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Review Article

HIV-Associated Bone Loss and Fracture Risk: Molecular Mechanisms, Osteoimmunology, and Emerging Biotechnological Interventions

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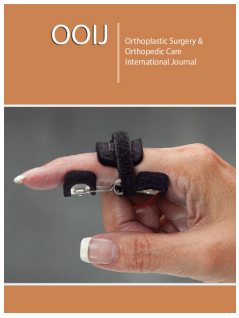

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Abstract

With effective Antiretroviral Therapy (ART), People Living with HIV (PLWH) now approach the life expectancy of the general population, and skeletal fragility has become an important component of long-term care. HIV-associated bone loss reflects the overlapping effects of persistent immune activation, viral proteins, ART exposure, ageing, endocrine and nutritional factors, and conventional fracture risks, making the relative contribution of each determinant difficult to isolate in individual patients. This review synthesizes foundational and more recent evidence on epidemiology, molecular mechanisms, osteoimmune signaling, clinical assessment, established treatment and emerging biotechnology. It integrates immune-cell crosstalk, bone quality, medication-related effects and precision monitoring into a translational framework that distinguishes established practice from investigational concepts.

A structured narrative search considered peer-reviewed meta-analyses, randomized trials, cohort studies, mechanistic research and professional guidance across the available literature, retaining foundational studies where necessary; the evidence base includes both older landmark studies and more recent publications. Meta-analyses show increased fracture risk in PLWH, with pooled relative risks of approximately 1.5 for fragility fracture and about 4 for hip fracture, and comparative trials report smaller Bone Mineral Density (BMD) losses with Tenofovir Alafenamide (TAF) than with Tenofovir Disoproxil Fumarate (TDF), although changes in surrogate measures do not prove fracture reduction. RANKL-RANK-OPG signalling, inflammatory cytokines and impaired osteoblast function are plausible mechanisms linking immune dysregulation with bone remodelling. DXA and clinical risk assessment remain central, bisphosphonates have the strongest HIV-specific treatment evidence, and denosumab, anabolic agents, AI, omics, advanced imaging and targeted delivery require further validation in HIV populations. Integrated, risk-stratified bone care should accompany, not compete with, effective HIV treatment.

Keywords: HIV; Osteoporosis; Fracture risk; Osteoimmunology and Antiretroviral therapy

Abbreviations: BMD: Bone Mineral Density; TDF: Tenofovir Disoproxil Fumarate; TAF: Tenofovir Alafenamide; TNF-α: Tumour Necrosis Factor-α; BMSi: Bone Material Strength Index; OPG: Osteoprotegerin; IL-6: Interleukin-6; ART: Antiretroviral Therapy; PLWH: People Living with HIV

Highlights

1. HIV-associated skeletal fragility is multifactorial, with immune, medication-related and conventional risks interacting across the life course, and BMD alone explains only part of the excess fracture risk.

2. RANKL-RANK-OPG signaling and inflammatory cytokines connect immune activation to osteoclast activity, while osteoblast dysfunction can impair bone replacement.

3. Precision imaging and AI are promising, but fracture-prevention decisions should currently rest on validated clinical assessment and established osteoporosis care.

Introduction

Effective ART has transformed HIV infection from a frequently fatal illness into a manageable chronic condition, and modelling studies of cohorts from the United States and

Canada show that life expectancy among treated individuals has risen substantially over the past two decades [1,2]. As survival has lengthened, clinical attention has shifted toward comorbidities of ageing, and comparisons with demographically similar uninfected individuals indicate that PLWH accumulate several age-related conditions, including bone disease, earlier or more frequently [3]. The skeletal consequences were recognized early: a meta-analytic review that compared 884 HIV-infected individuals with 654 uninfected controls reported 6.4-fold higher odds of reduced BMD and 3.7-fold higher odds of osteoporosis among those with HIV [4]. More recent syntheses confirm that PLWH have lower BMD and a greater burden of fractures than HIV-negative comparison groups [5-7]. Because bone loss is clinically silent until a fracture occurs, and because a low-trauma fracture can lead to persistent pain, reduced mobility and a higher probability of subsequent fracture [8], prevention depends on identifying risk before clinical injury [9,10]. Skeletal health should therefore be integrated into routine long-term HIV care rather than addressed only after a fracture has occurred.

HIV-related skeletal disease cannot be explained by ART exposure alone, because age, low body mass, smoking, alcohol use, coinfections, renal disease, hypogonadism, menopause and reduced physical activity also affect bone [11,12]. In a large cohort of male veterans, for example, the unadjusted hazard ratio for fragility fracture associated with HIV was 1.32, but the association fell to 1.10 after adjustment for body mass index and was no longer statistically significant [13]. Initiation of ART is commonly followed by an early BMD decline of approximately 2-6% over the first two years, a magnitude comparable to that seen during the first two years of menopause [9], and the extent of loss varies with regimen, pre-treatment immune status and baseline health [14]. Comparative evidence generally shows a more favorable BMD profile for TAF than for TDF; in two pooled phase 3 trials of 1,733 treatment-naive adults, spine BMD changed by -1.30% with TAF and -2.86% with TDF at 48 weeks [15]. Bone outcomes must nevertheless be balanced against virologic, metabolic, renal and access considerations, and these associations do not justify delaying or stopping effective ART, because sustained viral suppression remains essential to the health of the individual [16,17]. The clinical objective is to optimize bone protection alongside durable HIV control.

Osteoimmunology explains how immune cells and inflammatory mediators influence the cells responsible for bone resorption and formation [18,19]. The receptor activator of nuclear factor-κB ligand (RANKL)-RANK-osteoprotegerin (OPG) axis, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), T-cell and B-cell activity, and Wnt/β-catenin signalling are among the pathways investigated in HIV-associated bone loss [20-22]. Experimental work with HIV envelope and accessory proteins demonstrates mechanistic plausibility [23,24], but cell-culture and animal findings cannot by themselves quantify how much each pathway contributes to fractures in treated humans. Similarly, BMD is an important risk marker, yet a meta-analysis estimated that the modest BMD deficit observed in PLWH accounts for only a minor proportion of the excess fracture risk [5], and investigators studying bone quality have argued that changes in tissue-level material properties may partly explain this paradox [25]. The central scientific challenge is therefore to connect molecular mechanisms with clinically useful prediction and prevention.

This review examines epidemiological estimates, molecular mechanisms, osteoimmune interactions, ART-associated skeletal effects, diagnostic tools, therapies and emerging biotechnology [12,26]. The evidence emphasis is on peer-reviewed literature published from 2021 through 2026, with earlier landmark studies retained where they establish key methods, mechanisms or baseline epidemiology. Published numerical estimates are reported as source findings rather than recalculated pooled effects, and case reports are treated as hypothesis-generating rather than definitive evidence. Clinical recommendations are deliberately separated from experimental opportunities to avoid presenting emerging technologies as established standard care. Where possible, the discussion distinguishes four tiers of evidence-randomized trials, prospective cohorts and meta-analyses, mechanistic laboratory studies, and expert opinion or case reports-because the clinical weight that each can bear is very different. Readers should note that most HIV-specific skeletal data derive from surrogate outcomes, mainly BMD, and from populations in high-income settings [5,7]. The review's contribution is an integrated and evidence-conscious framework linking mechanism, measurement and intervention, and its structure moves from epidemiology and mechanism to assessment, treatment and the research frontier so that readers can see where evidence is strong and where it remains provisional.

Review Methodology and Evidence Appraisal

Search strategy and eligibility

A structured narrative approach was used because the topic crosses clinical epidemiology, immunology, pharmacology, imaging, osteoporosis treatment and early-stage biotechnology, and because the heterogeneity of study designs would not support a single quantitative synthesis [12,26]. Search concepts included HIV, bone mineral density, fracture, osteoporosis, osteoimmunology, RANKL, OPG, tenofovir disoproxil fumarate, tenofovir alafenamide, DXA, bone micro indentation, bisphosphonates, denosumab and artificial intelligence. Priority was assigned to peer-reviewed meta-analyses, systematic reviews, randomized studies, prospective cohorts, clinical guidelines and primary mechanistic studies across the available literature, including recent publications and foundational studies needed to interpret key findings [7,25,27]. Foundational journal articles published earlier were retained when needed to interpret risk estimates, document the origin of a mechanistic concept or describe established treatment principles [4,20]. Only peer-reviewed journal articles are cited; websites, fact sheets, registries and unpublished guidance documents were excluded from the reference list. This strategy supports a broad synthesis but should not be mistaken for a protocol-registered systematic review.

Studies were considered relevant if they addressed HIV status, ART exposure, bone outcomes, immune mechanisms, fracture-risk assessment or interventions with plausible clinical relevance. Meta-analyses were used to summarize pooled epidemiological

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estimates [5,6], randomized trials were used for comparative treatment effects [15,25], and observational cohorts were used for associations [13,28]. Cellular and animal studies were used to describe biological pathways but were not treated as proof of clinical efficacy [23,29]. Evidence from the general osteoporosis literature, such as pivotal trials of denosumab, teriparatide and romosozumab, is cited only to describe mechanisms and effects in populations without HIV, and is explicitly distinguished from HIV-specific evidence [30-32]. Where several publications reported overlapping cohorts or analyses, the most complete and relevant report was preferred, and conference abstracts and preprints were not used as the basis for numerical statements. Reported effect sizes are given with confidence intervals wherever the source provided them, so readers can judge precision as well as magnitude [5,6]. Because no original patient dataset was analyzed, this review does not calculate new pooled risk ratios or treatment effects.

Epidemiology of Bone Loss and Fracture Risk

Fracture burden and pooled estimates

Meta-analytic evidence indicates that PLWH have an increased risk of fractures compared with HIV-negative controls, although the magnitude differs among populations and study designs [5,6]. A 2020 systematic review and meta-regression reported a pooled fracture prevalence of 6.6% (95% CI 3.8-11.1) and an odds ratio of 1.91 (95% CI 1.14-3.22) compared with the general population [6]. The same analysis estimated fracture incidence at 11.3 per 1,000 person-years (95% CI 7.9-14.5), with an incidence-rate ratio of 1.50 (95% CI 1.27-1.78) [6]. These estimates were derived from studies available up to 2019 and therefore should be interpreted as published baseline evidence rather than a complete summary of every study published through 2026. More recent pooled prevalence estimates are higher but are heavily influenced by the populations sampled: a 2025 meta-analysis reported fracture prevalence of 21%, osteopenia prevalence of 43% and osteoporosis prevalence of 14% among PLWH, and a pooled relative risk for osteoporosis of 1.25 whose 95% confidence interval (0.87-1.78) included the null [7]. The quantitative conclusion is a clinically meaningful excess burden that varies with the study population, not a universal individual probability.

A separate systematic review and meta-analysis that screened nearly 2,400 publications and pooled data from more than 60,000PLWH reported increased relative risks of any fracture (RR 1.53; 95% CI 1.46-1.61), fragility fracture (RR 1.51; 95% CI 1.41-1.63) and hip fracture (RR 4.05; 95% CI 2.99-5.49) [5,12]. That analysis also found lower BMD at the hip and lumbar spine compared with controls, while emphasizing that BMD differences did not fully explain the fracture excess [5,18,22,23,33] (Table 1) (Figure 1). Individual studies show the same direction of effect with wider uncertainty: a nationwide case-control study using the Spanish SIDIAP primary-care database in Catalonia, Spain, reported an odds ratio of 2.89 (95% CI 1.99-4.18) for any fracture and 8.99 for hip fracture, although the interval for the latter (1.39-58.0) was very wide because few exposed participants were involved [34]. Variability in age, sex, prior fracture, follow-up duration and fracture ascertainment can change estimates across studies [35]. Absolute risk is therefore likely to be higher in older adults and in those with prior fracture, low body mass or several concurrent risk factors than in younger low-risk populations. The practical lesson is to interpret pooled relative risks alongside a patient's baseline absolute risk.

Table 1: Selected quantitative results from published studies [5-7,9,15,25,27,34,64,65].

Source / Design	Published Quantitative Finding	Interpretation
Pramukti et al. [6] systematic review/meta-regression; studies through 2019	Fracture prevalence 6.6% (95% CI 3.8-11.1); OR 1.91 (95% CI 1.14-3.22) vs general population	Pooled historical evidence; heterogeneity across studies
Same review [6]	Incidence 11.3 per 1,000 person-years (95% CI 7.9-14.5); IRR 1.50 (95% CI 1.27-1.78)	Incidence estimate depends on included cohorts and follow-up
Starup-Linde et al. [5] systematic review/meta-analysis of osteoporosis management in PLWH [5]	Any fracture RR 1.53 (95% CI 1.46-1.61); fragility fracture RR 1.51 (95% CI 1.41-1.63); hip fracture RR 4.05 (95% CI 2.99-5.49)	Relative risks; not individual absolute probabilities
Afraie et al. [7] systematic review/meta-analysis, 2025	Pooled prevalence: fractures 21%, osteopenia 43%, osteoporosis 14%; osteoporosis RR 1.25 (95% CI 0.87-1.78)	Prevalence varies by population; RR interval includes the null
Prieto-Alhambra et al. [35] Spanish SIDIAP primary-care database, Catalonia, Spain	Any fracture OR 2.89 (95% CI 1.99-4.18); hip fracture OR 8.99 (95% CI 1.39-58.0)	Registry-based; very wide interval for hip fracture
McComsey et al. [9] clinical review	ART initiation associated with a 2-6% BMD decrease over the first 2 years	Summary estimate across prior evidence; regimen and population vary
Pooled phase 3 trials of E/C/F/TAF vs E/C/F/TDF, n=1,733, 48 weeks [15]	Spine BMD -1.30% vs -2.86%; hip BMD -0.66% vs -2.95% (TAF vs TDF; both P<0.0001)	Surrogate endpoint; shows a smaller BMD decline with TAF, not fracture prevention
TDF-to-TAF pilot randomized study, n=24, 24 weeks [25]	BMSi +5.1% in TAF arm (P=0.041); CTX -10% in TAF arm; no significant BMD change in either arm	Small pilot; surrogate endpoints, weight change a possible confounder
Zoledronic acid phase IIb trial, n=63, treatment-naive adults [66,67]	Single 5mg infusion reduced ART-associated bone loss by about 74%, 65% and 56% at 12, 24 and 48 weeks; effect durable to 3 years	Single-site proof of concept; fracture outcomes not established
Denosumab case report, one woman with HIV, 4 years [27]	BMD improved; no new fractures; no HIV reactivation or opportunistic infection	Hypothesis-generating only; cannot establish effectiveness or safety

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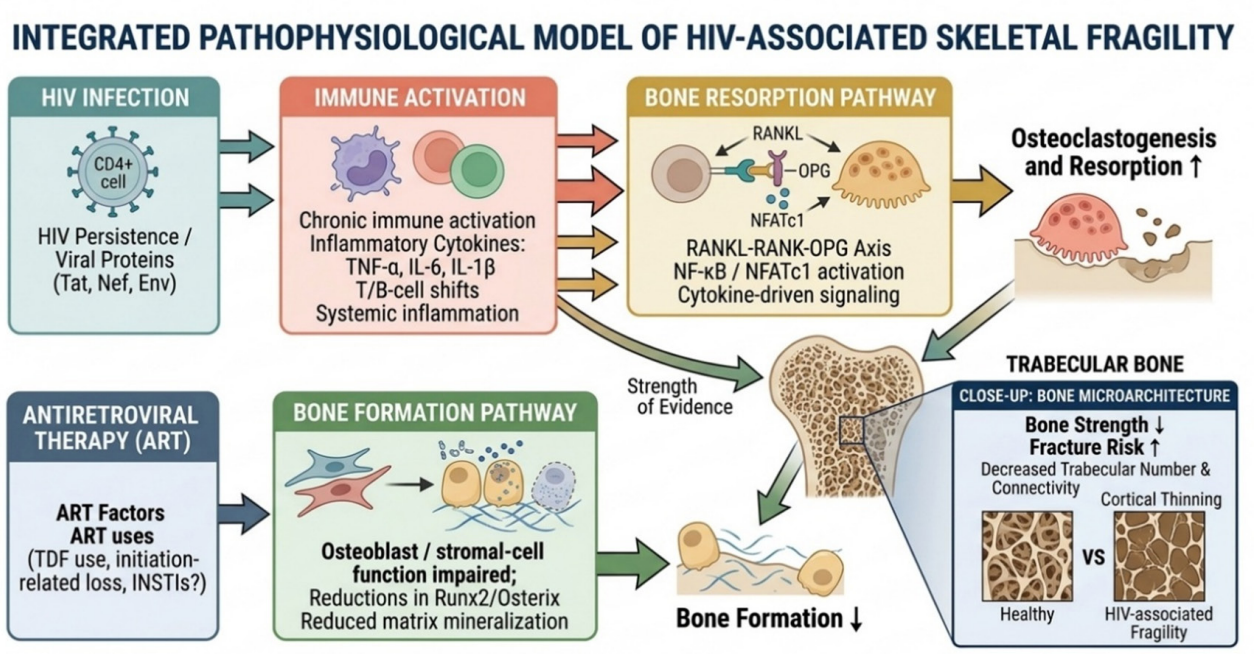

Figure 1: Conceptual pathways linking HIV persistence, immune activation, ART-related effects and skeletal fragility; this schematic synthesizes mechanisms discussed in the cited literature [18,22,23,33].

Traditional and HIV-related risk factors

Age, smoking, low body mass, high alcohol intake, glucocorticoid use, hypogonadism and postmenopausal status are recognized contributors to low BMD and fracture risk in the general population [8,36]. Among PLWH, studies have also identified associations with hepatitis C coinfection, lower nadir CD4 count, longer disease history and ART exposure, although not every association is independent of confounding [6,37]. A meta-analysis of HIV-hepatitis C coinfection reported that low BMD was more prevalent in coinfected individuals than in those with HIV alone (pooled OR 1.98; 95% CI 1.18-3.31) [38]. Low body mass is particularly influential: in male veterans, adjustment for BMI attenuated the association between HIV and fragility fracture to a hazard ratio of 1.10 (95% CI 0.97-1.25) [13]. Bone density itself remains informative within HIV populations, since in a cohort of men aged 49 years or older with or at risk for HIV, incident fracture rates rose from 1.4 per 100 person-years with normal BMD to 3.6 with osteopenia and 6.5 with osteoporosis [28]. Chronic kidney disease and renal phosphate wasting may contribute to defective mineralization and can complicate the diagnosis of osteoporosis [39]. Skeletal risk assessment should therefore include medical history, medication review, physical function and social context.

Risk profiles vary across sex, menopausal status, age and geography, so a single screening approach may miss people with elevated risk. In the Women's Interagency HIV Study, overall fracture rates did not differ significantly between women with HIV and women without HIV (1.79 versus 1.41 per 100 person-years; P = 0.13), but a history of an AIDS-defining illness and older age were associated with higher fracture risk among women with HIV [40]. Postmenopausal women may experience overlapping effects of estrogen deficiency and HIV-related factors, while men with hypogonadism or low body mass may also have substantial risk [11]. Reduced access to DXA, specialist services and osteoporosis medicines may lead to underdiagnosis in resource-constrained settings, and risk scores developed in one country may not be perfectly calibrated in another because background fracture rates and population characteristics differ [12,41]. The practical conclusion is to combine validated tools with clinical judgment and locally appropriate care pathways.

Molecular Mechanisms of HIV-Associated Bone Loss

RANKL-RANK-OPG signaling

The RANKL-RANK-OPG axis is a core regulator of osteoclast differentiation and activity [20,42]. RANKL binds RANK on osteoclast precursors and activates intracellular pathways, including NF-κB and NFATc1, that support osteoclast formation and bone resorption [20]. OPG acts as a soluble decoy receptor that limits RANKL availability and thereby restrains osteoclastogenesis [42]. Inflammatory states can alter the balance among these signals, creating a plausible connection between chronic immune activation and skeletal remodeling [18,19]. In HIV infection, dysregulated expression of RANKL and OPG by B cells has been correlated with loss of BMD [21], and the initiation of ART has been linked to T-cell reconstitution and increased osteoclastic signaling in both patient samples and animal models [22]. Evidence from the general osteoporosis field supports the centrality of this pathway, because blockade of RANKL with a monoclonal antibody reduces fracture incidence in postmenopausal women [30]. This provides a rationale for examining whether the same pathway is disproportionately activated in HIV-associated bone loss, although such a hypothesis

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requires HIV-specific confirmation. The mechanistic result is that a shift toward RANKL-mediated signaling can favor resorption over replacement.

Activated T cells and B cells can influence osteoclast activity through cytokine secretion and expression of RANKL or OPG, although effects depend on cell state and local context [18,43]. TNF-α and M-CSF, together with RANKL, are indispensable for osteoclast differentiation in inflammatory bone resorption, whereas regulatory cytokines such as IL-4, IL-10 and the interferons restrain excessive activation [44]. Persistent immune activation can continue despite effective plasma viral suppression, meaning that an undetectable viral load does not necessarily indicate complete normalization of every inflammatory pathway [43,45]. However, circulating cytokines or RANKL/OPG ratios are not yet validated as standalone clinical predictors of fracture in PLWH [12,26]. In practice, this means that the same cytokine may be pro-resorptive in one setting and neutral or protective in another, which complicates the interpretation of single time-point plasma measurements. Cross-sectional associations between a circulating mediator and BMD also cannot distinguish cause from consequence, since bone turnover itself releases factors into the circulation [43,44]. The conclusion is that osteoimmune signaling is biologically credible but requires stronger prospective validation before it can serve as a clinical biomarker.

HIV proteins and osteoclast activation

Experimental studies have investigated HIV proteins as potential modulators of osteoclast differentiation and bone-cell function. The gp120 envelope glycoprotein has been reported to promote osteoclastogenesis through RANKL secretion, an effect that was modulated by interferon-γ and certain protease inhibitors *in vitro* [23]. Studies in cultured human osteoblasts have also shown that HIV proteins can alter bone-marker secretion and transcription-factor activity, with potential implications for osteoblast function and development [24]. Reported cellular effects depend on the experimental model, protein concentration and exposure conditions [26]. Such experiments can establish mechanistic plausibility but do not determine how much each viral protein contributes to fracture risk in treated patients, in whom plasma viral replication is suppressed and viral proteins are present at far lower concentrations. Clinical interpretation must also account for ART, immune status, age and conventional risk factors that coexist with HIV infection [11].

Bone remodeling involves communication among osteoclasts, osteoblasts, osteocytes and marrow stromal cells, so viral effects on one cell population may indirectly influence others [18]. Inflammatory cytokines can modify cell survival and differentiation and may amplify changes initiated by viral proteins [44]. Human studies need to connect mechanistic signatures to longitudinal changes in BMD, bone quality and incident fractures; the available clinical evidence for ART-induced bone loss points to a prominent role for T-cell reconstitution in the early period after treatment initiation [22]. Prospective work should distinguish the effects of active viral replication from persistent immune dysregulation under suppressive ART [43]. Osteocytes, which constitute the majority of bone cells, are a major source of both RANKL and sclerostin and therefore integrate mechanical and inflammatory signals; their behavior in HIV infection remains comparatively understudied [19,46]. Addressing this gap would help determine whether skeletal effects arise predominantly from altered resorption, from altered formation, or from the uncoupling of the two. Mechanistic complexity therefore requires studies that link molecular readouts with clinically meaningful skeletal outcomes, rather than relying on isolated *in vitro* observations.

Osteoblast dysfunction and Wnt/β-catenin signaling

Osteoblasts build new bone matrix, and impaired osteoblast differentiation can reduce the replacement of bone removed during normal remodeling [46]. Mesenchymal stromal cells can differentiate into osteoblasts or adipocytes, making lineage allocation a potential determinant of marrow and skeletal health [26]. Wnt/β-catenin signaling supports osteoblast differentiation and bone formation, while inhibitory signals such as sclerostin can suppress this pathway, which is the rationale for anti-sclerostin therapy in osteoporosis [32,46]. Inflammation, oxidative stress and altered cellular signaling have been proposed as contributors to impaired osteogenesis in HIV-associated bone disease [24,26]. Bone formation is also coupled to resorption through signals released during remodeling, so a sustained increase in osteoclast activity does not simply produce a mirror-image rise in osteoblast activity; when coupling fails, net bone loss accelerates [46]. Review articles describe uncoupling of formation and resorption as a feature of HIV-associated bone loss, although the pattern differs between untreated infection and early ART [12,26]. The biological result is that excessive resorption and insufficient formation can act together to weaken bone.

Bone material strength and microarchitecture may provide information not captured by areal BMD measured using DXA. Micro indentation permits *in vivo* assessment of bone tissue resistance to a controlled impact, expressed as the Bone Material Strength Index (BMSi) [47], and HIV infection has been associated with worse bone material properties independently of BMD [48]. High-resolution peripheral quantitative computed tomography has similarly documented trabecular and cortical microstructural alterations in older men with HIV receiving successful ART [49]. The small HIV-specific TDF-to-TAF pilot trial reported a short-term improvement in BMSi without significant BMD changes; its design and results are described in Section 6.1 [25]. The small sample and short duration mean that this finding cannot establish reduced fracture incidence or long-term clinical benefit. Further studies should assess whether bone-quality measurements predict fractures beyond age, prior fracture, DXA and standard clinical variables. Bone quality is thus a promising research target, but it is not yet a substitute for established fracture assessment.

Endocrine, renal and nutritional pathways

Vitamin D deficiency, hypogonadism, renal disease and inadequate calcium or protein intake can contribute to skeletal

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abnormalities in PLWH [11,39]. TDF use has been associated with higher plasma vitamin D-binding protein and lower free calcitriol concentrations, a pattern that could produce a functional vitamin D deficiency and secondary hyperparathyroidism despite adequate total 25-hydroxyvitamin D [33]. Proximal renal tubular dysfunction associated with TDF may also lead to phosphate wasting and, in some cases, osteomalacia rather than uncomplicated osteoporosis [9,39]. Distinguishing osteomalacia from osteoporosis is important because the underlying pathophysiology and treatment approach differ. Low 25-hydroxyvitamin D concentrations are common in people with HIV [10], and measured values can be modified by season, skin pigmentation, latitude and antiretroviral drugs, which is one reason that single measurements should be interpreted cautiously; in the TDF-to-TAF pilot, for example, vitamin D levels fell significantly in both arms between baseline and week 24, which the authors attributed to seasonal variation [25]. Laboratory tests should therefore be selected in response to risk factors and clinical findings rather than ordered indiscriminately for every patient, and correctable secondary causes should be identified before long-term osteoporosis therapy is initiated [10].

Calcium and vitamin D intake should be assessed in the context of diet, deficiency risk, kidney function and relevant clinical guidelines [36,50]. In a randomized trial of adults starting ART, supplementation with vitamin D3 and calcium attenuated the bone loss that followed treatment initiation [51], which supports supplementation when deficiency or inadequate intake is identified; however, supplements alone do not replace fracture-risk assessment or indicated pharmacotherapy. Serum calcium, phosphate, alkaline phosphatase, renal indices and parathyroid hormone can help investigate selected secondary causes, but they are not sensitive universal screening tests for low BMD [10]. Medication review should consider glucocorticoids and other drugs that can impair bone health as well as ART [11]. Dietary calcium requirements and the safe upper limit of supplementation depend on age, sex and kidney function, and excessive calcium supplementation can increase the risk of nephrolithiasis, which is relevant for people who are also receiving tenofovir-containing therapy [39,50]. The clinical conclusion is that targeted investigation is more useful than blanket laboratory testing.

Osteoimmunology and Cellular Crosstalk

T cells, B cells and myeloid-lineage cells

Bone marrow is both a hematopoietic environment and a site where immune cells communicate with osteoblasts, osteoclast precursors and stromal cells [18,19]. Activated T cells can express RANKL and release cytokines that affect osteoclast formation, while B cells may contribute either pro-resorptive or regulatory signals depending on their state [21,43]. Monocyte/macrophage-lineage cells are precursors of osteoclasts and may respond to inflammatory mediators generated during chronic infection [20,44]. These interactions create a local remodeling environment influenced by systemic immune status. In the setting of ART initiation, the expansion and activation of T cells that accompanies immune reconstitution has been proposed as a driver of the early bone resorption observed after treatment starts [22], and lower pre-treatment CD4 counts predict greater subsequent BMD loss [14]. Immune-cell composition and activation state can therefore shape bone turnover in both untreated and treated infection.

Immune effects are not uniformly destructive, because regulatory T cells and anti-inflammatory mediators can restrain osteoclastogenesis in particular contexts [44]. The net skeletal effect depends on cytokine concentration, cell source, timing and concurrent signals rather than one isolated inflammatory marker [18,44]. Broad immune suppression solely to improve BMD would therefore be inappropriate without evidence of benefit and a clear safety rationale [43]. Interventions should preserve antiviral defense and account for the infection risks relevant to people receiving HIV treatment [17]. An important implication is that biomarker panels should capture both pro- and anti-resorptive mediators; a rise in one inflammatory cytokine, in the absence of information on its regulatory counterparts, is a poor guide to the net effect on bone [46].

Gut barrier, microbial translocation and inflammation

Gut barrier dysfunction and microbial translocation have been studied as contributors to persistent immune activation in HIV; translocation of microbial products from the gut was associated with systemic immune activation in chronic infection [52], and markers of gut epithelial barrier dysfunction and innate immune activation predicted mortality in people with treated HIV [45]. Innate immune activation can influence cytokine pathways that also regulate osteoclast differentiation, providing a plausible indirect gut-bone link [43,44]. However, direct evidence that a particular microbiome signature predicts fractures in PLWH remains insufficient for clinical use [26]. Mechanistic bridges between the gut and bone have been proposed in general osteoporosis research, but the extent to which they operate in people with HIV who are virally suppressed has not been tested directly. Differences in diet, antibiotic exposure and enteric infection between HIV-positive and comparison groups further complicate observational comparisons. Associations from animal models or general-population cohorts should not be assumed to have the same magnitude in treated HIV. The current conclusion is that microbiome research is hypothesis-generating rather than an established basis for bone treatment.

Longitudinal studies could combine microbiome profiles with ART exposure, inflammatory markers, bone turnover, DXA and fracture outcomes [43]. Analyses should account for diet, antibiotics, geography, gastrointestinal illness, smoking and medication use because these factors can alter microbial communities. Intervention trials would be needed to determine whether microbiome-directed treatment changes bone outcomes rather than only surrogate inflammatory markers [12]. Studies should prespecify clinically meaningful endpoints and report null findings to limit selective interpretation. Sampling strategy also matters: stool, mucosal biopsy and plasma markers capture different aspects of gut-immune interaction, and none has been validated as a predictor of fracture. A pragmatic first step would be to embed microbiome and translocation measurements within existing cohorts that

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already collect DXA and fracture data, rather than to establish new, underpowered cohorts, so that associations can be tested against hard skeletal outcomes with adequate statistical power [5,45]. A gut-bone mechanism must therefore be demonstrated in humans before microbiome interventions are recommended.

Systems biology and bone quality

Bone strength depends on mineral density, cortical and trabecular architecture, collagen and mineral properties, skeletal geometry and mechanical loading [8,47]. Because HIV and its comorbidities can influence several of these dimensions simultaneously, BMD alone cannot describe the entire skeletal phenotype [48,49]. Muscle strength, falls, mobility and medication exposure also influence whether reduced skeletal strength becomes a clinical fracture [11]. A systems approach can therefore combine clinical risk factors with imaging, selected laboratory evaluation and functional assessment [10]. This view is consistent with the observation that most fractures in the general population occur in people who are above the densitometric threshold for osteoporosis, and that the excess fracture risk in PLWH is only partly accounted for by BMD [5,8]. Material properties of the bone matrix, microdamage accumulation and the geometry of the proximal femur are plausible additional contributors that standard DXA does not capture [25]. Multidimensional assessment is biologically appropriate, while each added test must prove clinical value.

Multi-omics may eventually identify patterns associated with high resorption, low formation, renal-mineral disturbance or accelerated ageing [26]. High-dimensional datasets are vulnerable to overfitting, batch effects, missing data and poor generalization across populations. Any prediction model should be externally validated and tested against simpler baselines such as age, prior fracture, FRAX and DXA [41]. Cost, feasibility and equitable access should be considered alongside predictive accuracy. Before such approaches are adopted, they should be benchmarked in a staged manner: first, demonstration of analytical reproducibility; second, association with bone outcomes in an independent cohort; third, incremental predictive value over FRAX with BMD; and fourth, evidence that acting on the result changes outcomes [41,53]. Few candidate biomarkers in any field of bone disease have progressed beyond the second stage, and HIV-specific candidates are no exception. Equity is a further consideration, because molecular assays are least available in the regions where the burden of HIV is highest. Precision medicine should improve decisions without creating unnecessary complexity or unequal access.

ART and Skeletal Effects

TDF compared with TAF

Comparative ART studies and current guidance generally associate TDF-containing regimens with greater BMD decline than TAF-containing regimens [5,15,16]. In two pooled phase 3 trials of treatment-naive adults, the mean percentage change in BMD at 48 weeks was -1.30% versus -2.86% at the spine and -0.66% versus -2.95% at the hip for TAF versus TDF, respectively (both $P < 0.0001$) [15]. A randomized switch study in virologically suppressed adults, and a meta-analysis of randomized trials of single-tablet regimens for initial therapy, point in the same direction [51,52], and a trial of bictegravir, emtricitabine and TAF in people aged 65 years or older reported gains in BMD after switching from TDF-containing therapy [54]. The comparison with abacavir-based regimens and with TDF-sparing regimens is consistent: the ASSERT study reported differences in bone density and turnover favouring abacavir-lamivudine over tenofovir-emtricitabine [55], and the NEAT001 sub study compared BMD and bone biomarkers in treatment-naive adults receiving darunavir-ritonavir with either raltegravir or tenofovir-emtricitabine [56]. Nonetheless, BMD is a surrogate outcome, and a favorable BMD trajectory does not automatically establish fewer fractures [5]. The conclusion is to consider bone profile when selecting among clinically appropriate ART options, not to make regimen decisions from BMD alone.

Several mechanisms have been proposed for the skeletal effects of tenofovir. TAF is a prodrug that is activated largely inside target cells and yields approximately 90% lower plasma tenofovir exposure than TDF, which is the most likely explanation for its more favorable renal and bone profile [15,57,58]. In mice, tenofovir caused bone loss through reduced bone formation and increased bone resorption, and the effect could be counteracted by dipyridamole, a finding that implicates altered purinergic signaling [29]. In people taking TDF, higher vitamin D-binding protein and lower free calcitriol concentrations may further promote secondary hyperparathyroidism and resorption [33]. Taken together, these data suggest that the effects of TDF on bone are neither purely renal nor purely immune, and that regimen selection can modify one modifiable contributor to skeletal risk without eliminating the others.

In the 24-person pilot study, an open-label single-center trial conducted in Barcelona, virologically suppressed adults taking TDF-based regimens were randomized 1:1 to switch to bictegravir-TAF-emtricitabine or to continue TDF, with assessments at baseline and 24 weeks [25]. The TAF arm showed an increase in BMSi from a median of 81.6 to 86 (+5.1%; $P = 0.041$), whereas the TDF arm remained stable (82.35 to 82; $P = 0.812$), and the between-arm difference at week 24 was statistically significant ($P = 0.049$); BMD changes were not significant in either group [25]. Bone formation (P1NP) decreased in both arms, while the resorption marker CTX decreased by 10% only in the TAF arm ($P = 0.028$) [25]. Participants who switched to TAF also gained weight, and the change in weight correlated with the change in BMSi (Spearman $\rho = 0.510$; $P = 0.021$), so the contribution of body mass to the observed improvement cannot be excluded [25]. Because the study was small, brief and conducted at one site, it could not assess long-term fracture prevention or uncommon adverse outcomes. The result is a promising surrogate signal that warrants replication in larger studies with fracture, renal, bone-quality and patient-reported endpoints rather than a universal switching mandate.

ART initiation and immune reconstitution

Initiation of ART is often associated with an early decline in BMD, with changes frequently most evident in the first 24-48 weeks

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[9,14]. A decrease of approximately 2-6% over the first two years of therapy has been described across regimens, similar in magnitude to bone loss in the first two years of menopause [9]. Pooled estimates from a meta-analysis place the average change after one year at approximately -1.5% at both the lumbar spine and hip, and the two-year change at -1.8% and -2.5%, respectively [5]. The magnitude varies by regimen, baseline disease, patient characteristics and the skeletal measurement used: pre-treatment immune deficiency, older age, female sex, lower BMI, higher HIV-1 RNA, and assignment to a protease-inhibitor- or tenofovir-containing regimen were each associated with greater BMD decline in pooled trial data [14]. In the START bone sub study, immediate initiation of ART led to greater bone loss than deferral, consistent with a treatment-initiation effect that is partly separable from the effect of untreated infection [59]. These skeletal effects must be weighed against the substantial individual and public-health benefits of prompt effective ART. The clinical lesson is to recognize bone risk early while maintaining effective HIV treatment.

People with prior fragility fracture, established osteoporosis, renal tubular dysfunction or several concurrent risk factors may warrant closer assessment when ART is selected or reviewed [10,60]. Observational analyses link cumulative exposure to TDF with higher osteoporotic fracture risk [61], and a large international cohort examined associations between specific antiretrovirals, fractures and osteonecrosis [37], although residual confounding by disease severity and prescribing patterns cannot be excluded in either design. Guidelines for ART therefore advise that skeletal risk be considered, alongside virologic history, resistance, renal function, interactions, adherence and cost, when a regimen is chosen [16]. A single DXA value should not be used in isolation to dictate ART changes, and any switch must preserve viral suppression. The result is an individualized medication review coordinated between HIV and bone-health clinicians.

Polypharmacy and comorbidity

Glucocorticoids and other medications can add to skeletal risk, while kidney disease, diabetes, liver disease and hypogonadism may act as competing or interacting causes [8,11]. Observational associations between a particular ART class and fracture may be confounded by disease duration, historical prescribing and baseline comorbidity [6,37]. Medication reconciliation should therefore consider cumulative exposure, the indication for each drug and clinically suitable alternatives. Effective ART should not be stopped without an appropriate alternative because the consequences of loss of viral control can outweigh uncertain skeletal benefits [17]. Individual drug classes illustrate this complexity. Proton-pump inhibitors, anticonvulsants, aromatase inhibitors and long-term systemic glucocorticoids are all recognized contributors to bone loss in the general population, and each may be prescribed to PLWH for reasons unrelated to HIV [8,50]. A structured medication review at the time of fracture-risk assessment is therefore a low-cost intervention that can address a modifiable cause. Bone-focused prescribing must therefore be coordinated and evidence-based, with explicit documentation of the reason for any regimen change.

Before osteoporosis medication is initiated, clinicians should review renal function, calcium and vitamin D status, prior fractures, dental history and relevant contraindications [36,50]. Renal impairment may alter the safety or selection of particular antiresorptive agents and may indicate a need to investigate mineral and bone disorder [39]. Shared decision-making should include dosing burden, adverse effects, cost, follow-up and the patient's preferences [50]. Coordination among HIV clinicians, primary care, endocrinology, rheumatology and pharmacy can reduce fragmented treatment decisions [17]. Dental assessment is relevant because osteonecrosis of the jaw, although rare, is associated with antiresorptive therapy and is more likely after invasive dental procedures [8]. Baseline calcium, creatinine and 25-hydroxyvitamin D should be documented before treatment, so that hypocalcaemia and renal impairment can be anticipated and monitored after initiation [50]. Safe care depends on the whole clinical picture rather than a single medication effect.

Clinical Assessment and Diagnostic Technologies

FRAX, DXA and vertebral imaging

Clinical risk assessment and DXA remain central tools for identifying people who may benefit from fracture-prevention intervention [10,36]. Expert recommendations advise screening for fracture risk as part of routine HIV care in older adults, and DXA for postmenopausal women, men aged 50 years or older and people at high risk of fracture at any age [10]; primary care guidance recommends baseline DXA in postmenopausal women and men aged 50 years or older [60]. FRAX, developed to estimate ten-year fracture probability from clinical risk factors with or without femoral-neck BMD, was not developed specifically for HIV populations and may not fully capture ART exposure, HIV-related factors or falls [10,41]. DXA measures areal BMD at the hip and spine and can refine fracture-risk estimates when used in an appropriate clinical context; in men with or at risk for HIV, fracture incidence increased stepwise with the DXA category [61]. A practical pathway therefore rests on history, validated risk assessment and targeted imaging.

Vertebral fractures may be clinically silent, so vertebral imaging can be considered when height loss, back pain or other clinical indicators raise suspicion [8,36]. A prior fragility fracture can signal high future risk even when a patient's BMD does not meet a densitometric osteoporosis threshold [5,8]. Risk assessment should consider age, falls, body weight, smoking, glucocorticoid use, renal disease, endocrine factors and ART history [11]. FRAX thresholds and DXA access should be interpreted according to local guidelines and individual circumstances [36,50]. Vertebral fracture assessment can be performed on modern DXA systems at low radiation dose, and identification of a previously unrecognized vertebral deformity may change the treatment category of a patient from moderate to high risk [8,36]. Because height loss is often under-recorded in routine clinics, simple measures such as periodic height measurement and a structured history of back pain can serve as inexpensive triggers for imaging. No single score or scan replaces clinical interpretation.

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Bone turnover markers and advanced imaging

Bone turnover markers such as CTX and P1NP may provide information about resorption and formation, and international working groups have recommended them as reference markers for fracture-risk prediction and treatment monitoring, but results can vary with fasting status, time of day, renal function and recent fracture [53]. High-resolution peripheral quantitative computed tomography can characterize aspects of cortical and trabecular microarchitecture that are not directly measured by standard DXA [49]. Bone micro indentation has been used in small HIV studies to estimate bone material strength, including the TDF-to-TAF pilot [25,48], and in a study of glucocorticoid-induced osteoporosis it detected changes in tissue properties before BMD changes were apparent [62]. These methods differ in cost, availability, normative reference data and validation against future fracture outcomes. Advanced tests should therefore be used selectively until their incremental clinical value is established (Figure 2).

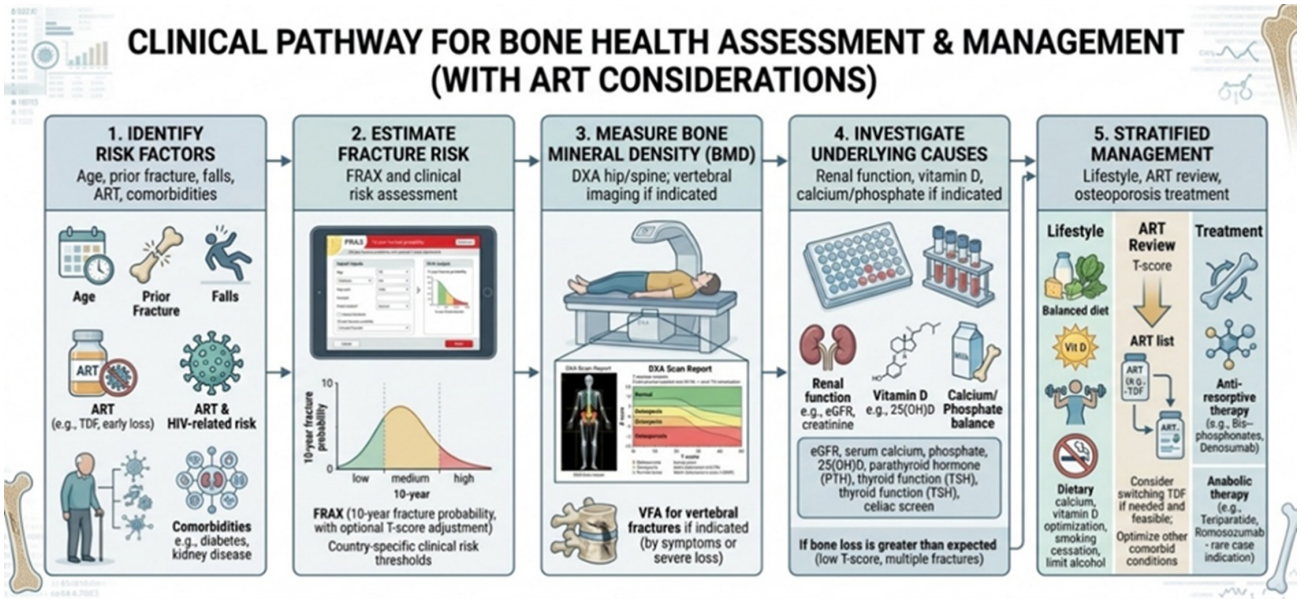

Figure 2: Practical pathway for fracture-risk assessment and management, based on contemporary HIV bone-health recommendations and osteoporosis guidance [10,36,60].

RANKL/OPG ratios, inflammatory cytokines, sclerostin and osteocalcin are plausible research biomarkers but are not validated as standalone routine screening tests for HIV-associated fracture risk [21,26]. Studies should standardize assays and establish whether markers add prediction beyond age, prior fracture, FRAX and DXA [41]. Biomarker studies should report assay methods, pre-analytical conditions and relevant renal or metabolic confounders [53]. External validation is essential before a molecular signature can guide therapy in populations different from the discovery cohort. The experience with micro indentation illustrates the distance between a promising measurement and a validated one: although it is sensitive to tissue-level changes, there are no HIV-specific reference ranges linking a given BMSi value to fracture probability, and the technique is available in few centers [25,47]. Standard clinical indices therefore remain the benchmark against which new tools must be compared. Biological plausibility is not enough for clinical adoption.

Established and Emerging Interventions

Lifestyle and nutrition

Weight-bearing and resistance exercise, adequate nutrition, smoking cessation, moderation of alcohol intake and fall prevention are foundational components of osteoporosis care [36,50]. Exercise plans should be adapted to mobility, comorbidities and prior fracture, with balance training considered when falls risk is elevated. Calcium and vitamin D intake should be assessed and deficiencies corrected when indicated; in a randomized trial among people starting ART, vitamin D3 and calcium supplementation attenuated bone loss [51], but indiscriminate high-dose supplementation should be avoided. These measures complement rather than replace pharmacotherapy when a patient meets treatment criteria [8]. Smoking cessation and alcohol moderation merit emphasis in HIV clinics because both are modifiable contributors to fracture risk [8]. Integrating brief behavioral counselling into routine HIV visits uses an existing, regular point of contact that few other chronic conditions enjoy. The result is a broad prevention platform with benefits beyond BMD alone.

Nutrition assessment should consider total protein and energy intake as well as calcium and vitamin D, especially in people with low body mass or dietary restriction, since low BMI was a major determinant of the HIV-associated fracture signal in a large veteran cohort [13]. Vitamin D and calcium may be relevant when deficiency or inadequate intake is present, but supplementation alone is not a substitute for diagnosis or osteoporosis treatment. Renal disease, nephrolithiasis risk and medication interactions should inform the supplementation plan [39]. Falls prevention may require

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review of sedating medicines, vision, footwear, home hazards and muscle strength. Lifestyle and nutrition advice should therefore be individualized rather than based on a uniform supplement prescription.

Bisphosphonates

Bisphosphonates have the strongest HIV-specific evidence among pharmacological osteoporosis treatments, with randomized studies and meta-analyses reporting improvement in BMD [5]. A randomized trial of annual zoledronate in men with HIV receiving ART increased BMD [63]. In a phase IIb trial of 63 non-osteoporotic, treatment-naive adults, a single 5 mg infusion of zoledronic acid given at ART initiation reduced the relative loss of BMD by about 74%, 65% and 56% at 12, 24 and 48 weeks, respectively, and was safe and well tolerated [64]. A follow-up analysis showed that the effect on bone resorption and BMD loss persisted for three years after a single dose [65]. Choice of agent and route should consider renal function, gastrointestinal tolerance, adherence and overall fracture risk [50]. Clinicians should assess for osteomalacia or secondary causes before treatment when the clinical history or laboratory findings raise concern [39]. Indicated osteoporosis should therefore be treated using established principles rather than withheld solely because a patient has HIV.

Direct HIV-specific evidence for fracture reduction and comparisons among newer therapies remains more limited than the evidence for BMD change [5]; the zoledronic acid studies were single-site proof-of-concept trials whose authors called for larger multicenter phase 3 confirmation [65]. Potential adverse effects and treatment duration should be discussed, including rare osteonecrosis of the jaw and atypical femoral fracture with prolonged exposure [8]. Bisphosphonates are generally not recommended in women of childbearing age because of concern about neonatal complications, which is one reason alternative agents have been explored in younger women [27]. Follow-up should assess adherence, tolerability, new fractures, falls and whether the patient's risk profile has changed [50]. In practice, the absence of fracture-endpoint trials means that treatment thresholds for PLWH are extrapolated from general-population guidelines [36,50], so clinicians must exercise judgment about when HIV-specific factors justify earlier assessment or treatment. Medication choice must therefore be paired with reassessment and safety monitoring.

Denosumab and RANKL inhibition

Denosumab inhibits RANKL and therefore targets a central signaling pathway in osteoclast formation [20]. In postmenopausal women with osteoporosis, denosumab reduced new vertebral fractures over 36 months in the FREEDOM trial [30], but that population did not include people living with HIV. HIV-specific evidence is limited to case-level experience, including a report of a 38-year-old woman with osteoporosis and vertebral fractures who received denosumab; the case and its four-year follow-up are summarized in Section 9.1 [27]. A single case cannot establish comparative effectiveness, quantify rare harms or demonstrate that the same outcome would occur in other patient groups. Potential concerns include hypocalcaemia, renal-mineral abnormalities and rebound bone turnover with multiple vertebral fractures after discontinuation or delayed dosing [66]. Denosumab may be considered in selected cases under specialist supervision, but HIV-specific evidence remains limited.

Future studies should enroll larger and more diverse PLWH populations and include fracture outcomes, calcium disturbances, infections and discontinuation strategies [27]. Renal function and mineral metabolism should be assessed because they can influence treatment safety [39]. A planned transition to another antiresorptive is recommended when denosumab is discontinued [66]. Trials should compare patient-important outcomes rather than rely solely on short-term BMD change [5]. Practical considerations include the six-monthly dosing schedule, which may suit patients with adherence challenges but also creates risk if appointments are missed; the need to ensure adequate calcium and vitamin D intake before each injection; and the requirement for a clear plan, agreed in advance, for what will follow if treatment is stopped [50,66].

Anabolic and sclerostin-directed therapies

Anabolic osteoporosis agents stimulate bone formation or relieve signaling that constrains osteoblast activity, offering a different approach from suppressing resorption [8]. Teriparatide reduced vertebral fractures in postmenopausal women with osteoporosis [31], and the anti-sclerostin antibody romosozumab reduced new vertebral fractures at 12 months compared with placebo in the FRAME trial [32]; sclerostin inhibition acts on the Wnt pathway discussed above [46]. HIV-specific trial evidence for these agents is limited, so treatment decisions generally rely on established osteoporosis indications and specialist assessment [5]. Contraindications, reproductive considerations, cardiovascular risk where relevant and the patient's overall fracture profile must inform selection [50]. Sequencing is a further consideration, since anabolic treatment is typically followed by an antiresorptive to consolidate gains in bone density, and the optimal sequence in PLWH is unknown [36,50]. The result is a potentially valuable but under-studied therapeutic area for PLWH.

Mechanism-informed research could test whether high-resorption and low-formation phenotypes respond differently to antiresorptive and anabolic approaches [43]. Biomarker-based treatment selection would require prospective validation and demonstration that it improves outcomes compared with standard clinical selection [53]. Early trials should report safety, adherence, changes in BMD and bone quality, and longer-term fractures where feasible. Researchers should avoid presenting experimental pathway targeting as established HIV-specific care. Trial design could follow an enrichment strategy in which participants with a high-resorption biochemical profile are randomized to an antiresorptive and those with a low-formation profile to an anabolic agent, with fracture, BMD and bone-quality outcomes compared against usual care. Such designs are ambitious and would require validated, standardized turnover markers, but they represent the logical test of whether mechanistic stratification improves on current practice [43,53]. Precision therapeutics should be developed without abandoning evidence-based safeguards.

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AI, digital health and precision monitoring

Digital systems could combine clinical history, ART exposure, laboratory data, DXA results and falls history to flag patients who may need further bone assessment [41]. AI-based imaging tools may help identify osteoporosis or vertebral fractures on images acquired for other reasons. A deep-learning model trained on 13,026 chest radiographs paired with DXA results was externally tested on a separate cohort of 1,089 radiographs and showed promising performance for opportunistic osteoporosis screening [67]; deep learning applied to hip radiographs with clinical covariates has been explored for osteoporosis classification [68]; and automated algorithms have been described for detecting vertebral compression fractures on CT [69]. None of these studies was designed specifically for PLWH, so models require external validation, calibration across demographic groups and evaluation of missing-data bias before implementation. AI outputs should support rather than replace clinician judgment and validated imaging interpretation. AI is promising as workflow support but is not yet a substitute for established assessment.

Prospective implementation studies should measure diagnostic yield, time to treatment, treatment uptake, equity, cost and incident fractures. Data governance should define consent, privacy, access controls, retention and responsibility for model updates. Models trained in one health system should not be assumed to perform equally well in another without local validation [67]. Clinically meaningful benefit must be shown beyond retrospective model accuracy. Early implementation can be piloted at low risk by running a model in the background, comparing its flags with clinician decisions without altering care, and reporting concordance, false-positive burden and the number of additional DXA referrals generated; this "silent" evaluation provides local performance data before any influence on treatment [67]. Safe implementation science is as important as technical performance.

Case Studies and Translational Examples

Published example: Denosumab case report

A published case report described denosumab use in a 38-year-old woman living with HIV who had osteoporosis and vertebral fractures. Over four years, BMD improved, no new fractures were reported, and neither HIV reactivation nor opportunistic infections were observed [27]. These patient details and the limits of the evidence are introduced in Section 8.3; the case should be interpreted as hypothesis-generating, not as evidence of comparative effectiveness or established safety in the wider HIV population.

The case illustrates the importance of considering age, fracture history, reproductive status, prior therapy and patient priorities when selecting treatment [27,50]. Future registries should record both positive and negative treatment courses, including discontinuation, adverse effects and incident fractures; the rebound vertebral fractures documented after denosumab discontinuation in the general population make this particularly important [66]. Comparative studies should determine whether denosumab offers advantages over bisphosphonates in defined HIV subgroups [5]. Treatment selection should remain consistent with specialist guidance and individual risk assessment [36]. The report also highlights a reproductive-health dimension of osteoporosis care in women with HIV that is often overlooked in guidelines written for postmenopausal populations: when treatment is required in a woman who may become pregnant, the usual first-line agents may be inappropriate, and specialist input and contraceptive counselling become part of the treatment decision [27]. Case evidence is informative but insufficient for broad treatment recommendations.

Published example: TDF-To-TAF pilot trial

The 2023 randomized pilot study enrolled 24 virologically suppressed adults with HIV receiving TDF-based ART and compared switching to bictegravir-TAF-emtricitabine with continuing TDF over 24 weeks [25]. Its main findings, including the BMSi increase in the TAF arm and the absence of significant BMD change, are described in Section 6.1. The trial illustrates that a bone-quality measure can change when conventional DXA does not show a significant difference, but its small sample and short follow-up do not establish fracture prevention or justify a universal ART-switch recommendation [25,62].

Clinicians may consider bone profile when selecting among equally effective ART regimens for patients with elevated skeletal risk [16]. Any switch must also account for virologic history, resistance, renal and metabolic status, drug interactions, access and patient preference [17]. Future trials should stratify by age, sex, menopause, prior fracture, baseline BMD and renal function, and should measure weight and body composition, given the correlation observed between weight gain and BMSi change [25]. Trials should capture incident fractures and patient-reported function as well as BMD and bone-quality endpoints [5]. The balance of considerations will differ between settings. In resource-limited health systems, TDF-based regimens remain widely used because of cost and availability, so the practical question is often how to monitor and mitigate skeletal risk during TDF exposure rather than whether to avoid it altogether. Surrogate findings must be balanced with the broader objectives of safe and durable HIV treatment.

Hypothetical risk-stratification vignette

Consider a hypothetical 58-year-old man with long-standing HIV, suppressed viral load, low body mass, prior smoking, chronic TDF exposure and a recent low-trauma wrist fracture. The combination of prior fragility fracture and modifiable risks would prompt clinical assessment, review of falls and medication history, and DXA when indicated [10,60]. Renal function, calcium and phosphate status, vitamin D and other secondary causes should be investigated when the history or clinical findings suggest a disorder of mineralization [33,39]. This vignette is illustrative and is not a real patient record or a prediction of treatment response. A sensible next step would be to calculate FRAX with the clinical risk factors available, recognizing that the tool may still underestimate risk in HIV, and to treat the prior wrist fracture as a sentinel event that independently increases the probability of future fracture [41]. A fracture should trigger a comprehensive evaluation even when viral replication is controlled.

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If osteoporosis or high fracture risk is confirmed, management may include indicated medication, correction of nutritional deficiencies, resistance and balance exercise, smoking cessation and falls prevention [36,50]. The HIV clinician should review whether an alternative to TDF is appropriate without compromising virologic effectiveness [16]. Referral may be required for vertebral imaging, endocrine evaluation or specialist osteoporosis management. Follow-up should assess adherence, adverse effects, falls, function and new fractures [17]. In this hypothetical case, the choice of therapy would depend on renal function, calcium and vitamin D status, dental health and patient preference, and the response should be reviewed with repeat DXA at an interval appropriate to the treatment chosen, together with clinical review of adherence and any new fracture or fall [50]. An integrated care plan is more actionable than a single BMD threshold.

Quantitative Evidence and Study Comparison

Quantitative evidence is useful only when its source population, outcome definition and follow-up are clear. The estimates below are reproduced from published sources and are not newly calculated pooled effects. Meta-analytic estimates, randomized-trial results and small pilot-trial outcomes answer different questions and should not be compared as if they were interchangeable. Clinical interpretation must distinguish relative risk, absolute prevalence, incidence rates and surrogate changes in bone measurements. Three cautions apply to the comparisons in Table 1. First, pooled estimates differ in their reference populations, some comparing PLWH with the general population and others with matched HIV-negative controls. Second, confidence intervals vary widely in width, as the hip-fracture estimates illustrate. Third, effects on surrogate endpoints, such as the percentage change in BMD, cannot be converted into expected fracture reductions without outcome data. The table provides a concise quantitative map of the evidence and its main limitations.

Emerging Biotechnology and Research Frontiers

Omics and biomarker-based phenotyping

Genomics, transcriptomics, proteomics, metabolomics and single-cell methods may help characterize biological subgroups with different patterns of bone remodeling [26,43]. Combining molecular profiles with ART history, immune markers, DXA, bone-quality measures and incident fractures could clarify why similar BMD values do not always imply similar fracture risk [5,25]. High-dimensional analyses can overfit small datasets and may be affected by batch effects, missing data and unmeasured confounding. Candidate markers must be tested in independent cohorts and shown to add value beyond simple clinical predictors such as those captured by FRAX [41]. Single-cell approaches in particular could resolve which immune and stromal populations in bone marrow respond to infection and ART, but the invasive nature of marrow sampling limits the sample sizes that can realistically be assembled in people with HIV [43]. Omics is therefore a discovery platform, not yet a routine clinical test.

The intended use of a biomarker must be defined as diagnosis, prognosis, treatment selection or monitoring because each purpose requires a different validation strategy [53]. Assay reproducibility, reference ranges, cost and feasibility are important for translation into routine care. Studies should evaluate whether biomarker-guided decisions improve fractures, function or quality of life rather than only changing a laboratory value. Negative studies and external validations should be reported to limit publication bias. For example, a prognostic marker intended to identify people at high risk of fracture should be evaluated by discrimination and calibration against incident fractures, whereas a monitoring marker intended to track the response to antiresorptive treatment should be evaluated by its within-person variability and its relationship to subsequent fracture reduction [53]. Translational success depends on clinical utility and reproducibility, not technological sophistication alone.

Targeted immune modulation

Inflammatory cytokines and RANKL signaling are plausible targets because they influence osteoclast formation and bone remodeling [18,44]. Systemic immune blockade can have infection and other safety consequences, making nonspecific immunosuppression inappropriate solely for low BMD [43]. Research should prioritize selective targets with a strong mechanism, suitable preclinical safety and measurable target engagement, such as the T-cell-dependent pathways implicated in early ART-associated bone loss [22]. Trials in PLWH should consider viral suppression, immune function, infection events and skeletal outcomes together [17]. Denosumab itself is, in effect, a form of targeted immune-bone modulation, since it neutralizes a molecule produced by activated immune cells as well as by osteoblast-lineage cells; this makes evaluation of RANKL inhibition in PLWH a logical first test of the pathway hypothesis [27,30]. The result is a cautious rationale for targeted research rather than current routine immune-directed treatment.

Potential strategies include selective modulation of osteoclast signaling, restoration of osteoblast differentiation and approaches targeting regulators of bone formation [44,46]. Evidence from other inflammatory diseases or postmenopausal osteoporosis may inform study design but cannot replace HIV-specific evaluation [30]. Early-phase trials should establish safety and target engagement before claims of fracture prevention are made. Long-term effects on infection risk, renal function and interactions with ART require planned assessment. Importantly, any intervention that modifies T-cell or cytokine signaling in a person with HIV must be evaluated for effects on viral reservoirs, immune reconstitution and susceptibility to opportunistic and bacterial infection, since the clinical benefit of ART depends on preserved immune competence [17,22]. Early-phase trials should therefore include prespecified immunological safety endpoints in addition to skeletal ones. Mechanism-driven innovation must be paired with disease-specific safety evidence.

Nanotechnology and targeted delivery

Bone-targeted nanocarriers and controlled-release systems are being explored across skeletal research as ways to alter drug distribution or local exposure. One example is an engineered

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exosome platform in which mesenchymal-stem-cell-derived vesicles were modified with a bone-targeting peptide and loaded with siRNA against Shn3 to deliver the cargo to osteoblasts in osteoporosis models [70]. Such concepts, including carriers directed toward bone mineral or osteoclast-lineage cells, remain preclinical and have not been evaluated for HIV-associated skeletal disease [70]. Translational barriers include biodistribution, immunogenicity, manufacturing consistency, toxicity and regulatory requirements. People with HIV may have additional complexities because immune-cell interactions, ART and renal or hepatic comorbidity can affect safety [17]. Targeted delivery is therefore a research opportunity rather than an established clinical intervention.

Preclinical work should establish pharmacokinetics, tissue distribution, immune effects and skeletal efficacy before human testing [70]. Studies should also investigate whether delivery systems interact with HIV reservoirs or alter immune-cell function. Early human studies should prioritize safety and target engagement rather than prematurely claiming fracture prevention. Clear development milestones and stopping rules can reduce the risk of translating weak preclinical signals. Regulatory expectations for novel delivery systems, including characterization of particle size, stability, batch-to-batch consistency and clearance, are substantial and add years to development timelines; sponsors and academic groups should plan for this burden early and should consider whether the same skeletal benefit could be achieved with existing, licensed agents at lower cost [70]. Nanotechnology should be advanced through staged and evidence-based development.

AI-Enabled imaging and decision support

AI may assist osteoporosis screening, vertebral-fracture detection, image triage and identification of patients who need a formal fracture-risk assessment [67,69]. Model performance should be evaluated across age, sex, ethnicity, body habitus, equipment and healthcare settings to identify bias, and external testing of the kind reported for chest-radiograph screening is a minimum requirement [67]. Retrospective accuracy alone does not establish that AI improves treatment uptake or prevents fractures. Clinical systems should preserve human review, provide interpretable outputs and document the basis for recommendations. In HIV care specifically, the data needed for such tools, including nadir CD4 count, cumulative exposure to specific antiretrovirals, renal function and prior fracture, are usually already recorded in electronic records, which makes integration technically feasible; the barrier is more likely to be validation, clinical workflow and trust than data availability. AI should augment validated clinical pathways, not replace them.

Prospective implementation studies should measure diagnostic yield, time to treatment, adherence, equity, cost and incident fractures. Data governance should specify consent, access controls, retention and accountability for software updates. Models should be recalibrated when deployed in a population or imaging environment different from the development dataset [67,68]. Patient-centered outcomes are required to establish whether a technically accurate model produces meaningful benefit. Equity audits should accompany deployment so that differences in performance by sex, ethnicity and age can be identified early, and so that tools trained largely on populations in high-income countries are not applied uncritically in regions where HIV is most prevalent [67]. Governance and implementation are essential components of safe clinical AI.

Future Recommendations

First, prospective multicenter cohorts should measure incident fractures alongside BMD, bone quality and turnover markers [5,49]. Data collection should include ART initiation and cumulative exposure, viral suppression, CD4 history, renal function, falls, muscle strength, menopause, smoking, alcohol, nutrition and coinfections [6,14]. Harmonized definitions of fragility fracture and consistent imaging protocols would improve comparability across studies. Research should include participants from low- and middle-income countries and report affordability and access barriers. Nested within such cohorts, repeated measurement of BMD, micro indentation or HR-pQCT, and turnover markers would permit direct tests of whether bone-quality indices predict fracture independently of DXA [47,49]. The result would be more reliable estimates of absolute risk and real-world burden.

Second, HIV-specific trials should evaluate osteoporosis treatments with adequate representation of women, older adults, renal disease and diverse geographic populations [17,40]. Outcomes should include fractures, adverse events, adherence, discontinuation, function, quality of life and cost-effectiveness alongside BMD [5]. Prospective registries can complement trials by capturing longer-term safety and treatment persistence, including outcomes after discontinuation of denosumab [66]. Investigators should distinguish efficacy in controlled conditions from effectiveness in routine clinical care. Non-inferiority designs comparing established agents such as zoledronic acid and denosumab may be more feasible than placebo-controlled fracture trials, which would require very large samples, and pragmatic trials embedded in HIV clinics could assess both effectiveness and implementation [65]. Patient-important outcomes and representation should be central design requirements.

Third, precision models should combine clinical variables with advanced imaging or biomarkers only when these additions improve prediction or decisions beyond standard care [41]. External validation, calibration, prespecified analysis and comparison against simpler baselines should be mandatory before clinical deployment [67]. AI and molecular tools should be evaluated for cost, privacy, interpretability and equitable performance. Research findings should be communicated with transparent uncertainty and reproducible methods. Reporting should follow established standards for prediction-model studies, including transparent description of missing-data handling, and the code and de-identified data supporting model development should be shared where privacy law permits. The result is a pathway toward precision prevention that remains evidence-driven.

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Fourth, HIV clinics should establish a practical workflow for risk identification, DXA referral, ART review, exercise and nutrition counselling, medication initiation and follow-up [10,60]. Local implementation studies should track referral completion, waiting times, treatment uptake and barriers to adherence. Digital reminders may improve workflow but should protect privacy and avoid adding unnecessary burden to patients. Care pathways should identify who is responsible for each action and when reassessment should occur. Simple process indicators, for example the proportion of eligible patients who have a documented fracture-risk assessment within a defined period, provide a practical way to audit performance and to demonstrate improvement [60]. Evidence reduces fractures only when it is delivered reliably.

Limitations

This manuscript is a narrative review rather than a registered systematic review, and it does not claim exhaustive capture of all eligible publications. Published numerical findings are reproduced from source studies and are not recalculated into new pooled estimates. Mechanistic evidence may derive from cell or animal models and therefore cannot establish the magnitude of a pathway's effect in humans [23,29]. Some treatment studies are small and rely on surrogate endpoints rather than incident fractures [25,65]. In addition, the evidence base is dominated by studies from high-income settings and by populations of predominantly men, so that conclusions for women, for adolescents and for people in sub-Saharan Africa, where most people with HIV live, rest on comparatively limited data [7,40]. Recommendations must therefore remain proportional to the strength and directness of available evidence.

Conclusion

HIV-associated bone loss and fracture risk arise from interacting biological, treatment-related and conventional determinants, and should be addressed as part of long-term HIV care. Meta-analytic evidence indicates an increased fracture burden among PLWH, with pooled relative risks of approximately 1.5 for fragility fracture and 4 for hip fracture, while molecular research links chronic immune activation, RANKL-RANK-OPG signaling, osteoclast activity and impaired bone formation to skeletal fragility. Comparative evidence generally shows a more favorable BMD profile with TAF than TDF, but improvement in a surrogate marker does not establish fracture prevention. The most defensible approach is to combine effective ART with individualized risk assessment, DXA when indicated, falls prevention, correction of secondary causes and established osteoporosis treatment. Bisphosphonates have the strongest HIV-specific treatment evidence, whereas denosumab, anabolic agents, advanced imaging, omics, AI and targeted delivery need further validation in appropriately designed studies. The future of care should be precision-informed but grounded in patient-important outcomes, safety, affordability and equitable implementation.

Conflict of Interest

Authors declare that they have no conflict of interest with this publication.

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