Osteoporosis International (2019) 30:1125–1135
https://doi.org/10.1007/s00198-018-4794-0

CONSENSUS STATEMENT

Diagnosis, prevention, and treatment of bone fragility in people living with HIV: a position statement from the Swiss Association against Osteoporosis

E. Biver[1] · A. Calmy[2] · B. Aubry-Rozier[3] · M. Birkhäuser[4] · H. A. Bischoff-Ferrari[5] · S. Ferrari[1] · D. Frey[6] · R. W. Kressig[7] · O. Lamy[3] · K. Lippuner[8] · N. Suhm[9] · C. Meier[10]

Received: 22 August 2018 / Accepted: 29 November 2018 / Published online: 2 January 2019

Abstract

Life expectancy of people living with HIV (PLWH) is reaching similar length as in the general population. Accordingly, age-related comorbidities, including osteoporosis, are increasing. Fracture risk is higher and increases approximately 10 years earlier in PLWH. Classical risk factors of bone fragility are highly prevalent in PLWH but factors specific for HIV infection itself and the type of antiretroviral therapy (ART) (triple combination antiretroviral therapy) regimen (especially tenofovir and protease inhibitors) also contribute to bone loss. The majority of bone loss occurs during virus activity and at initiation of ART (immune reconstitution) and is associated with an increase of bone resorption (upregulation RANKL). Recent data indicate that calcium and vitamin D supplements as ART initiation lower BMD loss. The reduction of tenofovir plasma concentrations with tenofovir alafenamide attenuates BMD loss but it remains unknown whether it will contribute to reduce fracture risk. Hence, special considerations for the management of bone fragility in PLWH are warranted. Based on the current state of epidemiology and pathophysiology of osteoporosis in PLWH, we provide the consensus of the Swiss Association against Osteoporosis on best practice for diagnosis, prevention, and management of osteoporosis in this population. Periodic assessment of fracture risk is indicated in all HIV patients and general preventive measures should be implemented. All postmenopausal women, men above 50 years of age, and patients with other clinical risk for fragility fractures qualify for BMD measurement. An algorithm clarifies when treatment with bisphosphonates and review of ART regimen in favour of more bone-friendly options are indicated.

Keywords Bone fragility · Diagnosis · HIV · Management · Osteoporosis · Prevention

✉ C. Meier
christian.meier@unibas.ch

[1] Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland

[2] HIV/Aids Unit, Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland

[3] Center of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland

[4] Gynecological Endocrinology and Reproductive Medicine, University of Berne, Basel, Switzerland

[5] Department of Geriatrics and Aging Research, University of Zurich and University Hospital of Zurich, Zurich, Switzerland

[6] Division of Rheumatology, University Hospital Zürich, Zürich, Switzerland

[7] University Center for Medicine of Aging, Basel Mobility Center, University of Basel, Basel, Switzerland

[8] Department of Osteoporosis, University Hospital, University of Berne, Berne, Switzerland

[9] Department of Orthopedics and Traumatology, Geriatric Fracture Center, University Hospital Basel, Basel, Switzerland

[10] Division of Endocrinology, Diabetology & Metabolism, University Hospital and University of Basel, Missionsstrasse 24, CH-4055 Basel, Switzerland

Introduction

Currently, there are an estimated 15,000 to 20,000 people living with HIV infection (PLWH) in Switzerland (prevalence 0.24% of the 8.42 million Swiss residents), with roughly 550 registered incident cases every year, corresponding to an incidence of 6.4 per 100,000 inhabitants in 2016 [1]. Residual life expectancy of a 20-year-old PLWH enrolled in the Swiss HIV Cohort Study (SHCS), a prospective longitudinal research effort that includes the majority of PLWH residents in Switzerland, has increased from 11.8 years in 1988–1991 to 54.9 years in 2006–2013, resulting in a life expectancy similar to the one in the general population [2]. The proportion of PLWH aged above 50 years old is increasing, reaching more than 50% in the SHCS participants in 2016 (unpublished data) or in the USA [3]. This development reflects the continuous improvement of efficacy of anti-HIV treatment options, particularly since the introduction of triple combination antiretroviral therapy (ART) in 1996. Accordingly, the proportion of PLWH older than 50 years has steadily increased [4]. It is likely that the proportion of elderly PLWH in the Swiss HIV population has grown further in the meantime. Consequently, an increasing number of patients suffer from common age-related comorbidities such as type 2 diabetes, non-AIDS cancerous diseases, cardiovascular disease, and osteoporosis. Like in the general population, the incidence rates of osteoporosis and fractures in the HIV population increased with age [5]. Prevalence of low bone mineral density (BMD), osteoporosis, and fractures is higher than in the general population, owing to high prevalence of classical risk factors associated with osteoporosis among PLWH as well as specific risk factors related to HIV infection itself and ART [6, 7]. Therefore, special considerations for treatment of osteoporosis in PLWH are warranted. In this article, we summarise the current state of epidemiology and pathophysiology of osteoporosis in PLWH and present the position of the Swiss Association against Osteoporosis (SVGO/ASCO) on best practice for diagnosis, prevention, and management of osteoporosis in HIV-infected patients.

Risk factors of osteoporosis and bone fragility in PLWH

Bone fragility in PLWH may reflect overrepresentation of traditional risk factors of osteoporosis such as smoking, alcohol abuse, drug use, low body mass index (BMI), and high prevalence of vitamin D deficiency coupled with effects of long-term HIV infection, continued immune dysfunction, and ART-induced toxicities (Table 1) [7, 8]. In addition, some endocrine diseases that negatively influence bone metabolism, such as hypogonadism in men, are highly prevalent in PLWH [9]. Sarcopenia may also contribute to the risk of fracture in PLWH [10]. Recently, frailty has been identified as additional risk factor for low BMD in HIV-positive women and osteoporosis in HIV-infected men [11]. Disease-specific risk factors include direct impact of HIV and chronic inflammation and ART-specific side effects on BMD as well as a high prevalence of co-infection with HCV, which translates into higher risk of osteoporosis [12]. Both permanently elevated levels of pro-inflammatory cytokines and toxic effects of certain viral proteins on bone metabolism result in bone loss as a consequence of increased bone resorption [13–15]. In the START study HIV population (median age 32 years, 80% non-white, 26% women), the annual decline of hip BMD in ART-naïve adults was 0.3–0.6%, which is only slightly higher as expected in the general population [16]. Indeed, annual loss of BMD at the hip and lumbar spine for premenopausal women as well as men aged below 50 years is approximately 0.15–0.4% [17]. A moderate direct impact of HIV infection on BMD is thus supported. It is likely that HIV-related and menopause-induced BMD declines are additive in middle-aged women infected with HIV [13, 18].

Table 1 Risk factors of osteoporosis and bone fragility in PLWH

Traditional risk factors	HIV-related risk factors
Age	Antiretroviral therapy
Caucasian race	Hepatitis C or B co-infection
Low BMI	Immune system modulation
Prior low-trauma fracture	Viral proteins
Parents history of hip fracture	Chronic inflammation
Poor nutrition (low calcium and protein intakes)	Drugs use
Vitamin D deficiency	
Menopause and male hypogonadism	
Alcohol abuse	
Tobacco use	
Low physical activity	
Glucocorticoids	
Proton pump inhibitors	
Comorbidities	

BMD changes at ART initiation and clinical significance

Additionally, BMD of PLWH is affected by ART (Table 2). A decline in BMD following ART initiation occurs within the first year independently of the regimen, with bone loss being more pronounced when starting a regimen containing tenofovir disoproxil fumarate (TDF) either in HIV-infected patients or in HIV-uninfected patients using this drug as a chemoprophylaxis (PreP) [19–21]. The role of boosted protease inhibitor in bone loss has been demonstrated in small studies [22–24]. A recent drug class, the integrase inhibitors,

Table 2 Classes and mechanisms of action of antiretroviral therapies on bones

ART class	Main drugs		Specific bone toxicity	Common bone toxicity
Nucleos(t)ide reverse-transcriptase inhibitors (NRTIs)	ABC	abacavir	- TDF associated with greater loss of BMD than other NRTIs. - TDF also associated in some patients with renal tubulopathy and urine phosphate wasting. - Smaller BMD decline with TAF than with TDF, thanks to target-specific intracellular activation of the prodrug in infected immune cells and lower concentrations of circulating tenofovir. - TDF-induced BMD decline attenuated by a switch to abacavir or TAF.	- Decrease in BMD observed after the initiation of any ART regimen. - Increase of bone resorption associated with immune reconstitution. - Subsequent stabilisation with continued use.
	ZDV	zidovudine		
	d4T	stavudine		
	ddI	didanosine		
	3TC	lamivudine		
	FTC	emtricitabine		
	TDF	tenofovir disoproxil fumarate		
	TAF	tenofovir alafenamide		
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	EFV	efavirenz	- EFV associated with lower vitamin D levels via a modulation of various cytochromes and enzymes involved in activation or deactivation of vitamin D or vitamin D–binding protein.	
	ETV	etravirine		
	NVP	nevirapine		
	RPV	rilpivirine		
	DOR	doravirine		
Protease inhibitors (PIs)	ATV	atazanavir	- PIs associated in some studies only with greater loss of BMD than other ART class.	
	DRV	darunavir		
Boosting	RTV	ritonavir (used as booster=/r)		
	COBI	cobicistat (used as booster=/c)		
Fusion inhibitor (FI)	ENF	enfuvirtide		
Integrase strand transfer inhibitor (INSTI)	RAL	raltegravir	- TDF-induced BMD decline attenuated by a switch to INSTI.	
	DTG	dolutegravir		
	EVG/c	elvitegravir		
	BIC	bictegravir		
CCR5 Inhibitor	MVC	maraviroc		

ART, antiretroviral therapies; *BMD*, bone mineral density. Only currently used and upcoming ART in Switzerland is reported

seems to lower the effect of bone loss as compared to both booster protease inhibitors [25].

The extent of initial bone loss (2–4%) is similar to the one induced by oral glucocorticoids [19, 26]. Increased bone resorption within the first 1–2 years is followed by stabilisation, which makes bone loss transient in nature, possibly associated with immune reconstitution [19]. A recent longitudinal study found no difference in BMD decline between HIV-positive and HIV-negative patients, the only factor associated with greater BMD decline in HIV-positive patients being ART initiation within the previous 3 months [27]. The START study, a randomised clinical trial comparing BMD dynamics in HIV patients who either received immediate or deferred ART, found an annual BMD decline of 2% at both the hip and spine in HIV patients who received immediate ART (vs. a decline of 0.3–0.6% in patients in the deferred ART study arm) [16], suggesting that contribution of ART or immune reconstitution to BMD decline is greater than that of HIV infection itself. A cross-sectional study of bone health in elderly long-term HIV-infected men under successful ART (median ART duration 15 years) revealed spine and hip areal BMD values only 3–7% lower than in age-matched non-infected case controls. Furthermore, altered bone microstructure in both trabecular and cortical bones were observed [28]. In summary, these data reinforce the statement of a transient, not sustained effect of ART on bone loss.

However, BMD loss at ART initiation is not unavoidable, and clinical trials have shown that some interventions, in particular vitamin D and calcium supplements, can prevent early initial bone loss. In a randomised controlled clinical trial that followed 165 PLWH over 48 months, supplementation with 4000 IU/day cholecalciferol and 500 mg of calcium carbonate twice daily attenuated bone loss related to initiation of efavirenz/emtricitabine/TDF [29]. In another randomised controlled trial in HIV-infected youth aged 16–24 years on stable TDF-containing ART regimens, spine BMD significantly increased over 48 weeks in the intervention group receiving monthly 50,000 IU vitamin D_3 plus multivitamin (containing daily vitamin D 400 IU and calcium 162 mg), but not in the control group receiving placebo plus multivitamin [30]. Another phase 2 study showed that a single dose of zoledronic acid administered at ART initiation prevented ART-induced bone loss through the first 48 weeks of ART [31].

TDF-induced BMD decline may also be attenuated or even improved by a switch to other drugs such as abacavir or an integrase inhibitor, or by a switch to alternative tenofovir prodrug tenofovir alafenamide (TAF) [32–34]. In contrast to TDF, TAF acts target-specifically with intracellular activation of the prodrug in infected immune cells with lower concentrations of circulating tenofovir and similar antiviral efficacy [35]. A meta-analysis of clinical studies comparing efficacy and safety data of TDF versus TAF in ART-naïve patients or

patients switching from a TDF-containing to an equivalent TAF-containing regimen favoured TAF. Significant differences in BMD at the hip and spine after 2 years were observed (− 2.4% and − 2.0% for TDF, respectively vs. + 0.07% and − 0.06% for TAF, respectively), while discontinuations due to bone toxicities were not significantly different [36]. However, a recent study in virologically suppressed HIV adults showed that the magnitude of BMD improvement was lower in patients switching from TDF to abacavir or raltegravir than in patients with annual 5-mg zoledronic acid added to TDF [37]. In addition, there is currently no data showing that initiating or switching to a bone-protective ART regimen lowers fracture incidence in PLWH.

For clinical interpretation of BMD changes associated with ART initiation or with switch to a bone-protective regimen in PLWH, various scenarios are presented in Fig. 1. It should be noted that these changes (± 2–5% BMD) have relatively little impact on fracture risk calculated by FRAX® compared to clinical risk factors at baseline. Therefore, it is a matter of debate whether the magnitude of these BMD changes is clinically significant in terms of actual increased fracture risk beyond the traditional underlying risk factors of bone fragility.

Pathophysiology of bone fragility in PLWH

Virus-associated and ART-related factors as well as the patient's clinical risk factors jointly contribute to bone fragility in PLWH, which is mainly characterised by an increase of bone resorption (reviewed in [7]). Experiments using an HIV-transgenic rat model reflecting the human disease in terms of BMD decline, elevated bone resorption, and lower BMI revealed osteoclast activation by enhanced production of receptor activator of nuclear factor kappa-B ligand (RANKL) by B cells accompanied by downregulation of antagonist osteoprotegrin (OPG) expression [38]. In line with these results, correlations of RANKL/OPG ratio and BMD at hip and femoral neck (but not spine) were observed in treatment-naïve HIV-infected patients. RANKL/OPG imbalances were likely caused by virus-induced B cell dysregulation as reflected in changes in RANKL- and OPG-expressing B cell subpopulations [39]. Osteoclast activation could be further driven by elevated RANKL levels induced by increased concentrations of pro-inflammatory cytokines (interleukins (IL) 1 and 6, tumour necrosis factor α (TNF-α)) as a consequence of HIV-related chronic inflammation. Furthermore, osteoblast and osteoclast activity was found to be directly affected in vitro by virus proteins (reviewed in [13, 24, 40]).

The details of the impact of ART on bone resorption still remain incompletely understood. Depending on the ART regimens in which TDF was used, bone effects of variable magnitude were observed, with efavirenz/emtricitabine/TDF being less toxic towards bone than TDF administered with a PI or cobicistat [4]. Drug-induced immune reconstitution emerged as an important factor. Initiation of lopinavir/ritonavir combined with TDF/emtricitabine was found to result in a surge in CTX, RANKL, and TNFα plasma levels. It has been hypothesised that these osteoclastogenic cytokines would be produced by B and T cells as a response to reconstitution of the $CD4^+$ T cell subpopulation with ART initiation [41, 42]. Whether ART, especially TDF, has direct effects on bone metabolism is less clear. A role for tenofovir plasma concentration is supported by the fact that lower tenofovir plasma concentration using the tenofovir prodrug TAF has been found to be favourable in terms of toxicity towards both the kidney and bone [34, 43]. In addition to its contribution to immune reconstitution, TDF-related bone loss has been associated to renal phosphate wasting caused by the toxicity of high tenofovir plasma concentrations towards renal proximal tubular cells [34, 44, 45]. However, clinical research aiming to characterise the role of TDF-mediated renal phosphate wasting has produced contradictory results: while a longitudinal study of 90 HIV-infected patients on TDF-containing ART did find a statistically significant relationship of phosphaturia and BMD at the femoral neck [46], AIDS Clinical Trials group A5224s, a study investigating renal phosphate wasting in patients receiving TDF/emtricitabine versus abacavir/lamivudine combined with atazanivir/ritonavir or efavirenz, could not find any evidence of a correlation of BMD at the spine or hip to phosphaturia in patients receiving TDF [47].

Finally, HIV infection as such and ART may also interfere with vitamin D metabolism, in addition to the high prevalence of vitamin D insufficiency in the HIV-positive population, in combination with risk factors that also apply to the general population. A recent report suggests that there is a relationship between monocyte activation, IL-6 levels, and vitamin D insufficiency in HIV-infected patients [48]. Furthermore, the popular first-line non-nucleoside reverse-transcriptase inhibitor efavirenz seems to be associated with decline of vitamin D levels that leads to higher risk of vitamin D insufficiency [49, 50]. Efavirenz-induced modulation of various cytochromes and enzymes involved in activation or deactivation of vitamin D or vitamin D–binding protein has been implicated as a pathophysiological mechanism [49].

Epidemiology of fragility fractures in PLWH

Incidence of fractures has been found to be increased in the HIV-positive compared to the general population in some cohort and registry studies (reviewed in [7, 51]). However, there were some limitations in these initial reports, such as insufficient cohort size or number of cases, young populations, or the lack of discrimination of traumatic versus low-impact fracture,

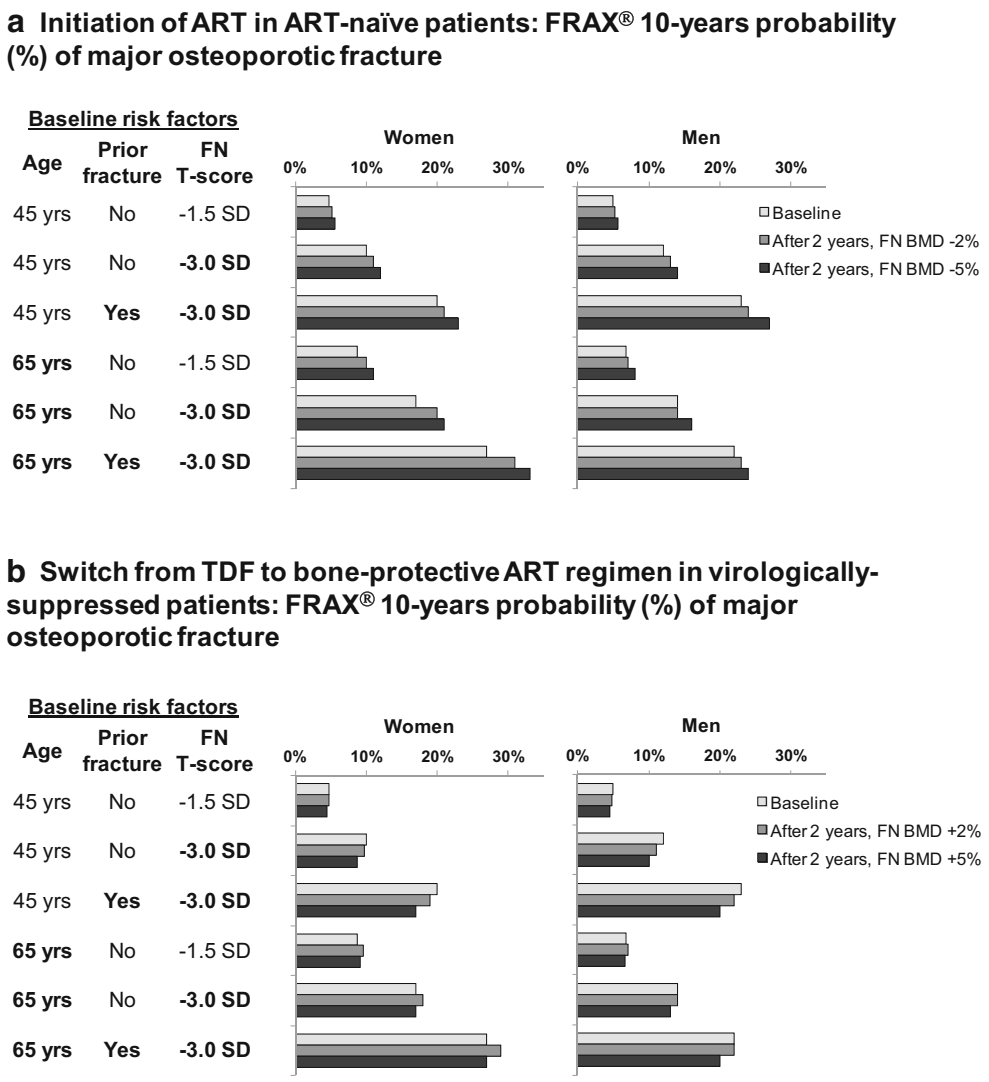

Fig. 1 Change of 10-year probability of major osteoporotic fracture assessed by FRAX® 2 years after ART initiation (**a**) or switch from TDF to a bone-protective ART regimen (**b**), according to various clinical risk factors of bone fragility at baseline and various scenarios of BMD changes (mean ± 2% and worst/best ± 5%). Fracture probability mainly depends of baseline clinical risk factors and is marginally affected by BMD changes, even in the worst/best scenarios. Fracture probability was assessed with FRAX® for a BMI of 23 kg/m^2, not taking into account other clinical risk factors than gender, age, fracture history, and femoral neck BMD. As BMD was included within FRAX®, entering HIV in the secondary cause box was not considered in the FRAX® algorithms, as it is assumed that secondary osteoporosis affects fracture risk solely through BMD. However, if the contribution of HIV infection to fracture risk is partially independent of BMD, fracture probability may be underestimated by FRAX®. In the general population, the intervention threshold at the age of 65 proposed by SVGO/ASCO is a 10-years probability of major osteoporotic fracture ≥ 20%. FN, femoral neck; BMD, bone mineral density; FRAX®, fracture risk assessment tool; ART, antiretroviral therapy

rendering it difficult to draw any generalised conclusions in terms of bone fragility [52]. Although long-term data on fracture risk in the HIV population are limited, particularly for elderly patients who have been on ART for long periods of time, recent reports, with longer follow-up than the initial ones, confirm that an increase in fracture incidence is emerging in PLWH. In a prospective study of fracture incidence in HIV-positive versus HIV-negative men older than 40 years, incidence of all fractures (traumatic and low-impact) was higher in HIV-positive men aged 50–59 compared to HIV-negative controls, indicating that fracture incidence increases approximately 10 years earlier in the HIV-infected versus the general male populations [53]. Whether PLWH are at higher risk of non-traumatic vertebral fractures associated with bone fragility remains a matter of debate. The prevalence of morphometric vertebral fractures has been investigated in few studies in PLWH, with prevalence varying between 12 and 47% depending of the age and characteristics of the population and the method of vertebral fractures assessment (reviewed in [6]). Again, one of the main limitations of these studies is that it was not possible to distinguish fragility versus prior traumatic fractures in rather young populations. This is

supported by the absence of association between spine BMD and vertebral fractures reported in some of these studies. For instance, in an Italian cohort of 141 HIV-infected patients (87% males, median age 43 years), the prevalence of vertebral fracture was 13.5%. Only 2/19 patients with vertebral fractures had BMD below expected range for age. On the other side, it should be noted that the risk of fracture underestimation through observational cohort analyses is also much greater for vertebral versus peripheral clinical fractures.

Assessment of absolute fracture risk in PLWH

Assessment of absolute fracture risk using FRAX® has been recommended for routine evaluation of fracture risk in PLWH [54]. In fact, HIV infection has been added to the set of secondary risks for osteoporosis that can be selected to refine the result. Nevertheless, there are concerns that FRAX® has limited predictive value for PLWH because important factors associated with HIV infection are not adequately reflected in the calculation, which may lead to underestimation of actual fracture risk (reviewed in [55]): (i) a general limitation of the FRAX® tool is that it is only validated above 40 years of age. The calculated fracture risk usually remains below the intervention threshold for patients aged 40–50, an age at which fracture risk of some PLWH may already be elevated; (ii) there is uncertainty if the FRAX® value (including HIV infection as a secondary risk factor or femoral neck BMD) is superior to case finding by dual X-ray absorptiometry (DXA) alone; (iii) significant risk factors specific for the ageing HIV population such as type of ART and its duration, HCV co-infection, or history of falls are not incorporated. Therefore, we do not propose FRAX® as a first-line screening tool in PLWH but to refine fracture risk in those who qualify for a DXA (based on clinical risk factors which suggest a high risk of fragility fractures), and in whom only a moderately low BMD was identified (T-score between − 1 and − 2.5 SD) (Fig. 2).

The addition of trabecular bone score (TBS) measured on the spine to femoral neck BMD has recently been proposed to adjust fracture probability in the FRAX® algorithm for the general population [56]. Whether the predictive accuracy of FRAX® is improved with TBS in PLWH has not been investigated. One study points out the potential interest of TBS for fracture risk assessment in PLWH. In the Italian cohort reported above (19 vertebral fractures in 141 HIV-infected patients), no significant differences were found stratifying vertebral fracture prevalence by BMD, whereas patients in the lowest quartile of TBS showed a higher prevalence of sub-clinical vertebral fractures [57]. This observation is however not supported by other reports. No difference in TBS (but some in hip BMD) was found in another study including 23 pairs of adults with and without a prior fracture after their HIV diagnosis, matched on age, sex, race, and smoking history [58]. A cross-sectional study in 174 HIV-infected men and 178 controls found that despite being associated with decreased BMD, HIV was not associated with lower TBS [59]. Another one found lower BMD values but no difference of TBS in PLWH treated with tenofovir compared to abacavir for more than 5 years [60]. The value of TBS for fracture risk assessment in the context of HIV needs therefore further investigations.

Diagnosis, prevention, and management of osteoporosis in PLWH

Based on the data presented above, we propose the algorithm presented in Fig. 2 for diagnosis, prevention, and management of osteoporosis in PLWH.

Diagnosis

Osteoporosis risk factors are highly prevalent in PLWH and should be assessed regularly in all PLWH, independent of age or sex. This especially applies to nutritional and lifestyle habits, vitamin D status, and risk of fall, which are alterable risk factors. Screening for osteoporosis with DXA should be performed in all HIV-positive men ≥ 50 years of age, postmenopausal women, and PLWH with high risk of fragility fracture as in the general population: history of low-trauma fracture (i.e. following a fall from standing height or lower), evidence of vertebral fracture from previous thoracic and abdominal X-rays or CT scans, clinical hypogonadism, oral glucocorticoid use of at least 2.5 mg qd prednisone equivalent for > 3 months, malabsorption, inflammatory bowel disease, or primary hyperparathyroidism. It should be noted that a DXA is covered by the Swiss obligatory health insurance for PLWH. Premenopausal women and men < 50 years of age should be referred to an osteoporosis specialist if significant risk for osteoporosis emerges following risk assessment. Additionally, vertebral fracture assessment (VFA) concomitantly of DXA should be performed in PLWH at high risk of sub-clinical vertebral fractures.

Prevention

Preventive measures against osteoporosis should be implemented in all PLWH. Measures described in the Swiss Association against Osteoporosis guideline for the general population basically also apply to the HIV population [61]. Regular physical activity and a balanced diet containing sufficient amounts of calcium and protein should be promoted (mean recommendations 1000 mg calcium and 1 g/kg protein per day). Additionally, fall prevention and ways to stop toxic habits (smoking, alcohol abuse) should be discussed. In addition to nutrition improvement, supplements may be considered, especially for vitamin D ± calcium. Dietary calcium intake can be roughly estimated and improved with the consumption of dairy products (≅ 300 mg calcium per serving)

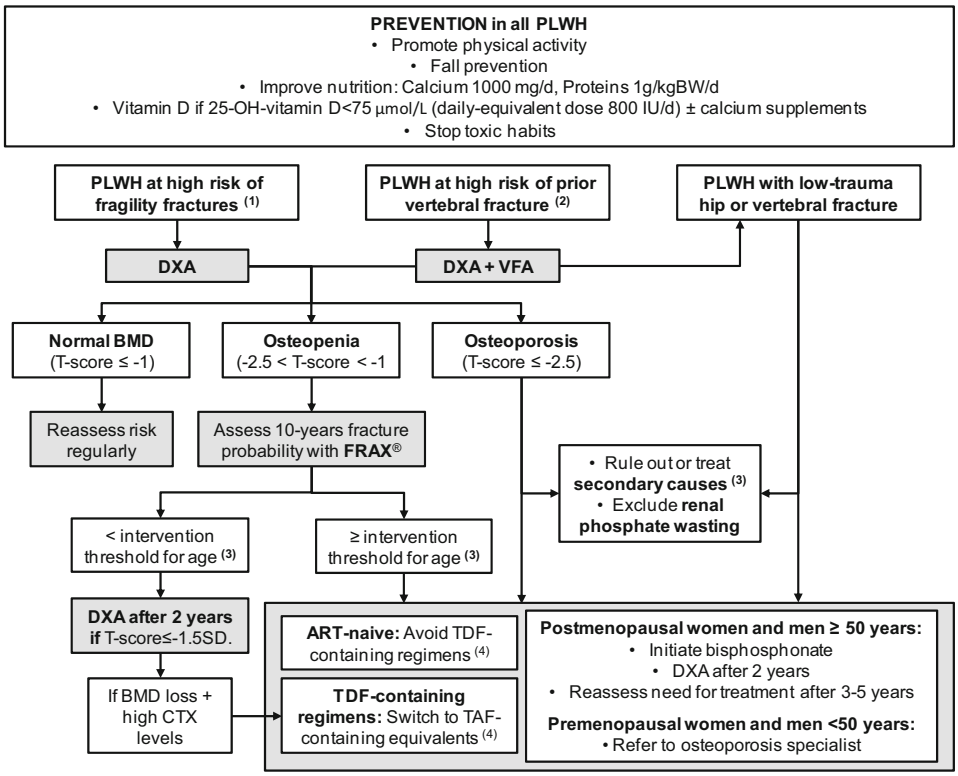

Fig. 2 Algorithm for diagnosis, prevention and management of bone fragility in PLWH

(1) Postmenopausal women and men ≥ 50 years, history of clinical low-trauma fracture(s), vertebral fracture on previous thoracic and abdominal X-rays and CT scans, oral glucocorticoids >2.5 mg/d, hypogonadism, malabsorption, inflammatory bowel diseases, primary hyperparathyroidism.

(2) Age ≥ 70 years, significant height loss (>4cm) or kyphosis, prior non-vertebral low-trauma fracture, oral glucocorticoid use ≥ 2.5mg/d, chronic inflammatory disease, hypogonadism.

(3) According to Swiss Association against Osteoporosis guidelines for the general population.

(4) If possible according to virological status.

and mineral waters rich in calcium. A balanced diet containing dairy products usually covers the recommended daily intake of calcium (1000 mg/day), while a diet without dairy products and a vegan diet only provide 300 mg/day and 500 mg/day, respectively. In the case of low calcium intake, a daily supplement combining calcium and vitamin D should be considered. Schematically, if a balanced diet with three dairy products per day or mineral waters rich in calcium is consumed, additional calcium supplementation is not necessary. A diet with one to three dairy products per day and no mineral water should be supplemented by 500 mg/day calcium, while a diet containing neither requires supplementation with 1 g/day calcium. PLWH are at high risk of vitamin D deficiency and measurement of 25(OH)D serum concentrations is recommended in this population [62]. Very little vitamin D is provided by the diet and supplements (recommended daily equivalent dose 800 IU/day) are required in case of insufficiency (< 20 ng/mL or 50 nmol/L) or deficiency (< 10 ng/mL or 25 nmol/L). This seems particularly important since two randomised controlled trials showed that vitamin D supplementation attenuated bone loss related to initiation of ART [29, 30].

Pharmacological treatment

Basically, treatment of osteoporosis in PLWH should follow the recommendations in the Swiss Association against Osteoporosis guidelines for the HIV-negative population [61]. There is no indication for treatment with bisphosphonate systematically at the initiation of ART. Treatment is indicated in patients with prior low-trauma vertebral or hip fracture, in patients whose 10-year fracture probability is above the age-appropriate intervention threshold, and in case of low BMD (osteoporosis based on a T-score below to − 2.5 at any site) in postmenopausal women and men ≥ 50 years of age (Fig. 2). An age-dependant FRAX intervention threshold is used in the Swiss population (men and women), corresponding to a 10-year fracture probability equal to or exceeding that of a woman of the same age with a prior fragility fracture (Table 3) [61, 63]. Prior to treatment initiation, secondary causes of osteoporosis should be ruled out or treated and renal phosphate wasting should be excluded. Bisphosphonate treatment (alendronate or zolendronate) is currently the preferred option because clinical data suggest that they are well tolerated, safe, and

Table 3 FRAX intervention thresholds according to Swiss Association against Osteoporosis guidelines for the general population [61]

Age	FRAX intervention threshold (MOF)
50 years	≥ 10%
55 years	≥ 13%
60 years	≥ 17%
65 years	≥ 20%
70 years	≥ 23%
75 years	≥ 28%
≥ 80 years	≥ 33%

efficacious in PLWH [13, 64]. BMD response to alendronate in HIV-infected patients was observed to be greater in those with increased CTX and TNFα levels at baseline, while no change could be measured in OPG, RANKL, and other inflammatory markers [65]. Apart from a single case report about successful use of teriparatide in an HIV-positive man [66], data on the use of therapeutic options other than BP for treatment of osteoporosis in PLWH, such as raloxifene, denosumab, or teriparatide, are currently lacking [64]. Response to bisphosphonate treatment should be assessed after 2 years by DXA scan. The need for further treatment should be re-evaluated after 3–5 years as in the general population.

ART regimens should be reviewed in patients with osteoporosis and those with a FRAX® above the recommended intervention threshold for age. In patients not reaching the FRAX® intervention threshold but with marked osteopenia (T-score < − 1.5/− 2 SD), the kinetics of bone loss should be assessed with repeated DXA after 2 years, and ART regimens should also be reviewed in case of bone loss, especially in patients with high levels of CTX. For these patients, TDF-sparing regimens may be preferred to TDF-containing regimens. This is also applicable to patients with confirmed hypophosphatemia of renal origin. In all cases, virological efficacy prevails and any change in ART should be discussed with the referent infectiologist.

In the case of osteoporosis or high fracture risk identified in treatment-naïve patients, TDF-containing regimens should be avoided and a first-line TAF-containing regimen (especially in the case of co-infection with hepatitis B) or abacavir-containing regimen (if not HLA B*5701) should be considered.

Acknowledgments The authors thank Dr. Isabel Hartmann for manuscript editing.

Compliance with ethical standards

Conflicts of interest Alexandra Calmy has received travel grants from Gilead and unrestricted educational grants from Gilead, ViiV, MSD, and AbbVie. Emmanuel Biver, Bérengère Aubry-Rozier, Martin Birkhäuser, Heike A. Bischoff-Ferrari, Serge Ferrari, Diana Frey, Reto W. Kressig, Olivier Lamy, Kurt Lippuner, Norbert Suhm, and Christian Meier declare that they have no conflict of interest.

References

1. Bundesamt für Gesundheit B (2017) HIV und Aids in der Schweiz im Jahr 2016. BAG-Bull 2017(43):12–19
2. Gueler A, Moser A, Calmy A, Gunthard HF, Bernasconi E, Furrer H, Fux CA, Battegay M, Cavassini M, Vernazza P, Zwahlen M, Egger M, Swiss Hiv Cohort Study SNC (2017) Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. AIDS 31(3):427–436. https://doi.org/10.1097/QAD.0000000000001335
3. Alvarez E, Belloso WH, Boyd MA, Inkaya AC, Hsieh E, Kambugu A, Kaminski G, Martinez E, Stellbrink HJ, Walmsley S, Brown TT, Mallon PW (2016) Which HIV patients should be screened for osteoporosis: an international perspective. Curr Opin HIV AIDS 11(3):268–276. https://doi.org/10.1097/coh.0000000000000269
4. Bedimo R, Rosenblatt L, Myers J (2016) Systematic review of renal and bone safety of the antiretroviral regimen efavirenz, emtricitabine, and tenofovir disoproxil fumarate in patients with HIV infection. HIV Clin Trials 17(6):246–266. https://doi.org/10.1080/15284336.2016.1243363
5. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, Bertisch B, Bernasconi E, Weber R, Swiss HIVCS (2011) Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis 53(11):1130–1139. https://doi.org/10.1093/cid/cir626
6. Compston J (2016) HIV infection and bone disease. J Intern Med 280(4):350–358. https://doi.org/10.1111/joim.12520
7. Biver E, Calmy A, Rizzoli R (2017) Bone health in HIV and hepatitis B or C infections. Ther Adv Musculoskelet Dis 9(1):22–34. https://doi.org/10.1177/1759720X16671927
8. Goh SSL, Lai PSM, Tan ATB, Ponnampalavanar S (2017) Reduced bone mineral density in human immunodeficiency virus-infected individuals: a meta-analysis of its prevalence and risk factors. Osteoporos Int 29:595–613. https://doi.org/10.1007/s00198-017-4305-8
9. Lachatre M, Pasquet A, Ajana F, Soudan B, Lion G, Bocket L, Cornavin P, Senneville E, Boufassa F, Cheret A (2017) HIV and hypogonadism: a new challenge for young-aged and middle-aged men on effective antiretroviral therapy. AIDS 31(3):451–453. https://doi.org/10.1097/qad.0000000000001348
10. Echeverría P, Bonjoch A, Puig J, Estany C, Ornelas A, Clotet B, Negredo E (2018) High prevalence of sarcopenia in HIV-infected individuals. Biomed Res Int 2018:5074923. https://doi.org/10.1155/2018/5074923 eCollection 2018
11. Bregigeon S, Galinier A, Zaegel-Faucher O, Cano CE, Obry V, Laroche H, Trijau S, Saout A, Poizot-Martin I (2017) Frailty in HIV infected people: a new risk factor for bone mineral density loss. AIDS 31(11):1573–1577. https://doi.org/10.1097/QAD.0000000000001507
12. Kovari H, Rauch A, Kouyos R, Rougemont M, Cavassini M, Schmid P, Stockle M, Bernasconi E, Weber R, Ledergerber B, Swiss HIVCS (2017) Hepatitis C infection and the risk of non-liver-related morbidity and mortality in HIV-infected persons in the Swiss HIV Cohort Study. Clin Infect Dis 64(4):490–497. https://doi.org/10.1093/cid/ciw809
13. Finnerty F, Walker-Bone K, Tariq S (2017) Osteoporosis in postmenopausal women living with HIV. Maturitas 95:50–54. https://doi.org/10.1016/j.maturitas.2016.10.015
14. Slama L, Reddy S, Phair J, Palella FJ Jr, Brown TT, ACSg M (2017) Changes in bone turnover markers with HIV seroconversion and ART initiation. J Antimicrob Chemother 72(5):1456–1461. https://doi.org/10.1093/jac/dkx011

15. Hileman CO, Labbato DE, Storer NJ, Tangpricha V, McComsey GA (2014) Is bone loss linked to chronic inflammation in antiretroviral-naive HIV-infected adults? A 48-week matched cohort study. AIDS 28(12):1759–1767. https://doi.org/10.1097/QAD.0000000000000320
16. Hoy JF, Grund B, Roediger M, Schwartz AV, Shepherd J, Avihingsanon A, Badal-Faesen S, de Wit S, Jacoby S, La Rosa A, Pujari S, Schechter M, White D, Engen NW, Ensrud K, Aagaard PD, Carr A, Group ISBMDS (2017) Immediate initiation of antiretroviral therapy for HIV infection accelerates bone loss relative to deferring therapy: findings from the START Bone Mineral Density Substudy, a randomized trial. J Bone Miner Res 32(9):1945–1955. https://doi.org/10.1002/jbmr.3183
17. Warming L, Hassager C, Christiansen C (2002) Changes in bone mineral density with age in men and women: a longitudinal study. Osteoporos Int 13(2):105–112. https://doi.org/10.1007/s001980200001
18. Weitzmann MN, Ofotokun I, Titanji K, Sharma A, Yin MT (2016) Bone loss among women living with HIV. Curr HIV/AIDS Rep 13(6):367–373. https://doi.org/10.1007/s11904-016-0336-6
19. Bolland MJ, Grey A, Reid IR (2015) Skeletal health in adults with HIV infection. Lancet Diabetes Endocrinol 3(1):63–74. https://doi.org/10.1016/S2213-8587(13)70181-5
20. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, Thompson M, Grant R, Pathak S, O'Hara B, Gvetadze R, Chillag K, Grohskopf L, Buchbinder SP (2011) Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One 6(8):e23688. https://doi.org/10.1371/journal.pone.0023688
21. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, Ramirez-Cardich ME, Namwongprom S, Chodacki P, de Mendonca LM, Wang F, Lama JR, Chariyalertsak S, Guanira JV, Buchbinder S, Bekker LG, Schechter M, Veloso VG, Grant RM (2015) Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 61(4):572–580. https://doi.org/10.1093/cid/civ324
22. Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy RL, Katlama C, Costagliola D (2009) Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS 23(7):817–824. https://doi.org/10.1097/QAD.0b013e328328f789
23. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, Myers L, Melbourne K, Ha B, Sax PE (2011) Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis 203(12):1791–1801. https://doi.org/10.1093/infdis/jir188
24. Moran CA, Weitzmann MN, Ofotokun I (2016) The protease inhibitors and HIV-associated bone loss. Curr Opin HIV AIDS 11(3):333–342. https://doi.org/10.1097/COH.0000000000000260
25. Brown TT, Moser C, Currier JS, Ribaudo HJ, Rothenberg J, Kelesidis T, Yang O, Dube MP, Murphy RL, Stein JH, McComsey GA (2015) Changes in bone mineral density after initiation of antiretroviral treatment with tenofovir disoproxil fumarate/emtricitabine plus atazanavir/ritonavir, darunavir/ritonavir, or raltegravir. J Infect Dis 212(8):1241–1249. https://doi.org/10.1093/infdis/jiv194
26. van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13(10):777–787. https://doi.org/10.1007/s001980200108
27. Tinago W, Cotter AG, Sabin CA, Macken A, Kavanagh E, Brady JJ, McCarthy G, Compston J, Mallon PW (2017) Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and negative patients. AIDS 31(5):643–652. https://doi.org/10.1097/qad.0000000000001372
28. Biver E, Calmy A, Delhumeau C, Durosier C, Zawadynski S, Rizzoli R (2014) Microstructural alterations of trabecular and cortical bone in long-term HIV-infected elderly men on successful antiretroviral therapy. AIDS 28(16):2417–2427
29. Overton ET, Chan ES, Brown TT, Tebas P, McComsey GA, Melbourne KM, Napoli A, Hardin WR, Ribaudo HJ, Yin MT (2015) Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. Ann Intern Med 162(12):815–824. https://doi.org/10.7326/M14-1409
30. Havens PL, Stephensen CB, Van Loan MD, Schuster GU, Woodhouse LR, Flynn PM, Gordon CM, Pan CG, Rutledge B, Harris DR, Price G, Baker A, Meyer WA 3rd, Wilson CM, Hazra R, Kapogiannis BG, Mulligan K (2018) Vitamin D3 supplementation increases spine bone mineral density in adolescents and young adults with human immunodeficiency virus infection being treated with tenofovir disoproxil fumarate: a randomized, placebo-controlled trial. Clin Infect Dis 66(2):220–228. https://doi.org/10.1093/cid/cix753
31. Ofotokun I, Titanji K, Lahiri CD, Vunnava A, Foster A, Sanford SE, Sheth AN, Lennox JL, Knezevic A, Ward L, Easley KA, Powers P, Weitzmann MN (2016) A single-dose zoledronic acid infusion prevents antiretroviral therapy-induced bone loss in treatment-naive HIV-infected patients: a phase IIb trial. Clin Infect Dis 63(5):663–671. https://doi.org/10.1093/cid/ciw331
32. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, Carr A (2009) Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. Clin Infect Dis 49(10):1591–1601. https://doi.org/10.1086/644769
33. McComsey GA, Lupo S, Parks D, Poggio MC, De Wet J, Kahl LP, Angelis K, Wynne B, Vandermeulen K, Gartland M, Cupo M, Aboud M (2018) Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. AIDS 32(4):477–485. https://doi.org/10.1097/qad.0000000000001725
34. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, Elion R, Cavassini M, Madruga JV, Brunetta J, Shamblaw D, DeJesus E, Orkin C, Wohl DA, Brar I, Stephens JL, Girard PM, Huhn G, Plummer A, Liu YP, Cheng AK, McCallister S, team G-U (2016) Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 16(1):43–52. https://doi.org/10.1016/S1473-3099(15)00348-5
35. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, Pozniak A, Thompson M, Podzamczer D, Molina JM, Oka S, Koenig E, Trottier B, Andrade-Villanueva J, Crofoot G, Custodio JM, Plummer A, Zhong L, Cao H, Martin H, Callebaut C, Cheng AK, Fordyce MW, McCallister S (2015) Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 385(9987):2606–2615. https://doi.org/10.1016/s0140-6736(15)60616-x
36. Gotham D, Hill A, Pozniak AL (2017) Candidates for inclusion in a universal antiretroviral regimen: tenofovir alafenamide. Curr Opin HIV AIDS 12(4):324–333. https://doi.org/10.1097/COH.0000000000000379
37. Hoy JF, Richardson R, Ebeling PR, Rojas J, Pocock N, Kerr SJ, Martinez E, Carr A, ZEST Study Investigators (2018) Zoledronic acid is superior to tenofovir disoproxil fumarate-switching for low bone mineral density in adults with HIV. AIDSAIDS 32(14):1967–1975. https://doi.org/10.1097/QAD.0000000000001911
38. Vikulina T, Fan X, Yamaguchi M, Roser-Page S, Zayzafoon M, Guidot DM, Ofotokun I, Weitzmann MN (2010) Alterations in the immuno-skeletal interface drive bone destruction in HIV-1 transgenic rats. Proc Natl Acad Sci U S A 107(31):13848–13853. https://doi.org/10.1073/pnas.1003020107

39. Titanji K, Vunnava A, Sheth AN, Delille C, Lennox JL, Sanford SE, Foster A, Knezevic A, Easley KA, Weitzmann MN, Ofotokun I (2014) Dysregulated B cell expression of RANKL and OPG correlates with loss of bone mineral density in HIV infection. PLoS Pathog 10(10):e1004497. https://doi.org/10.1371/journal.ppat.1004497
40. Moran CA, Weitzmann MN, Ofotokun I (2017) Bone loss in HIV infection. Curr Treat Options Infect Dis 9(1):52–67. https://doi.org/10.1007/s40506-017-0109-9
41. Ofotokun I, Titanji K, Vunnava A, Roser-Page S, Vikulina T, Villinger F, Rogers K, Sheth AN, Lahiri CD, Lennox JL, Weitzmann MN (2016) Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection. AIDS 30(3): 405–414. https://doi.org/10.1097/QAD.0000000000000918
42. Ofotokun I, Titanji K, Vikulina T, Roser-Page S, Yamaguchi M, Zayzafoon M, Williams IR, Weitzmann MN (2015) Role of T-cell reconstitution in HIV-1 antiretroviral therapy-induced bone loss. Nat Commun 6:8282. https://doi.org/10.1038/ncomms9282
43. Rockstroh JOC, Yazdanpanah Y, Di Perri G, Sax PE, Arribas JR, Brinkman K, Wohl DA, Cheng A, Zhong L, McCallister S, Das M (2017) Switching from TDF to TAF improves bone and renal safety independent of age, sex, race, or 3rd agent: results from pooled analysis (N=2816) of virologically suppressed HIV-1 infected adults. Abstract MOPEB0289, 9th IAS Conference on HIV Science, Paris. Available at http://www.ias2017.org/Portals/1/Files/IAS2017_LO.compressed.pdf?ver=2017-07-27-211231-197
44. Casado JL, Del Rey JM, Banon S, Santiuste C, Rodriguez M, Moreno A, Perez-Elias MJ, Liano F, Moreno S (2016) Changes in kidney function and in the rate of tubular dysfunction after tenofovir withdrawal or continuation in HIV-infected patients. J Acquir Immune Defic Syndr 72(4):416–422. https://doi.org/10.1097/QAI.0000000000000986
45. Casado JL, Banon S, Santiuste C, Serna J, Guzman P, Tenorio M, Liano F, del Rey JM (2016) Prevalence and significance of proximal renal tubular abnormalities in HIV-infected patients receiving tenofovir. AIDS 30(2):231–239. https://doi.org/10.1097/QAD.0000000000000901
46. Casado JL, Santiuste C, Vazquez M, Banon S, Rosillo M, Gomez A, Perez-Elias MJ, Caballero C, Rey JM, Moreno S (2016) Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS 30(9): 1423–1431. https://doi.org/10.1097/QAD.0000000000001067
47. Gupta SK, Yeh E, Kitch DW, Brown TT, Venuto CS, Morse GD, Ha B, Melbourne K, McComsey GA (2017) Bone mineral density reductions after tenofovir disoproxil fumarate initiation and changes in phosphaturia: a secondary analysis of ACTG A5224s. J Antimicrob Chemother 72(7):2042–2048. https://doi.org/10.1093/jac/dkx076
48. Manion M, Hullsiek KH, Wilson EMP, Rhame F, Kojic E, Gibson D, Hammer J, Patel P, Brooks JT, Baker JV, Sereti I, Study to Understand the Natural History of HIVAitEoEATI (2017) Vitamin D deficiency is associated with IL-6 levels and monocyte activation in HIV-infected persons. PLoS One 12(5):e0175517. https://doi.org/10.1371/journal.pone.0175517
49. Havers FP, Detrick B, Cardoso SW, Berendes S, Lama JR, Sugandhavesa P, Mwelase NH, Campbell TB, Gupta A, Actg AP, Teams NS (2014) Change in vitamin d levels occurs early after antiretroviral therapy initiation and depends on treatment regimen in resource-limited settings. PLoS One 9(4):e95164. https://doi.org/10.1371/journal.pone.0095164
50. Wohl DA, Orkin C, Doroana M, Pilotto JH, Sungkanuparph S, Yeni P, Vanveggel S, Deckx H, Boven K (2014) Change in vitamin D levels and risk of severe vitamin D deficiency over 48 weeks among HIV-1-infected, treatment-naive adults receiving rilpivirine or efavirenz in a phase III trial (ECHO). Antivir Ther 19(2):191–200. https://doi.org/10.3851/IMP2721
51. Hoy J, Young B (2016) Do people with HIV infection have a higher risk of fracture compared with those without HIV infection? Curr Opin HIV AIDS 11(3):301–305. https://doi.org/10.1097/COH.0000000000000249
52. Yin MT, Shi Q, Hoover DR, Anastos K, Sharma A, Young M, Levine A, Cohen MH, Shane E, Golub ET, Tien PC (2010) Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study. AIDS 24(17):2679–2686. https://doi.org/10.1097/QAD.0b013e32833f6294
53. Gonciulea A, Wang R, Althoff KN, Palella FJ, Lake J, Kingsley LA, Brown TT (2017) An increased rate of fracture occurs a decade earlier in HIV+ compared with HIV- men. AIDS 31(10):1435–1443. https://doi.org/10.1097/QAD.0000000000001493
54. Brown TT, Hoy J, Borderi M, Guaraldi G, Renjifo B, Vescini F, Yin MT, Powderly WG (2015) Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis 60(8):1242–1251. https://doi.org/10.1093/cid/civ010
55. Yin MT, Shiau S, Rimland D, Gibert CL, Bedimo RJ, Rodriguez-Barradas MC, Harwood K, Aschheim J, Justice AC, Womack JA (2016) Fracture prediction with modified-FRAX in older HIV-infected and uninfected men. J Acquir Immune Defic Syndr 72(5):513–520. https://doi.org/10.1097/QAI.0000000000000998
56. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, Elders PJ, Fujita Y, Gluer CC, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren O, Lorentzon M, Mellstrom D, Merlijn T, Oei L, Ohlsson C, Pasco JA, Rivadeneira F, Rosengren B, Sornay-Rendu E, Szulc P, Tamaki J, Kanis JA (2016) A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res 31(5):940–948. https://doi.org/10.1002/jbmr.2734
57. Ciullini L, Pennica A, Argento G, Novarini D, Teti E, Pugliese G, Aceti A, Conti FG (2018) Trabecular bone score (TBS) is associated with sub-clinical vertebral fractures in HIV-infected patients. J Bone Miner Metab 36(1):111–118. https://doi.org/10.1007/s00774-017-0819-6
58. Tan DH, Raboud J, Szadkowski L, Szabo E, Hu H, Wong Q, Cheung AM, Walmsley SL (2017) Novel imaging modalities for the comparison of bone microarchitecture among HIV+ patients with and without fractures: a pilot study. HIV Clin Trials 18(1): 28–38. https://doi.org/10.1080/15284336.2016.1266074
59. Bedimo RJ, Adams-Huet B, Poindexter J, Brown G, Farukhi I, Castanon R, Turner D, Moore T, Tebas P, Maalouf NM (2017) The differential effects of HIV and HCV on bone microarchitecture and fracture risk. Clin Infect Dis 66:1442–1447. https://doi.org/10.1093/cid/cix1011
60. Guerri-Fernandez R, Molina-Morant D, Villar-Garcia J, Herrera S, Gonzalez-Mena A, Guelar A, Trenchs-Rodriguez M, Diez-Perez A, Knobel H (2017) Bone density, microarchitecture, and tissue quality after long-term treatment with tenofovir/emtricitabine or abacavir/lamivudine. J Acquir Immune Defic Syndr 75(3):322–327. https://doi.org/10.1097/qai.0000000000001396
61. Recommendations of the Swiss Association against Osteoporosis (SVGO/ASCO) (2015) Prevention, diagnostic and treatment of osteoporosis. Available from: http://www.svgo.ch/content/documents/2015/SVGO%20Empfehlungen%202015.pdf
62. Bischoff Ferrari HA, Burckhardt P, QuackLoetscher K, Gerber B, l'Allemand D, Laimbacher J, Bachmannan M, Rizzoli R (2012) Vitamin D deficiency: evidence, safety, and recommendations for the Swiss population. Report written by a group of experts on behalf of the Federal Commission for Nutrition. Approved by the Federal Commission for Nutrition on November 3, 2011 http://www.bagadminch/themen/ernaehrung_bewegung/05207/13246/indexhtml?lang=de

63. Lippuner K, Johansson H, Kanis JA, Rizzoli R (2010) FRAX assessment of osteoporotic fracture probability in Switzerland. Osteoporos Int 21(3):381–389. https://doi.org/10.1007/s00198-009-0975-1
64. Negredo E, Warriner AH (2016) Pharmacologic approaches to the prevention and management of low bone mineral density in HIV-infected patients. Curr Opin HIV AIDS 11(3):351–357. https://doi.org/10.1097/COH.0000000000000271
65. Natsag J, Kendall MA, Sellmeyer DE, McComsey GA, Brown TT (2016) Vitamin D, osteoprotegerin/receptor activator of nuclear factor-kappaB ligand (OPG/RANKL) and inflammation with alendronate treatment in HIV-infected patients with reduced bone mineral density. HIV Med 17(3):196–205. https://doi.org/10.1111/hiv.12291
66. Wheeler AL, Tien PC, Grunfeld C, Schafer AL (2015) Teriparatide treatment of osteoporosis in an HIV-infected man: a case report and literature review. AIDS 29(2):245–246. https://doi.org/10.1097/QAD.0000000000000529