Adverse bone health among children and adolescents growing up with HIV

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Abstract

Adverse bone health is one of the important non-communicable conditions during the course of life-long HIV treatment. Adolescence is the critical period of bone mineral acquisition for attaining adult peak bone mass. With traditional and HIV-related risk factors, adolescents growing with HIV have a greater chance of having impaired bone mineral density (BMD). Prevalence of low BMD has been reported in 16–32% of HIV-infected adolescents from middle-income countries. The deep interaction between the immune and skeletal systems, called the immunoskeletal interface, is proposed as one of the underlying mechanisms of adverse bone health in HIV-infected individuals. Dual-energy X-ray absorptiometry (DXA) is a standard tool to assess BMD among HIV-infected adolescents. Non-invasive imaging techniques such as quantitative computed tomography (QCT) and quantitative magnetic resonance imaging (QMRI) provide more information on true volumetric density and bone microarchitecture. To date, there are no paediatric recommendations on the treatment and prevention of adverse bone health. Having a healthy lifestyle, routine weight-bearing exercises and adequate dietary intake are the standard approaches to optimise bone health. There are several ongoing randomised clinical trials using pharmacological treatment options, for example vitamin D, calcium and alendronate to improve bone health among this population.

Keywords: adverse bone health, bone mineral density (BMD), dual-energy X-ray absorptiometry (DXA), HIV-infected adolescents, immunoskeletal interface, non-communicable diseases (NCDs)

Introduction

The success of antiretroviral therapy (ART) has turned HIV/AIDS from a disease with a high mortality rate to a manageable chronic life-long illness. Treatment with ART can lead to restoration of immune function and sustained viral suppression, which in turn increases life expectancy for perinatally HIV-infected children and adolescents [1,2]. Currently, HIV-infected children are able to grow up and enter adolescence and young adulthood similarly to their healthy peers [3]. Yet, these individuals do experience several long-term, non-AIDS-related complications that are obstacles to the goal of normal life expectancy and quality of life. The emerging non-communicable diseases (NCDs) associated with HIV infection and antiretroviral treatment include adverse bone health, cardiovascular, liver and renal diseases, and other metabolic and endocrinological disorders [3–5]. Among these complications, adverse bone health has been recognised as an important area of investigation during the past decade in children and adolescents [6]. Since the maximum bone mineral accrual occurs during the first two decades of life [7], reduced bone deposition and increased bone resorption during these critical periods can lead to serious consequences, in particular, osteoporosis and bone fragility later in life [8,9]. This review focuses on current knowledge regarding adverse bone health among children and adolescents living with HIV, including the magnitude of the problem, immunopathogenesis and factors responsible for reduced bone mass, assessment of bone health in clinical practices and up-to-date research studies of management strategies to prevent bone loss and optimise bone health.

Prevalence of low bone mineral density among perinatally HIV-infected children and adolescents

Dual energy X-ray absorptiometry (DXA) is a commonly used technique to assess total body and lumbar spine bone mineral density (BMD) in children and adolescents. Because adults have already reached peak bone mass (PBM) [7], their BMD is assessed using T-scores. In contrast, BMD measurements in growing children need to be compared to healthy age-, sex- and race-matched population norms and are reported as Z-scores. BMD Z-scores less than or equal to −2 are regarded as low bone mass [10]. The prevalence of low BMD among perinatally HIV-infected children and adolescents is much higher in studies conducted in middle-income countries than that observed in resource-rich countries. The variation in prevalence might be explained by the differences in HIV clinical staging at time of ART initiation, duration of ART, lifestyles, nutritional status, food intake and dietary supplements across studies (Figure 1) [11–16].

Resource-rich countries

In a longitudinal study of 66 HIV-infected Dutch children with a median age of 6.7 years, almost all children (96%) were on ART for a median duration of 3.4 years and 58% had undetectable plasma viral load. The prevalence of lumbar spine and femoral neck BMD Z-scores below −2 were 8% and 4%, respectively. The median BMD Z-scores were 0.9 [interquartile range (IQR) −1.6 to 0.1] for lumbar spine and 0.5 (IQR −0.2 to 1.2) for femoral neck [11]. A large cross-sectional study was conducted among 350 HIV-infected adolescents living in the United States and Puerto Rico, with a median age of 12.6 years, median duration of ART 9.5 years and 55% with plasma HIV RNA <400 copies/mL. Similarly to the Dutch study, the prevalence of low BMD was 7% for total body and 4% for lumbar spine. This was higher than the low BMD prevalence in their uninfected peers of 2% for total body and 1% for lumbar spine [12]. Likewise, the Pediatric AIDS Clinical Trial Group (PACTG) 1045 found that post-pubertal HIV-infected adolescent males had significantly lower total body BMD [adjusted difference −0.10 g/cm2, 95% confidence interval (CI) −0.16 to −0.04 g/cm2] and lumbar spine BMD (adjusted difference −0.13 g/cm2, 95%CI −0.23 to −0.04 g/cm2), compared with HIV-uninfected males at similar Tanner stage [17].
Bone is not a static structure, but one that constantly undergoes bone remodelling involving bone resorption, by osteoclasts, and bone formation. Bone remodelling involves bone resorption, by osteoclasts, and bone formation, by osteoblasts. Osteoclasts are derived from monocyte and macrophage lineage. Differentiation and activity [40]. Osteoclasts are derived from mature cells of monocyte and macrophage lineage. Osteoclastogenesis requires the presence of RANK ligand (RANKL) and RANK interactions. RANKL is a receptor activator of nuclear factor \( \kappa B \) ligand expressed by osteoclastic lineage cells, while RANK is a receptor activator of nuclear factor \( \kappa B \) presented on the surface of osteoclast precursors and mature osteoclasts [41]. RANKL is recognised as a key osteoclastogenic cytokine and the final effector of osteoclast formation and activity [42–45]. Additionally, it is considered to have important immunological functions as a mediator for T cell proliferation and dendritic cell function [46,47]. The interactions between RANKL with RANK (RANKL–RANK system) induce the formation and activity of osteoclasts.

Pathogenesis of adverse bone health among HIV-infected population

Bone is a specialised supporting and protecting structure of the body. It contains two major components: calcium phosphate, a mineral compound that gives bone strength and rigidity; and collagen, a protein that provides a flexible framework [18,19]. Bone is not a static structure, but one that constantly undergoes longitudinal and radial growth, rebuilding and remodelling throughout life [18,20].

Bone remodelling involves bone resorption, by osteoclasts, and bone formation, by osteoblasts [18,20]. In general, bone formation predominates over bone resorption during childhood and young adulthood [20]. Thus, bone mass increases over time and reaches its peak during the third decade of life. Subsequently, bone remodelling becomes balanced between bone formation and resorption, resulting in stable bone mass with small variations [20]. Around 50 years of age, the rate of bone resorption begins to outpace that of bone formation, and thus bone mass declines [20].

Middle-income countries

There are four reports from Thailand [13,14] and Brazil [15,16]. The prevalence of low lumbar spine BMD among HIV-infected Thais was 16–24%. The median ages of Thai participants in these studies were 14.3–15.0 years. All of them were receiving stable ART for a median duration of 7.0–9.3 years; of whom 90–96% had virological suppression [13,14]. In a cross-sectional study among 48 HIV-infected Brazilian adolescents with a mean age of 12.7 years, the prevalence of low BMD was 17% for total body less head. Almost all participants (96%) were on ART, of whom 58% had plasma HIV RNA <50 copies/mL [15]. Another cross-sectional Brazilian study found a 32% prevalence of low BMD (total body and/or lumbar spine) among 74 HIV-infected adolescents with a mean age of 17.3 years. Approximately 91% of them received ART with a mean duration of 11 years, of whom 48% had undetectable virus [16].

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Changes in bone mass with the course of HIV disease

In HIV-infected individuals, the physiological regulation of bone remodelling can be disrupted by several factors: HIV itself, ART and other HIV-related factors [21–23]. Bone mass changes with the course of HIV disease. During the pre-treatment period, many conditions, for example wasting syndrome, disrupt immune system function through loss of CD4+ T and B cells [24,25].

Together with chronic systemic inflammation [26], this disturbs bone homeostasis. Untreated individuals tend to have raised inflammatory markers and dysregulated bone turnover compared with healthy individuals [27–29]. This finding supports the linkage between systemic inflammation and bone turnover imbalance, a likely cause of bone demineralisation in HIV-infected persons.

After ART initiation, HIV-infected persons usually have improved health status and restored immunological system function. Weight is regained and systemic inflammation is reduced [30]. However, such individuals may experience transient reduced bone mass and worsening of bone health during the first 1–2 years of ART [31–33]. Possible explanations are poor health status and wasting before ART initiation [21], ART causing an imbalance of bone turnover [34,35], and time lag between ART initiation and improvement of BMD [21,31]. Accelerated bone loss, as much as 2–6%, has been demonstrated in HIV-infected individuals on various ART regimens, including tenofovir disoproxil fumarate (TDF) [31], efavirenz (EFV) [32], nevirapine [33] and boosted protease inhibitors (PIs) [32,33]. In HIV-infected adults, both TDF and PIs have been associated with a 33% increase in osteocalcin (OC), a bone formation biomarker [34]. Another study demonstrated that switching to TDF vs staying on zidovudine resulted in a significant increase in both bone resorption marker, C-terminal cross-linked telopeptide of type I collagen (CTX) and bone formation markers, OC and procollagen type I amino-terminal propeptide (PINP), which correlate with reductions in lumbar spine BMD [35].

Immunoskeletal interface and bone health

In the context of untreated HIV infection, there are two concurrent and important alterations in bone health: progressive loss of immune function and accelerated bone resorption. Emerging evidence suggests that the immune and skeletal systems are deeply intertwined as a result of a centralisation of common cell types and cytokine mediators [22]. This is called the immunoskeletal interface (Figure 2). There is well-established evidence of the association between immune and skeletal systems observed in many inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus [36–38]. These immune alterations accelerate the natural skeletal ageing process, contributing to adverse bone health.

The immunoskeletal interface can be divided into two aspects: the interactions of immune cells with osteoblasts and with osteoclasts. Osteoblastic cells, derived from osteoprogenitor mesenchymal stem cells, are able to modulate the immune system by regulating the haematopoietic stem cell microenvironment in which immune cells are derived [39]. Immune cells can produce cytokine mediators, such as tumour necrosis factor-alpha (TNF–α), that functions as a potent inhibitor of osteoblast differentiation and activity [40]. Osteoclasts are derived from mature cells of monocyte and macrophage lineage. Osteoclastogenesis requires the presence of RANK ligand (RANKL) and RANK interactions. RANKL is a receptor activator of nuclear factor \( \kappa B \) ligand expressed by osteoclastic lineage cells, while RANK is a receptor activator of nuclear factor \( \kappa B \) presented on the surface of osteoclast precursors and mature osteoclasts [41]. RANKL is recognised as a key osteoclastogenic cytokine and the final effector of osteoclast formation and activity [42–45]. Additionally, it is considered to have important immunological functions as a mediator for T cell proliferation and dendritic cell function [46,47]. The interactions between RANKL with RANK (RANKL–RANK system) induce the formation and function of osteoclasts.
demonstrated by the disturbances of histomorphometric parameters and/or the dysregulation of biochemical markers of bone turnover. HIV infection is related to a high bone turnover state, as demonstrated in healthy individuals; however, the effects may be exaggerated in the HIV-infected population because they usually have significantly delayed linear growth and poor weight gains [71–74]. Although low vitamin D has been considered a traditional risk factor for poor bone health, there is no well-established evidence demonstrating the significant direct association between vitamin D deficiency or inadequate vitamin D intake and adverse bone health in HIV-infected adolescents [13,14,60]. Similarly, the evidence for inadequate calcium intake as a determinant of reduced bone mass is limited and controversial in this population [14,60,61]. A cross-sectional study among 19 HIV-infected girls whose calcium intake was 20–50% lower than the recommended daily allowance hypothesised that suboptimal calcium intake might lead to the increased bone resorption and impaired bone mineral acquisition [61]. In contrast, two cross-sectional studies carried out in Brazil and the United States did not find such an association [15,60]. Calcium supplementation may be only beneficial to individuals with insufficient calcium intake.

The relationship between weight-bearing physical activity and bone health among HIV-infected youth was demonstrated in a few studies [12,15,62]. The challenge of these studies is the best measure for physical activity level. Self-report and questionnaires are used by some [12,62], while an accelerometer is used by others [15].

Traditional risk factors

Weight and height are independently associated with bone mass in healthy individuals; however, the effects may be exaggerated in the HIV-infected population because they usually have significantly delayed linear growth and poor weight gains [71–74]. Although low vitamin D has been considered a traditional risk factor for poor bone health, there is no well-established evidence demonstrating the significant direct association between vitamin D deficiency or inadequate vitamin D intake and adverse bone health in HIV-infected adolescents [13,14,60]. Similarly, the evidence for inadequate calcium intake as a determinant of reduced bone mass is limited and controversial in this population [14,60,61]. A cross-sectional study among 19 HIV-infected girls whose calcium intake was 20–50% lower than the recommended daily allowance hypothesised that suboptimal calcium intake might lead to the increased bone resorption and impaired bone mineral acquisition [61]. In contrast, two cross-sectional studies carried out in Brazil and the United States did not find such an association [15,60]. Calcium supplementation may be only beneficial to individuals with insufficient calcium intake.

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HIV-specific factors

HIV per se is one factor for bone abnormalities. Higher prevalence of bone demineralisation was reported among treatment-naive HIV-infected adults compared with HIV-uninfected controls [75]. HIV infection is related to a high bone turnover state, as demonstrated by the disturbances of histomorphometric parameters and/or the dysregulation of biochemical markers of bone formation and bone resorption, for example significant increases in levels of RANKL and OPG [28,29,76].

Advanced HIV disease, uncontrolled viraemia and poor immunological status are predictors of adverse bone health among HIV-infected children and adolescents [11–16,63,64].

Figure 2. The immunopathogenesis and risk factors of low BMD among HIV-infected children and adolescents.

- Represents the immunoskeletal interface
- Represents important risk factors of low BMD
- Represents components of the immune system
- Represents components of the skeletal system

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Advanced HIV disease, uncontrolled viraemia and poor immunological status are predictors of adverse bone health among HIV-infected children and adolescents [11–16,63,64].
Individuals with severe clinical symptoms of HIV had a significant impairment of BMD, evaluated by DXA [14] and quantitative high-frequency ultrasound (QUS) techniques [63]. High plasma HIV RNA also correlated with low bone mass [11,12]. A positive correlation between current CD4 percentage and BMD/bone mineral content (BMC) was observed in HIV-infected youth [11,64].

Several studies demonstrated a significant linkage between ART exposure and reduced bone mass [12,13,15–17,62,66–70]. These were either performed in treatment-naïve patients [31–33,62,65] or treatment-experienced patients who switch treatment because of poorly controlled viraemia [69]. Although early loss of bone mass within the first 1–2 years of ART initiation has been observed in treatment-naïve adults and adolescents [31–33,62,65], there are no data in young children. Significant bone abnormalities after ART switching have also been demonstrated in children and adolescents [69]. Early bone loss is observed during the first 24–48 weeks of TDF but remained stable thereafter. Such an effect is, however, not detected among treatment-experienced children with stable clinical status and controlled viraemia prior to switch to TDF [77]. Tenofovir alafenamide (TAF), a prodrug of TDF, has a more favourable bone safety profile. Two randomised clinical trials in HIV-infected adults demonstrated significantly less bone toxicity (mean change of lumbar spine BMD: −1.3% vs −2.9%, P < 0.0001; total hip BMD: −0.7% vs −3.0%, P < 0.0001) among adults receiving TAF vs TDF in combination with elvitegravir/cobicistat/eminicitabine [78].

Consequences of adverse bone health in perinatally HIV-infected children and adolescents

Childhood and adolescence represent the critical periods for bone mineralisation and maturation, and at least 90% of final adult bone mass is achieved during these periods [79]. Any factor impairing bone mineral acquisition may diminish bone gain, induce bone loss and compromise adult PBM [7,80]. From two meta-analyses, the prevalence of osteopenia and osteoporosis among HIV-infected adults was 52–67% and 15%, respectively [81,82]. A study conducted in a large United States cohort reported higher prevalence of overall fracture in the HIV–infected group compared with uninfected controls (2.87 vs 1.77 patients with fractures per 100 persons) [8]. Furthermore, the HIV Outpatient Study revealed that the adjusted fracture rate among HIV-infected adults increased from 57.7 to 89.9 per 10,000 population between the years 2000 and 2008, respectively, and that it was 49.6–72.9% higher than in the uninfected population over the study period [9]. However, an increased risk of fracture events among HIV-infected children and adolescents has not been documented. A prospective cohort PACTG219/219C study, which followed more than 1,000 HIV–infected children for a median of 5 years showed a similar incidence rate of fracture among HIV-infected compared with HIV-exposed but uninfected children (1.2 vs 1.1 per 1,000 person-years) [83]. Since fracture is a long–term complication of adverse bone health, these populations may be too young to demonstrate the increase in the incidence of this condition.

Measurements to assess bone health in HIV-infected children and adolescents

Standard measurement in clinical practice

DXA is a non-invasive imaging technique that uses two X-ray beams with different photon energy levels aimed at the bone to be measured. The BMD can be determined from the absorption of each beam by bone once soft tissue absorption is subtracted. DXA is the most commonly used bone densitometric technique for children and adolescents throughout the world [10]. The measurements provided include bone mineral content (BMC, grams) and areal bone mineral density (BMD, g/cm²). The most appropriate skeletal sites for performing densitometry in children and adolescents are posterior–anterior (PA) lumbar spine and total body less head [10]. Compared with conventional radiographs, measurement of the spine provides more information about the trabecular bone status, while total body measurement focuses more on cortical bone status [84]. In children with short stature or delayed growth, the areal BMD and BMC should be adjusted in order to eliminate the influences of bone size and skeletal dimension. For total body less head, adjustment should be performed using the height Z-score. For the spine, adjustment can be made by using either bone mineral apparent density (BMAD) or the height Z-score [10]. According to the 2013 International Society for Clinical Densitometry (ISCD) Pediatric Official Positions, an areal BMD Z-score less than or equal to −2.0 SD is described as low bone mass or BMD [10,85].

Advanced measurements in research settings

During the past decade, the concept of bone strength has encompassed a number of bone characteristics, including trabecular and cortical architectures, bone turnover, mineralisation and cellularity, aspects of bone quality [86–88]. Summary of advanced techniques for assessing bone health are shown in Table 1.

Bone histomorphometry is a histological examination of bone biopsy specimens to obtain qualitative and quantitative information on in vivo bone structure and remodelling. It is the gold standard for bone metabolic and mineralisation evaluation [89,90]. Currently, there are non-invasive imaging techniques using three-dimensional reconstruction for bone microstructure and microarchitecture analysis [91]; therefore bone biopsy is frequently avoided.

Quantitative ultrasonography (QUS) is a non-invasive method using high–frequency sound waves that are transmitted through bone to assess the bone quality and strength. The longitudinal sound wave transmitted through the calcaneus is the accepted measurement to determine bone health status [92].

Quantitative computed tomography (QCT) is a three–dimensional imaging technique to assess true volumetric density (mg/cm³) without the overlapping of other tissues [93]. This technique ranges from a volumetric QCT to advanced imaging modalities such as high–resolution CT (hrCT) and microCT. Currently, there is no preferred QCT method for clinical evaluation in children and adolescents [94]. Most QCT studies in children investigated peripheral sites, primarily the radius and tibia, because of radiation exposure concerns [94]. The advantage of QCT over DXA is that it provides a separate analysis of trabecular or cortical components of bone.

Quantitative magnetic resonance imaging (QMRI) is a non–invasive, non-ionising radiation technique that provides three-dimensional imaging of trabecular bone architecture. Magnetic resonance is based on the application of a strong magnetic field and a series of radiofrequency waves to generate three-dimensional images of the hydrogen protons in the water within skeletal tissues [88].

Biochemical markers of bone turnover are helpful research tools to reflect the ongoing bone remodelling processes. Currently available markers are classified into biochemical markers of bone
formation and resorption [95–98]. Biomarkers of bone formation are products of active osteoblasts expressed during different developmental stages, including: (i) osteoblast-specific enzymes such as bone-specific alkaline phosphatase (BALP); (ii) osteoblast-related proteins such as OC; and (iii) by-products of collagen synthesis such as PINP. All can be measured in serum or plasma [95–98]. The biomarkers for bone resorption are classified into: (i) osteoclast-specific enzymes such as tartrate–resistant acid phosphatase (TRACP) 5b; and (ii) collagen degradation products such as hydroxyproline, pyridinoline, deoxypyridinoline, CTX, and N-terminal cross-linked telopeptide of type I collagen (NTX) [95–98]. The measurements can be performed from blood or urine.

**Bone–health assessment in HIV-infected children and adolescents in clinical practice**

The recommendations for the evaluation and management of bone disease in HIV-infected adults have recently been developed by HIV specialists from 16 countries [103]. Screening for adverse bone health depends on an individual’s risk for fragility fracture. For individuals with major risk factors, including a previous history of fragility fracture; receipt of glucocorticoid treatment for more than 3 months; and at high risk for falls; BMD assessed by DXA should be performed. Additionally, DXA, if available, is recommended for all men aged >50 years, postmenopausal women and individuals with a 10-year risk of major osteoporotic fracture >10% by the Fracture Risk Assessment Tool (FRAX) score. For those without major risk factors, including men aged 40–49 years and premenopausal women aged ≥40 years, FRAX (without DXA) is the recommended assessment [103]. FRAX is a prediction tool for assessing an individual’s fracture risk and is applicable for people aged between 40 and 90 years. The model incorporates several components such as age, race, sex, body mass index, smoking, alcohol consumption, long-term use of glucocorticoids, vitamin D deficiency, prior fragility fracture and parental history of hip fracture into the calculation [103]. Therapeutic management guidelines vary by country and are based on the availability, as well as cost of diagnostic tools and medications. In the United States, anti-osteoporosis treatments are prescribed in individuals presenting with hip or vertebral fracture, osteoporosis (T-score no more than −2.5), or osteopenia (T-score between −1.0 and −2.5) with a 10-year probability of hip fracture ≥3% or major osteoporosis-related fracture ≥20% based on FRAX [104]. The follow-up interval of DXA should be

| Table 1. Methods for assessment of bone health in HIV-infected children and adolescents |
|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Method of assessment**                      | **Advantages**                                   | **Disadvantages**                               | **Clinical data from HIV-infected children and adolescents** |
| Dual–energy X-ray absorptiometry (DXA)        | Widely available                                 | Subject to systematic errors                    | HIV-infected adolescents had high prevalence of BMD Z-score s−2 (16–32%) in middle–income countries [13–16] |
|                                               | Safe                                            | Cannot differentiate cortical and trabecular bones | BMD and BMC of HIV-infected adolescents is significantly lower than healthy controls [12,14] |
|                                               | Excellent precision                             | Limited paediatric normative data references    |                                                   |
|                                               | High reproducibility                            |                                                   |                                                   |
|                                               | Examination time 5 minutes                      |                                                   |                                                   |
| Speed of sound (SOS) and broadband ultrasound attenuation (BUA) | Radiation free                                 | Limited skeletal site of measurement | HIV-infected children with severe clinical symptoms had lower calcaneal BUA Z-score [63] and phalangeal SOS [99] compared with healthy controls |
|                                               | Portable and simple to operate                  | Lack of paediatric normative data for interpretation | Tibial and radial SOS were associated with lumbar spine BMC and BMD, and total body BMC and BMD [100] |
|                                               | Correlates well with DXA                        |                                                   |                                                   |
|                                               | Cost-effective                                  |                                                   |                                                   |
| Quantitative ultrasonography (QUS)            | More accurate assessment of BMD than DXA        | High radiation dose                              | Similar vertebral volumetric bone density in HIV–infected children compared with controls [101] |
|                                               | Provides separate analysis of cortical and trabecular bones | High cost | DXA Z-scores were significantly lower than QCT Z-scores in HIV-infected children [101] |
|                                               | Not susceptible to degenerative changes of bone calcifications | Hard to access | Cortical BMD (peripheral QCT) was positively associated with NNRTI use, but negatively associated with PI use [64] |
|                                               |                                                   | Lack of paediatric normative data for interpretation |                                                   |
|                                               |                                                   |                                                   |                                                   |
| Quantitative computed tomography (QCT)        | Lack of ionising radiation                      | Long acquisition time                            | None |
|                                               | Ability to investigate marrow fat content, marrow diffusion and marrow perfusion | Requires specialised machine |                                                   |
|                                               |                                                   | High cost |                                                   |
|                                               |                                                   | Lack of paediatric reference data |                                                   |
| Quantitative magnetic resonance imaging (QMRI) | Lack of non-invasive                            | Diurnal variation                                 | Higher serum BALP and urine NTX in ART–experienced HIV-infected children compared with untreated children and healthy controls [102] |
|                                               | Can be performed from blood and urine specimens | Limited paediatric normative data and cut-off levels | Significantly reduced osteocalcin and urinary deoxypyridinoline in HIV-infected children with severe clinical symptoms compared with healthy controls [63] |
|                                               | Helpful tools in diagnosis and treatment assessment of bone health and diseases |                                                   | CTX and PINP levels were not different between HIV–infected adolescents with and without low BMD, but PINP was significantly inversely correlated with BMD Z-score [13] |
| Bone biochemical markers                      | Non-invasive                                     |                                                   |                                                   |
|                                               | Can be performed from blood and urine specimens |                                                   |                                                   |
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*BALP: bone-specific alkaline phosphatase; CTX: C-terminal cross-linked telopeptide of type I collagen; NNRTI: non-nucleoside reverse transcriptase inhibitors; NTX: N-terminal cross-linked telopeptide of type I collagen; PI: protease inhibitor; PINP: procollagen type I amino-terminal propeptide*
adjusted according to degree of bone demineralisation, repeated after 1–2 years for those with advanced osteopenia (T-score between −2.0 and −2.5) and after 5 years for those with mild to moderate osteopenia (T-score between −1 and −2) [103].

The objective of bone health assessment in the paediatric population is to screen children who fail to achieve the expected gains in bone size, mass and strength, and which leaves them vulnerable to fracture as they age. The ISCD 2013 Statement recommends that DXA should be considered only in children and adolescents who may benefit from interventions and those whose DXA results will influence management [105]. Among chronic diseases, cystic fibrosis has a well-established recommendation for bone health assessment and monitoring. The European Cystic Fibrosis Mineralisation Guidelines recommend the first routine bone density scans at age around 8–10 years, to be repeated every 5 years if the BMD Z-score is above −1; every 2 years if the Z-score is between −1 and −2; and every year if the Z-score is below −2 [106]. However, to date, there is no specific recommendation for DXA screening among HIV-infected children and adolescents in any national or international guidelines. In settings where DXA is available and accessible, bone density scans may be performed at 6–12 months after ART initiation since transient reductions in bone mass may be occurring, with repeat measurements every year if BMD Z-score is less than or equal to −2. In settings where access to DXA is limited, one may consider performing bone density scans only in individuals who have a combination of multiple risk factors for bone demineralisation, for example history of wasting or stunting, advanced HIV disease, use of TDF with ritonavir-boosted PIs and vitamin D deficiency.

Management of adverse bone health in perinatally HIV-infected children and adolescents

As adverse bone health during childhood and adolescence may result in adult osteoporosis and bone fragility, several approaches, primarily to prevent bone loss and optimise bone health, should be implemented during these critical periods.

General management

Promoting a healthy lifestyle

Healthy lifestyle choices include avoiding smoking and heavy alcohol consumption. Smoking is a major lifestyle risk factor for osteoporosis. Studies in twins have provided a powerful study design by controlling for age, sex and genetic background to identify the effects of smoking on bone health [107–109]. A cross-sectional study of 41 pairs of female twins found that smoking one pack of cigarettes per day throughout adulthood would reduce BMD by approximately 5–10%, thus increasing the risk for osteoporosis by the time of menopause [107]. Similarly, a study of 146 female twin pairs showed that a discordance of 10 pack-years smoking was related to a 2.3–3.3% decrease in BMD at the lumbar spine, proximal femur and total body [108]. Furthermore, meta-analyses indicated that smoking substantially lowered bone mineral density (BMD) at the lumbar spine, proximal femur and total body [109]. A cross-sectional study of 41 pairs of female twins found that smoking one pack of cigarettes per day throughout adulthood would reduce BMD by approximately 5–10%, thus increasing the risk for osteoporosis by the time of menopause [107].

Alcohol consumption negatively impacts bone health in several ways. First, excessive alcohol consumption causes hypovitaminosis D, which in turn reduces calcium reserves [113,114]. Secondly, chronic heavy alcohol consumption can disturb testosterone production, a male hormone linked to the production of osteoblasts [115], while, cortisol, a hormone that arrests osteoblast differentiation, is increased [116].

Exercise

Weight-bearing and muscle strengthening exercises are important for building and maintaining bone density. Weight-bearing exercise can be either high impact, such as dancing, running, jumping, gymnastics, soccer, basketball or low impact, such as fast walking or low-impact aerobics. Muscle strengthening exercises include weight lifting, using elastic exercise bands or weight machines, or functional movements. Previous studies showed that children who usually participate in high-impact activities have higher bone mass compared with individuals who are less active or frequently engage in non-weight bearing exercises [117–120]. The American College of Sports Medicine recommends exercising for 10–20 minutes per day, at least 3 days per week [117]. These exercise prescriptions could improve bone strength in children and adolescents.

Nutrition

Key bone nutrition includes calcium and vitamin D [121]. The Institute of Medicine (IOM) recommendation for daily calcium intake for children and adolescents age 9–18 years is 1,300 mg per day [122]. In clinical practice, diet should be the primary source for calcium. Calcium supplementation should be provided to individuals who are unable to obtain adequate calcium from their diet and who are at high risk for adverse bone health. Common dietary sources of calcium are dairy products, soybeans, dark leaf greens and sardines. According to the IOM, the recommended vitamin D intake for children and adolescents age 9–25 years, is 600 IU per day [122]. The most common source of vitamin D is sunlight. However, in countries without year-round sunlight, foods containing vitamin D such as fatty fish (e.g. salmon, tuna and mackerel) and fish oils are among the best sources. Vitamin D-fortified foods may be available in resource-rich countries [123], but they are not in resource-limited settings.

A high prevalence of vitamin D deficiency and insufficiency among HIV-infected children and adolescents has been reported, ranging from 71% to 96% [124–127]. Vitamin D deficiency may diminish calcium absorption in the gastrointestinal tract. Therefore, if 25-hydroxyvitamin D (25-OH)D, a surrogate for vitamin D levels, is lower than 30 ng/mL, supplementation should be initiated. However, in settings where 25-OH measurement is not available, supplementation should be considered based on history of vitamin D intake and the clinician decision. However, evidence demonstrating the benefit of calcium and vitamin D supplementation on bone health among HIV-infected children and adolescents is limited and controversial [128,129].

A randomised clinical trial assessing the effects of calcium (1 g per day) and vitamin D3 (1,600 IU per day) supplementation for 2 years on bone mineral accrual among HIV-infected children and adolescents with normal baseline BMD in the United States found no significant difference in BMD when compared with placebo groups [128]. In contrast, a recent small observational study supplementing 1,200 mg calcium and 400 IU vitamin D3 daily for 6 months showed a significant improvement of lumbar spine BMD and BMD Z-scores among HIV-infected Thai adolescents with low BMD at baseline [129]. Currently, there are ongoing randomised clinical trials determining the impact of calcium and/or vitamin D supplementation on BMD among HIV–infected adolescents (Table 2).

Pharmacological interventions

There are several agents used in the treatment of low BMD in HIV-infected populations, including anti-resorptive therapies (bisphosphonates, serum oestrogen receptor modulators or
determine the efficacy of alendronate on bone density among
there are several ongoing randomised clinical trials that aim to
with longer follow-up periods should be performed. Currently,
recommended as an anti-osteoporosis treatment, larger studies
placebo groups [132–137]. Before bisphosphonates can be
demonstrated significant improvement of BMD compared to
(annually), in HIV-infected adults with low bone density
have taken place. Previous randomised clinical trials of the
bisphosphonates, alendronate (weekly) or zolendronate
individuals is scarce and no studies in children and adolescents
taken place. Adverse effects related to bisphosphonates are
rarely associated with the use of these agents in children and
adolescents. Furthermore, bisphosphonates may affect
bone mineralisation in children and adolescents, particularly those living in
middle-income countries. The pathogenesis of low BMD is
complex, and is related to HIV disease course and systemic
inflammation (immunoskeletal interface). Many factors, both
traditional and HIV specific, can lead to adverse bone health. An
important consequence of low bone density during childhood and
adolescence is compromised PBM, which may result in
osteoporosis and bone fracture later in life. Refraining from
smoking and heavy alcohol consumption, performing regular
weight-bearing exercises and adequate dietary intake of calcium
are basic health education messages for patients to optimise bone
health. More data are required to support the efficacy of calcium and vitamin D supplementation, and bisphosphonates in restoring
bone mineralisation and preventing bone loss among
HIV–infected children and adolescents.

Conclusions
Adverse bone health is common in perinatally HIV-infected
children and adolescents, particularly those living in middle-income countries. The pathogenesis of low BMD is
complex, and is related to HIV disease course and systemic
inflammation (immunoskeletal interface). Many factors, both
traditional and HIV specific, can lead to adverse bone health. An
important consequence of low bone density during childhood and
adolescence is compromised PBM, which may result in
osteoporosis and bone fracture later in life. Refraining from
smoking and heavy alcohol consumption, performing regular
weight-bearing exercises and adequate dietary intake of calcium
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Table 2. Ongoing randomised clinical trials on the interventions for improving bone health in HIV-infected adolescents and young adults

| Investigator, study name, (Trials identifier) | Study location | Study population | Intervention | Primary outcome |
|---------------------------------------------|----------------|------------------|--------------|----------------|
| Siberry GK et al. IMPAACT P1076 (NCT00921557) | United States, Brazil, Puerto Rico | Age 11–24 years Lumbar spine BMD Z-score <−1.5 or history of fragility fracture | ARM 1: Oral alendronate 70 mg weekly for 96 weeks ARM 2: Oral alendronate 70 mg weekly for 48 weeks plus placebo for 48 weeks ARM 3: Placebo for 96 weeks | Changes of LS BMD after 24 and 48 weeks of alendronate treatment versus placebo |
| Havens P et al. ATN109 (NCT01751646) | United States, Puerto Rico | Age 16–24 years receiving TDF-containing ART | ARM 1: Vitamin D3 50,000 IU orally every 4 weeks for 48 weeks | ARM 2: Placebo for 48 weeks | Changes in LS BMD after 48 weeks of supplementation |
| Sudjaritruk T et al. CAL-D (NCT02426840) | Thailand | Adolescents age 10–20 years receiving stable ART | ARM 1: Co-formulated oral calcium (600 mg elemental calcium)/vitamin D3 (200 IU) twice daily for 48 weeks | ARM 2: Co-formulated oral calcium/vitamin D3 twice daily plus vitamin D2 (20,000 IU/cap) once weekly for 48 weeks | Changes in LS BMD after 48 weeks of supplementation |
| Tan D et al. BATARI (NCT01968850) | Canada | ART-naive age >18 years with low fracture risk (FRAX 10-year fracture risk scores <10%) | ARM 1: Standard of care | ARM 2: Co-formulated oral alendronate (70 mg)/vitamin D3 (5,600 IU) weekly started at time of ART initiation for 24 weeks | ARM 3: Co-formulated oral alendronate weekly started at week 24–48 of ART | Changes in LS and proximal femur BMD at week 48 |
| Mallon PW et al. APART (NCT02322099) | Ireland | ART-naive adults age >30 years initiated with TDF/FTC | ARM 1: Oral alendronate (70 mg) weekly plus daily calcium (500 mg elemental calcium)/vitamin D3 (400 IU) for 14 weeks | ARM 2: Placebo plus calcium (500 mg elemental calcium)/vitamin D3 (400 IU) for 14 weeks | Between-group differences in the change in total hip, LS, femoral neck BMD and body composition to week 50 |
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