to deferred ART initiation (to CD4 < 350 cells/μL)

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Long-Term Effects of ART

A case-control study investigating long-term ART's effect on bone microstructure in patients matched for age and BMI, with a median of 18.2 years of reportedly successful ART, revealed significant microstructural alterations in both trabecular and cortical bone compartments among HIV positive men between the ages of 60 and 70 years old . These findings persisted despite adequate vitamin D supplementation and were associated with higher markersof bone resorption. Multivariate analyses further identified lower physical activity, and reduced estradiol levels as significant determinants of impaired bone architecture

Another investigation carried out to investigate specific risk factors related to bone alterations in individuals with long-term HIV treatment, specifically between the ages of 50–70 years old, revealed malnutrition and physical inactivity as significant contributors. The study also noted that the use of TDF in conjunction with PIs exacerbates the risk of trabecular bone deterioration

The HOPS Study's first results from the 2000–2008 cohort, pointed to an association between nadir CD4 cell counts of less than 200 cells/microL and a higher risk of fractures (aHR 1.60, 95% CIs: 1.11–2.31, $p < 0.01$)


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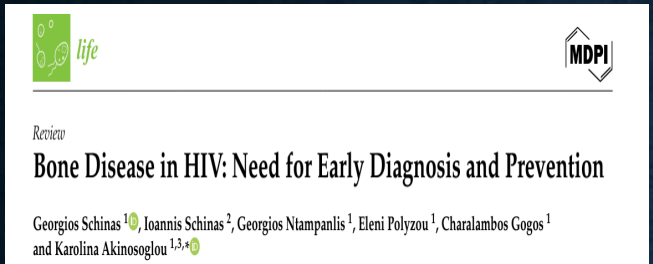
Impact of Hepatitis C on Bones

In two meta-analyses, it was shown that HCV is associated with osteoporosis in PLWHIV with a greater risk on fracture than HIV monoinfection

Carlo et al. observed that vitamin D deficiency might influence liver disease progression in HIV/HCV-coinfected patients

Another possible mechanism is the interaction between inflammation caused by the two viruses and the immune system, which may lead to upregulation of the receptor activator of the nuclear factor-kappaB ligand (RANKL) and osteoprotegerin (OPG) pathways and, hence, bone resorption, in addition to bone toxicity

Eradication of HCV is not associated with improvement in BMD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HIV and Endocrine/Metabolic Changes Relating to Impact on Bones

Insulin resistance and T2D have been identified as risk factors for osteoporosis and fractures in the general population. Diabetes has been reported as an independent risk factor for the incidence of fractures in PWH (aHR, 1.62; 95% CI, 1.00–2.64)
In a cross-sectional study of about 100 PWH, aged 50 years or older on ART, a high frequency of insulin resistance was identified (68.2%) among participants, while the prevalence of osteoporosis was 19%.

NAFLD, a condition often observed in long-term TDF-based antiretroviral therapy recipients, has been directly linked to decreased BMD in HIV. A case-control study involving 89 PWH on long-term TDF-based therapy revealed that the prevalence of osteopenia and osteoporosis was notably higher in the NAFLD subgroup, with incidence rates of osteopenia at 42.86% vs. 25.93%, and osteoporosis at 17.14% vs 3.70% for those with and without NAFLD

Hypogonadism affects about 20% of HIV-positive males.
A cross-sectional study involving 168 men on stable cART, with a median age of 53 years: hypogonadism was present in 26.2% of cases. The prevalence of osteopenia in this cohort was notably high at 87.5%, with vertebral fractures detected in 25% of patients, while elevated Follicle Stimulating Hormone (FSH) levels adversely affected femoral BMD. Higher SHBG levels were predictive of vertebral fractures and correlated inversely to BMD in the spine and femur


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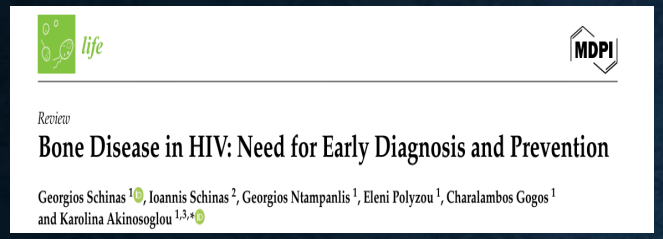
Modifiable Risk Factors: vitamin D deficiency, calcium insufficiency, lifestyle factors

Vitamin D plays a pivotal role in calcium homeostasis and bone metabolism, with deficiency in this nutrient being a well-recognized risk factor for bone loss and osteoporosis. High prevalence rates of vitamin D deficiency have been reported among PWH, regardless of treatment status

Hypocalcemia, which is closely related to vitamin D deficiency, has been observed at higher rates in patients with HIV (6.5%) compared to those without (1.1%), with vitamin D deficiency identified as the causative factor in most cases

Malnutrition, as determined by nutritional assessments, is associated with microstructural changes in the cortical bone compartment of long-term treated individuals living with HIV . Indirect indicators of malnutrition, such as low body weight and decreased albumin levels, have been linked to diminished BMD in PWH who have been HIV-positive for a median duration of 7.7 years on ART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Modifiable Risk Factors: smoking and alcohol use

Smoking has been described as an independent risk factor (aHR 1.3, 95% CI: 1.1–1.5) for fracture incidence in the HIV demographic by a metanalysis : the prevalence of smoking among PWH being 2–3 times higher than that of the general population

A specialized smoking cessation program for PWH observed a mean BMI increase of 2.3 kg/m2 three months post-cessation among participants, a change substantially more pronounced than that seen in the general population. This finding is particularly relevant given that low BMI and body weight, in general, has been identified as a significant predictor of low BMD

PWH engaging in at-risk alcohol consumption exhibited significantly lower serum levels of osteocalcin, a marker of bone formation, indicating a suppression of bone formation activity independent of systemic oxidative stress levels, as measured by relevant markers

The New Orleans Alcohol Use in HIV cohort demonstrated that alcohol use inversely correlates with both osteocalcin and P1NP levels, with these effects being more pronounced in individuals over 50 years of age and in postmenopausal women, highlighting the compounded risk in these subpopulations

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests
Osteoporosis • Postmenopausal women and men age ≥ 50 years with BMD T-score ≤ -2.5 at hip or lumbar spine • Premenopausal women and men age < 50 years with BMD Z-score ≤ -2 at hip or lumbar spine and fragility fracture	• Reduced bone mass and altered bone quality • Increased risk of fractures in persons with HIV • Asymptomatic until fractures occur • Aetiology multifactorial • Loss of BMD observed with ART initiation (mainly during 1st year) • Greater loss of BMD with initiation of certain ARVs[i]	Consider classic risk factors[ii] and estimate fracture risk using FRAX in people ≥ 40 years Consider DXA in any person with ≥ 1 risk of:[iii] 1. Postmenopausal women 2. Men ≥ 50 years 3. High risk for falls[iv] 4. Those with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA) 5. History of low impact fracture 6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction) 7. Oral glucocorticoid use (minimum 5 mg/d prednisone equivalent for > 3 months)	**DXA scan** In those with classic risk factors who require DXA, where feasible consider DXA scan prior to ART initiation or soon after initiation. Add DXA result to FRAX® to refine fracture risk prediction (www.shef.ac.uk/FRAX) • May underestimate risk in persons with HIV • Consider using HIV as a cause of secondary osteoporosis[v] • Trabecular Bone Score (TBS: derived from DXA scan result) may also be added to FRAX® risk prediction. **Rule out causes of secondary osteoporosis if BMD low**[vi] Vertebral fracture assessment on lateral DXA images or lateral spine X-rays (lumbar and thoracic) if osteoporosis on DXA, or significant height loss (≥ 4 cm) or kyphosis develops. (DXA-based vertebral fracture assessment can be used as an alternative to lateral spine X-ray)
Osteomalacia	• Defective bone mineralisation • Associated with vitamin D deficiency • Increased risk of fractures and bone pain • Vitamin D deficiency may cause proximal muscle weakness	• Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Renal phosphate wasting[vii]	Measure serum calcium, phosphate, alkaline phosphatase and 25(OH) vitamin D, see page 79. If deficient or insufficient, check PTH levels and consider vitamin D replacement if clinically indicated, see page 79 ng/mL / nmol/L Deficiency: < 10 / < 25 Insufficiency: < 20 / < 50
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in persons with HIV	**Risk factors:** • Low CD4 count • Glucocorticoid exposure • IVDU • Alcohol • Blood coagulation disorders	**MRI**

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Vitamin D Deficiency: Diagnosis and Management

Vitamin D	Test	Therapy[i]
Deficiency: < 10 ng/mL (< 25 nmol/L)[ii] **Insufficiency:** < 20 ng/mL (< 50 nmol/L)	Serum 25-hydroxy vitamin D (25(OH) vitamin D) If deficient, consider checking parathyroid hormone (PTH), calcium, phosphate[iii], alkaline phosphatase	If vitamin D deficient, replacement recommended. Various regimens suggested[iv] Supplementation with vitamin D may reduce bone loss with initiation of ART, see page 78 Consider re-checking 25(OH) vitamin D levels 3 months after replacement. After replacement, maintenance with 800-2,000 IU vitamin D daily
Vitamin D insufficiency is prevalent (>80%) in some cohorts of populations with and without HIV – may not be directly associated with HIV **Factors associated with lower vitamin D:** • Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Chronic kidney disease • Some ARVs[v]	Check vitamin D status in persons with history of: • low bone mineral density and/or fracture • high risk for fracture Consider assessment of vitamin D status in persons with other factors associated with lower vitamin D levels (see left column)	Replacement and/or supplementation of vitamin D is recommended for persons with both vitamin D insufficiency[vi] and one of the following: • osteoporosis • osteomalacia • increased PTH (once the cause has been identified) Consider re-testing after 6 months of vitamin D intake

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Approach to Fracture Reduction

Reducing risk of fractures	• Aim to decrease falls by addressing frailty and fall risks[i]
Persons at high risk of fractures: • Frail or sarcopenic persons • Previous fracture, particularly if recent • Low BMD • High FRAX score (refer to national guidelines) • High falls risk	• Consider bisphosphonate[ii] – Treatment based on fracture history and FRAX score (see section on Bone Disease: Screening and Diagnosis). – Ensure adequate calcium and vitamin D intake[iii] • Consider choice of ARV in those at high risk of fractures[iv] – No significant interactions between bisphosphonates and ARVs • Optimal management of frailty includes optimising nutrition, exercise (aerobic and resistance training), see section on frailty, page 123 • In complicated cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy), refer to osteoporosis specialist • If on bisphosphonate treatment, repeat DXA after 2 years. Persons without response to treatment refer to osteoporosis specialist for second line treatment. Re-assess need for continued treatment after 3-5 years

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Prevention and Management of Osteoporosis in PLWH

1. Encouragement of physical exercise and a balanced diet, with the discontinuation of harmful behaviors where relevant (smoking, excess alcohol intake and obesity)

2. Prevention of falls in the elderly population

3. Checking vitamin D levels at least once a year and taking supplements of calcium and vitamin D when needed

4. Health education for women about the risk of premature menopause and impact on the bones

5. A DEXA scan is indicated for all postmenopausal women, males older than 50 years, and patients with significant clinical risk factors for fragility fractures

6. The FRAX® tool has been recommended for regular assessment of fracture risk in PLWHIV over the age of 40 in the guidelines. FRAX score should not be recognized as a primary screening tool for bone fragility in PLWHIV, but it may aid in the decision to intervene with anti-osteoporotic medication in the event of significantly reduced BMD

7. Consider using ARVs with fewer side effects on BMD, especially with potential renal toxicity linked with bone fragility or renal hypophosphatemia

8. The addition of bisphosphonates to the cessation of TDF leads to greater increases in BMD than cessation of TDF alone

Bone Mineral Density Screening

Screening for osteoporosis is widely advocated for all postmenopausal women and men over 50 years of age with HIV, as HIV infection is considered an additional risk factor for osteoporosis

The gold standard for BMD assessment, dual-energy X-ray absorptiometry (DEXA), provides a reliable, quick, and low-radiation method for diagnosing osteoporosis despite some limitations, such as sensitivity to bone size and potential for artifact interference. However, its availability in certain settings, such as low-middle income settings, is limited, prompting the use of alternative diagnostic tools to guide the decision-making process for screening and treatment, such as the Fracture Risk Assessment Tool (FRAX)

The optimal interval for BMD rescreening in PWH is a matter of debate. Specifically, a rescreening period of about 15 years for women who have normal bone density or mild osteopenia, 5 years for those with moderate osteopenia, and annually for women exhibiting advanced osteopenia is suggested

A study within the HIV population proposed slightly different intervals based on T score tertiles, specifically 1 to 2 year interval for individuals in the lowest T score tertiles and interval of 6 years or more for those in the highest tertiles

Fracture Risk Assessment Tool (FRAX)

FRAX provides a 10-year fracture risk estimation using clinical risk factors, with or without BMD data, including age, gender, and lifestyle factors (https://frax.shef.ac.uk/ frax/, accessed on 1 April 2024)

However, FRAX does not incorporate HIV status as a covariate, nor has it been validated in the HIV population

A recent study investigating FRAX score's role in 774 PWH over 50 years old, suggests a significant discrepancy between FRAX scores and DXA scan results. Specifically, the prevalence of osteoporosis in the cohort was 12.2%, and osteopenia was 63.7%, yet FRAX major was >10% in only two patients, and 98.9% of patients with osteoporosis had a normal FRAX score

EACS make special recommendations on the use of the FRAX tool to refine fracture risk prediction in the HIV population:

- consider HIV as a cause of "secondary osteoporosis" in the calculation
- add the Trabecular Bone Score (TBS), derived from DXA scan results, to enhance the accuracy of FRAX risk predictions

Future Directions on Early Diagnosis

Quantitative computed tomography (QCT) can provide detailed analysis of both bone compartments -cortical and trabecular-, providing insights into the microstructure and is useful in research contexts for predicting fracture risk . It has been used in multiple studies involving PWH, demonstrating utility particularly in young patients

Magnetic resonance imaging (MRI) offers a non-radiative option for characterizing bone composition, making it an appealing option for younger individuals and is recommended in cases of suspected osteoporotic fractures, as it can reflect physiologic alterations based on signal intensity

Quantitative ultrasound (QUS) is a practical and accessible method, especially in resource-constrained environments, which correlates well with BMD and can aid in identifying patients at risk of fractures. Utilizing QUS to assess BMD in PWH has been investigated by some studies with mostly positive results

Vitamin D Supplementation

Replacement and/or supplementation of vitamin D is recommended for those with insufficiency and conditions such as osteoporosis, osteolamalacia or increased PTH. Targeting a 25-hydroxy-vitamin D level of at least 30 ng/mL is generally recommended for PWH with osteoporosis. This target is higher than the recommended threshold for bone health adequacy (above 20 ng/mL), considering the elevated fracture risk in the HIV population

One study demonstrated that young males on TDF regimens benefited from a monthly high-dose vitamin D supplement (50,000 IU), which resulted in improved lumbar spine BMD when combined with a daily multivitamin containing vitamin D and calcium

Other approaches may include nutritional support and patient education on improving dietary habits. A study proposed that medical nutrition therapy can improve the diet to promote bone health in people living with HIV, suggesting a significant increase in the intake of nutrients like calcium and vitamin D, and an increase in exercise length after the intervention. Among calcium-rich foods, yogurt intake has been reported as a protective predictor of lumbar spine BMD in PWH

Pharmacological Treatment

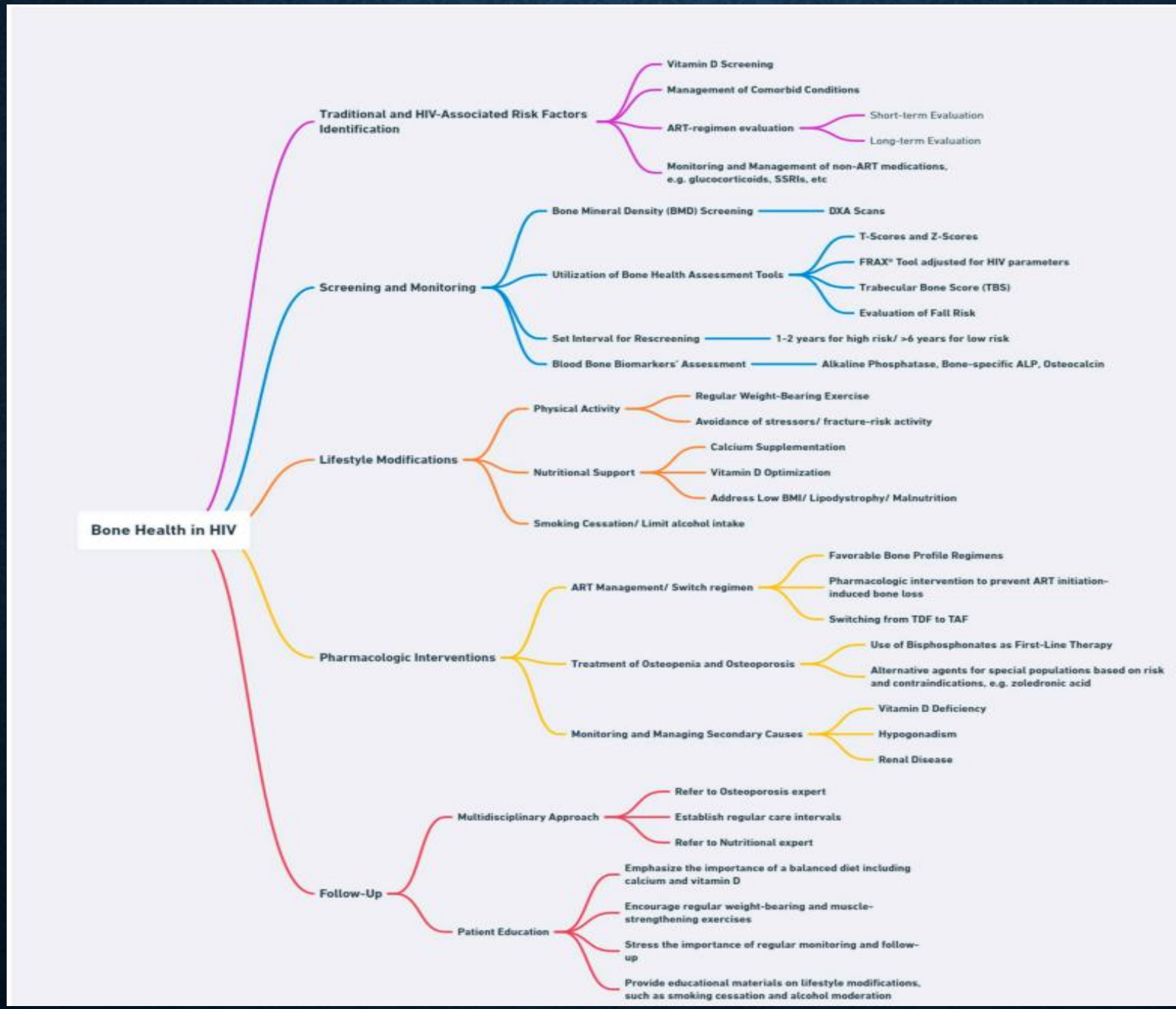
Bisphosphonates stand as the cornerstone of pharmacologic osteoporosis treatment

In a 48-week prospective RCT of 31 individuals showed that alendronate (70 mg weekly), in conjunction with vitamin D (400 IU daily) and calcium (1000 mg daily as calcium carbonate), led to a significant 5.2% increase in lumbar spine BMD in HIV-infected subjects on ART . This increase was greater than the 1.3% improvement observed in subjects who received only vitamin D and calcium supplementation

Administered annually, zoledronic acid has also been shown to increase BMD in PWH with osteopenia or osteoporosis . Of particular interest is an RCT of 43 individuals on HAART with osteopenia, which revealed significant BMD increases in the lumbar spine (8.9 percent) and total hip (3.8 percent) with zoledronic acid over a period of 2 years

As for prophylactic purposes, a phase 2, placebo-controlled trial explored the efficacy of a single dose of zoledronic acid in preventing ART-induced bone loss in 63 ART-naive adults with HIV . The study found significant reductions in bone resorption markers and modest improvements in BMD in the intervention group compared to placebo over the first 48 weeks of ART. The decrease in bone resorption markers was evident from 12 weeks (73% reduction; $p < 0.001$) and persisted until week 48 (57% reduction; $p < 0.001$)

Alternative treatments like denosumab may be beneficial for certain patients, especially when bisphosphonates are contraindicated or ineffective. A 12-month, open-label, prospective study showed that both denosumab and zoledronate improved BMD in 23 males with HIV, with no significant difference in lumbar spine BMD change or adverse events between the two groups


Bone Health in HIV
Traditional and HIV-Associated Risk Factors Identification
Vitamin D Screening
Management of Comorbid Conditions
ART-regimen evaluation
Short-term Evaluation
Long-term Evaluation
Monitoring and Management of non-ART medications, e.g. glucocorticoids, SSRIs, etc
Screening and Monitoring
Bone Mineral Density (BMD) Screening
DXA Scans
Utilization of Bone Health Assessment Tools
T-Scores and Z-Scores
FRAX® Tool adjusted for HIV parameters
Trabecular Bone Score (TBS)
Evaluation of Fall Risk
Set Interval for Rescreening
1-2 years for high risk/ >6 years for low risk
Blood Bone Biomarkers' Assessment
Alkaline Phosphatase, Bone-specific ALP, Osteocalcin
Lifestyle Modifications
Physical Activity
Regular Weight-Bearing Exercise
Avoidance of stressors/ fracture-risk activity
Nutritional Support
Calcium Supplementation
Vitamin D Optimization
Address Low BMI/ Lipodystrophy/ Malnutrition
Smoking Cessation/ Limit alcohol intake
Pharmacologic Interventions
ART Management/ Switch regimen
Favorable Bone Profile Regimens
Pharmacologic intervention to prevent ART initiation-induced bone loss
Switching from TDF to TAF
Treatment of Osteopenia and Osteoporosis
Use of Bisphosphonates as First-Line Therapy
Alternative agents for special populations based on risk and contraindications, e.g. zoledronic acid
Monitoring and Managing Secondary Causes
Vitamin D Deficiency
Hypogonadism
Renal Disease
Follow-Up
Multidisciplinary Approach
Refer to Osteoporosis expert
Establish regular care intervals
Refer to Nutritional expert
Patient Education
Emphasize the importance of a balanced diet including calcium and vitamin D
Encourage regular weight-bearing and muscle-strengthening exercises
Stress the importance of regular monitoring and follow-up
Provide educational materials on lifestyle modifications, such as smoking cessation and alcohol moderation