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IMPACT OF CHRONIC HIV INFECTION ON BONE HEALTH AND EARLY OSTEOPOROSIS RISK AMONG YOUNG ADULTS RECEIVING ART

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Abstract

Background: People living with human immunodeficiency virus (HIV) are increasingly vulnerable to skeletal complications despite improvements in survival associated with antiretroviral therapy (ART). Reduced bone mineral density (BMD) may develop during early adulthood due to treatment-related, nutritional, and inflammatory factors. This study assessed the prevalence of reduced BMD and its associated factors among young adults receiving ART in Lahore, Pakistan.

Study Type: Cross-sectional analytical study

Methodology: A hospital-based cross-sectional analytical study included 274 HIV-positive adults aged 18–40 years receiving ART for at least six months. BMD was assessed at the lumbar spine, total hip, and femoral neck using dual-energy X-ray absorptiometry (DXA). A Z-score ≤ −2.0 at any measured site indicated BMD below the expected range for age. ART duration, body mass index (BMI), vitamin D concentrations, C-reactive protein (CRP), and fracture history were evaluated. Multivariable

logistic regression identified factors independently associated with reduced BMD.

Results: Reduced BMD was observed in 7.7% of participants (95% CI: 5.1%–11.4%). Its prevalence increased with ART duration, reaching 14.3% among participants treated for five years or longer. Longer ART duration was independently associated with increased odds of reduced BMD (aOR = 1.41 per year; 95% CI: 1.18–1.69; $p < 0.001$), whereas higher BMI was associated with lower odds (aOR = 0.73; 95% CI: 0.62–0.86; $p < 0.001$). Vitamin D deficiency affected 40.9% of participants but showed no significant association with reduced BMD. CRP levels and tenofovir exposure were also not significantly associated. Previous fractures were more frequent among participants with reduced BMD (19.0% versus 3.2%; $p = 0.009$).

Conclusion: Reduced BMD affects a proportion of young adults receiving ART in Lahore. Longer treatment duration and lower BMI were the principal independent correlates. Incorporating nutritional evaluation and targeted skeletal risk assessment into HIV care may support earlier identification of vulnerable patients.

INTRODUCTION

Human immunodeficiency virus (HIV) remains an important public health problem in many countries, including Pakistan. In the past, HIV was mainly discussed as a life-threatening infection because many patients developed serious infections and other complications. The introduction of antiretroviral therapy (ART) has changed this situation. People living with HIV can now survive for many years and maintain a better quality of life when treatment is started early and taken regularly. However, longer survival has also brought attention to health problems that were previously less recognized. One of these problems is poor bone health, which may develop even in younger patients receiving treatment (Ahmed et al., 2023; Biver, 2022).

Bone health is important because bones provide support to the body and protect internal organs. Bone tissue is continuously renewed through the activities of cells responsible for bone formation and bone breakdown. When the balance between these processes is disturbed, bone mineral density (BMD) may decrease. If bone loss continues, bones may become weaker and more likely to fracture. Osteoporosis is usually associated with older people, particularly postmenopausal women. However, research has shown that individuals living with HIV may experience changes in bone health earlier than expected. These changes may occur because of the infection itself, its treatment, and other factors related to general health and lifestyle (Brown & Qaqish, 2006; McComsey et al., 2010).

Several international studies have reported reduced BMD among people living with HIV. Brown and Qaqish (2006), in their meta-analysis, found that low bone density and osteoporosis were more common in HIV-positive individuals than in HIV-negative populations. Later evidence also showed an increased risk of bone fractures among people living with HIV (Shiau et al., 2013). A systematic review by Starup-Linde et al. (2020) reported that individuals with HIV had lower BMD at the hip and lumbar spine compared with controls. These findings suggest that skeletal complications deserve greater attention in routine HIV care. Although many bone-related problems develop gradually, early identification may help prevent serious complications.

The relationship between HIV infection and bone loss is complex. Chronic HIV infection may cause persistent changes in the immune system, even when patients receive effective treatment. HIV-related immune activation can influence the activity of osteoclasts, which are responsible for bone breakdown. Inflammatory processes may also affect bone formation and mineral metabolism. As a result, the normal balance of bone renewal may be disturbed. Other factors, including reduced body weight, poor dietary intake, smoking, and limited physical activity, may increase the risk of reduced BMD. These factors often occur together, making it difficult to identify a single cause of bone loss (Biver, 2022; Jadzic et al., 2024).

Antiretroviral therapy is essential for controlling HIV infection, but some ART medicines may have unwanted effects on bone metabolism. Evidence suggests that a reduction in BMD can occur during the

early period after ART initiation. McComsey et al. (2010) reported that starting ART was associated with approximately 2% to 6% bone loss during the first two years of treatment. Certain medicines, particularly tenofovir disoproxil fumarate (TDF), have been associated with greater reductions in BMD. McComsey et al. (2011) also observed differences in bone loss between treatment regimens. Gupta et al. (2017) further investigated the relationship between TDF exposure, phosphate handling, and reduced BMD. These findings highlight the need to examine ART exposure carefully rather than treating all regimens as having equal skeletal effects. However, the benefits of effective ART remain substantial, and patients should not discontinue treatment because of concerns about bone health.

Vitamin D is another important factor in maintaining healthy bones. It helps regulate calcium absorption and supports normal bone mineralization. Low vitamin D levels may contribute to poor skeletal health, particularly when calcium intake is also insufficient. Vitamin D deficiency is common in South Asian populations. Siddiqee et al. (2021) reported a high prevalence of vitamin D deficiency across South Asian countries, including Pakistan. In people living with HIV, nutritional problems may exist alongside chronic inflammation and treatment-related metabolic changes. Measuring vitamin D levels may therefore provide useful information when assessing reduced bone density. Body mass index, dietary intake, and physical activity should also be considered because bone health depends on several related factors.

Young adults are an important group for studying these complications. During early adult life, individuals generally reach or maintain peak bone mass. Poor bone health during this period may have consequences in later years. A person who develops reduced BMD at a younger age may have less bone reserve as ageing continues. Moreover, many young adults living with HIV may require ART for several decades. This creates a need to understand how treatment history and other clinical factors are associated with bone health. International recommendations advise using age-appropriate methods when assessing BMD. In men younger than 50 years and premenopausal women, Z-scores are generally preferred, and reduced BMD alone should not be considered sufficient to diagnose osteoporosis (Brown et al., 2015).

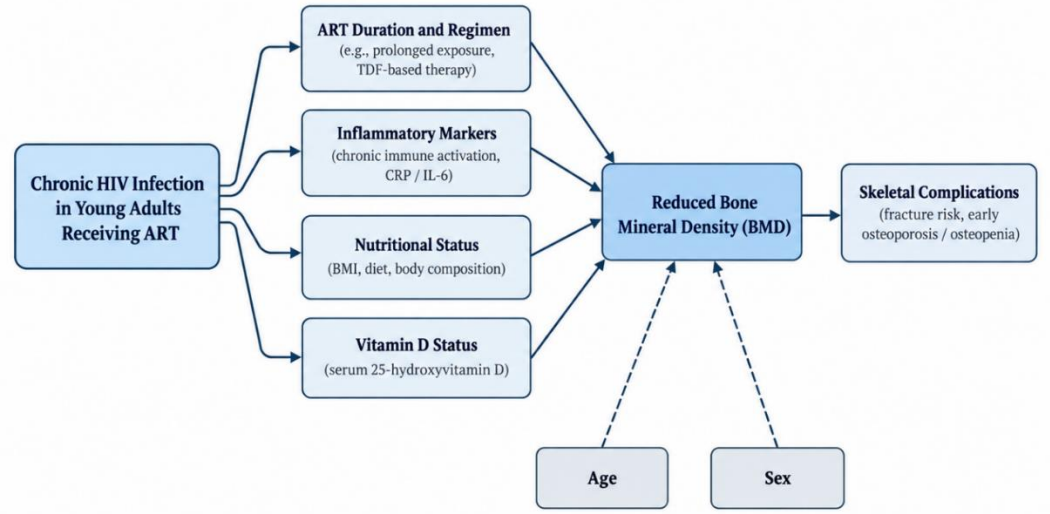
In Pakistan, HIV remains a growing concern, and earlier research has described its spread among several population groups. Bokhari et al. (2007) documented HIV-related risk patterns in Karachi and Lahore. Bergenstrom et al. (2015) also discussed the challenges of HIV prevention and treatment services in Pakistan. More recently, Zubair et al. (2025) investigated HIV genetic characteristics and drug resistance patterns among samples from Lahore. These studies provide useful information about the local HIV situation. However, they do not directly establish the burden of low BMD among young adults receiving ART in Lahore. Evidence from other countries may not fully reflect local nutritional conditions, treatment histories, or access to diagnostic services.

There is therefore a need for locally generated evidence on bone health among young adults living with HIV. Reduced BMD may remain unnoticed because patients often do not experience clear symptoms until

a fracture occurs. In clinical practice, attention may be directed mainly towards viral suppression, immune status, and treatment adherence, while skeletal health receives less attention. A better understanding of the relationship between ART duration, vitamin D, nutritional status, and inflammatory markers may help identify patients who require further assessment.

Figure 1. Conceptual framework for the Lahore-based cross-sectional analytical study

Impact of Chronic HIV Infection on Bone Health and Early Osteoporosis Risk Among Young Adults Receiving ART



Methodology

Study Design and Setting

A hospital-based cross-sectional analytical study was designed to assess bone mineral density and its associated factors among young adults living with HIV and receiving antiretroviral therapy (ART). The selected study setting was the HIV treatment centre of a tertiary care hospital in Lahore, Pakistan. An eight-month study period, from January 1 to August 31, 2026, was selected for recruitment and data collection. The study was structured to assess the frequency of reduced bone mineral density (BMD) and its relationship with the duration of ART, inflammatory markers, vitamin D levels, and nutritional status. Each participant was to be assessed at a single point during the study period.

Study Population and Sampling Technique

The target population included male and female patients aged 18–40 years with confirmed HIV infection who were receiving ART at the selected hospital. A non-probability consecutive sampling technique was selected. Patients attending the HIV treatment centre during the study period were to be screened according to predefined eligibility criteria. Eligible patients who provided written informed consent were to be enrolled until the required recruitment target or approved recruitment period was reached.

The sample size was calculated using the single-population proportion formula, with a 95% confidence level, an anticipated prevalence of reduced BMD of 20%, and a margin of error of 5%. The anticipated prevalence was used as a planning assumption rather than an established local estimate. The calculated minimum sample size was 246 participants. After allowing approximately 10% for incomplete investigations or missing information, the proposed recruitment target was increased to 274 participants.

Eligibility Criteria

Patients aged 18–40 years with documented HIV infection and a history of receiving ART for at least six months were considered eligible for inclusion. Both male and female patients were included in the proposed sampling frame. Participants were required to provide informed consent and to be able to undergo the planned clinical, laboratory, and bone density assessments.

Patients with previously diagnosed metabolic bone disorders unrelated to HIV, active malignancy affecting bone, advanced chronic kidney disease, untreated major thyroid or parathyroid disorders, or prolonged systemic corticosteroid exposure were excluded. Pregnant women and patients unable to undergo a technically valid DXA examination were also excluded. Patients with low body weight, vitamin D deficiency, or previous fractures were not excluded, as these characteristics were relevant to the research objectives.

Data Collection

Data collection was planned through a structured questionnaire, clinical examination, and review of hospital records. The questionnaire included demographic information, medical history, lifestyle habits, nutritional factors, and HIV-related clinical details.

Age, sex, smoking status, physical activity, dietary habits, previous fractures, and history of bone pain were recorded. Height and weight were measured using standard procedures. Height was recorded in metres and weight in kilograms. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in metres.

Nutritional assessment included BMI and a brief dietary history focusing on the usual consumption of milk, yogurt, eggs, fish, and other foods contributing to calcium and vitamin D intake. Information about nutritional supplements was also recorded. BMI was assessed as a continuous variable and described using standard adult BMI categories.

Relevant information about HIV infection was obtained from medical records. This included the duration since HIV diagnosis, date of ART initiation, current treatment regimen, previous treatment changes, and available CD4 cell count and viral load results.

Assessment of Antiretroviral Therapy

The duration of ART was calculated from the documented treatment initiation date to the date of assessment and expressed in months. For descriptive analysis, ART exposure was categorized as 6 to less than 24

months, 24 to less than 60 months, and 60 months or longer. Treatment duration was also retained as a continuous variable for correlation and regression analyses.

Current ART regimens and previous treatment exposure were documented using treatment records. Particular attention was given to tenofovir disoproxil fumarate (TDF), as previous research has shown differences in skeletal effects between certain antiretroviral regimens (McComsey et al., 2011; Gupta et al., 2017). Current or previous TDF exposure was recorded separately when a reliable treatment history was available. The study was intended to examine associations with ART duration and treatment exposure rather than establish a direct causal effect of ART on bone loss.

Bone Mineral Density Assessment

Bone mineral density was selected as the primary outcome and was to be measured using dual-energy X-ray absorptiometry (DXA). The proposed examination sites were the lumbar spine (L1–L4), total hip, and femoral neck. Measurements were expressed in grams per square centimetre (g/cm^2), together with the corresponding Z-scores.

The same DXA unit and standard patient-positioning procedures were to be used throughout the study wherever possible. Scan quality was to be checked for positioning errors and artifacts before interpretation. As the study involved young adults, age-matched Z-scores were selected for the primary classification of bone density. A Z-score of −2.0 or below at any valid measured site was classified as bone mineral density below the expected range for age. Values above −2.0 were classified as within the expected range for age. These classifications were selected in accordance with recommendations for BMD assessment in younger adults, as discussed by Brown et al. (2015).

A low Z-score alone was not used to establish a diagnosis of osteoporosis. Previous low-trauma fractures, relevant clinical history, and possible secondary causes of skeletal disease were assessed separately.

Laboratory Investigations

Laboratory assessment focused on vitamin D status, systemic inflammation, and factors related to bone metabolism. Venous blood samples were to be collected by trained laboratory personnel using standard aseptic techniques. Samples were processed according to the hospital laboratory's routine operating procedures.

Serum 25-hydroxyvitamin D [25(OH)D] was selected to assess vitamin D status. Results were recorded in ng/mL. For the planned analysis, vitamin D concentrations below 20 ng/mL were classified as low, while the measured concentrations were also retained as continuous values. Vitamin D was included because inadequate levels may contribute to poor bone mineralization, particularly in populations where nutritional deficiency is common (Siddiqee et al., 2021).

C-reactive protein (CRP) was selected as the main marker of systemic inflammation. Serum CRP values were recorded in mg/L. The relationship between CRP and bone mineral density was to be examined to explore the possible association between chronic inflammation and skeletal health.

Additional biochemical investigations included serum calcium, phosphate, alkaline phosphatase, albumin, and creatinine where available. CD4 cell count and HIV viral load were obtained from the clinical record when results were available within a defined period around the study assessment. These measurements were used to describe immune status and virological control.

Assessment of Skeletal Complications

History of previous fractures and persistent bone pain was assessed through patient interviews and available medical records. Participants were asked about the number and site of previous fractures, the approximate date, and the circumstances in which each fracture occurred.

Fractures associated with low-energy trauma, such as falling from standing height, were recorded separately from fractures caused by major accidents or other high-energy injuries. Reported fractures were verified from medical or radiological records whenever possible.

Bone pain was recorded according to anatomical location and duration. It was treated as a clinical symptom and not as independent evidence of osteoporosis. Fracture history and bone pain were considered secondary outcomes.

Quality Control and Bias Reduction

Standardized procedures were selected for data collection and clinical assessment. The same eligibility criteria and structured data collection form were to be applied to all participants. Clinical records were used to confirm HIV diagnosis, ART exposure, and relevant laboratory information whenever possible.

Consecutive recruitment was chosen to reduce selective enrolment among patients attending the clinic. Standard measurement procedures were specified for height, weight, laboratory investigations, and DXA examination.

Potential confounding variables, including age, sex, BMI, smoking, vitamin D status, ART duration, and treatment regimen, were identified before analysis. These variables were considered when examining associations between BMD and the main study exposures.

Because participants were selected from a single hospital, the findings would be most directly applicable to patients receiving care in that setting. The cross-sectional design also limits conclusions about the timing and causes of bone loss.

Statistical Analysis

IBM SPSS Statistics, version 26.0, was selected for the statistical analysis. Data were to be checked for incomplete entries, coding errors, and implausible values before analysis.

Continuous variables with approximately normal distributions were to be expressed as means and standard deviations. Skewed variables were to be summarized as medians and interquartile ranges. Categorical variables were to be presented as frequencies and percentages.

The prevalence of reduced BMD was defined as the proportion of participants with a Z-score of −2.0 or below at one or more valid DXA measurement sites. Prevalence estimates were to be reported with 95% confidence intervals.

The independent-samples t-test or Mann–Whitney U test was selected to compare continuous variables between participants with and without reduced BMD, according to the distribution of the data. Associations between categorical variables were to be assessed using the chi-square test or Fisher's exact test where appropriate.

Pearson's or Spearman's correlation analysis was selected to examine relationships between continuous BMD measurements and ART duration, vitamin D concentration, CRP level, and BMI.

Multivariable logistic regression was planned to assess independent associations with reduced BMD. Age, sex, BMI, ART duration, TDF exposure, serum vitamin D, and CRP were identified as clinically relevant candidate variables. The final number of variables entered into the model was to depend on the observed number of participants with reduced BMD and the completeness of the data, to reduce the risk of overfitting. Adjusted odds ratios with 95% confidence intervals were to be reported. Statistical significance was defined as a two-sided p-value below 0.05 for the primary analysis. Missing data were to be reported for major study variables, with complete-case analysis used where the amount of missing information was small and appropriate. All analyses were interpreted as associations rather than evidence of causation.

Results

Demographic and Clinical Characteristics

The dataset included 274 young adults living with HIV and receiving antiretroviral therapy (ART). The mean age was 29.25 ± 6.74 years. There were 200 males (73.0%) and 74 females (27.0%). The mean body mass index (BMI) was 22.41 ± 3.53 kg/m². Most participants (63.5%) had a normal BMI, while 12.8% were underweight, 22.3% were overweight, and 1.5% were obese.

The median duration of ART was 49.5 months (interquartile range [IQR]: 33.4–70.7). Of the total participants, 35 (12.8%) had received ART for less than two years, 141 (51.5%) for two to less than five years, and 98 (35.8%) for five years or longer. Tenofovir disoproxil fumarate (TDF) exposure was present in 179 (65.3%) participants. Smoking was reported by 76 (27.7%).

The mean serum vitamin D concentration was 22.47 ± 8.73 ng/mL, and 112 (40.9%) participants had concentrations below 20 ng/mL. Median C-reactive protein (CRP) was 2.4 mg/L (IQR: 1.4–4.0).

Table 1. Demographic and Clinical Characteristics of the Participants (N = 274)

Characteristics	Value
Age (years), mean ± SD	29.25 ± 6.74
Male, n (%)	200 (73.0)
Female, n (%)	74 (27.0)
BMI (kg/m²), mean ± SD	22.41 ± 3.53
Underweight, n (%)	35 (12.8)
Normal BMI, n (%)	174 (63.5)
Overweight, n (%)	61 (22.3)
Obese, n (%)	4 (1.5)
ART duration (months), median (IQR)	49.5 (33.4–70.7)
TDF exposure, n (%)	179 (65.3)
Current smoking, n (%)	76 (27.7)
Vitamin D (ng/mL), mean ± SD	22.47 ± 8.73
Vitamin D below 20 ng/mL, n (%)	112 (40.9)
CRP (mg/L), median (IQR)	2.4 (1.4–4.0)
CD4 count (cells/mm³), median (IQR)	472.9 (370.6–588.2)

Note. SD = standard deviation; BMI = body mass index; IQR = interquartile range; CRP = C-reactive protein.

Prevalence of Reduced Bone Mineral Density

Reduced bone mineral density was identified in 21 of the 274 participants, giving a prevalence of 7.7% (95% CI: 5.1%–11.4%). Reduced BMD was defined as a Z-score of −2.0 or below at one or more measured skeletal sites.

Fourteen participants (5.1%) had a low lumbar spine Z-score, 14 (5.1%) had a low femoral neck Z-score, and nine (3.3%) had a low total hip Z-score. Some participants had low values at more than one site.

The mean lumbar spine BMD was 1.00 ± 0.09 g/cm², compared with 0.95 ± 0.09 g/cm² at the total hip and 0.84 ± 0.09 g/cm² at the femoral neck.

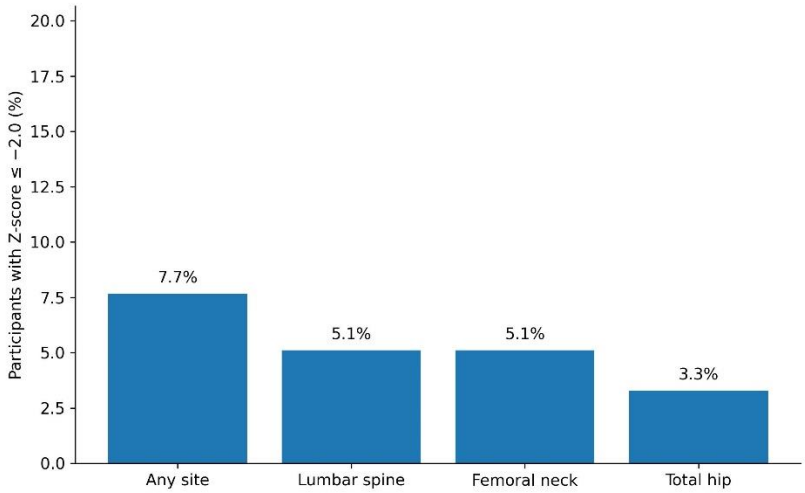


Figure 2. Prevalence of reduced bone mineral density by skeletal site

Table 2. Bone Mineral Density Findings

Skeletal site	Mean BMD (g/cm²) ± SD	Mean Z-score ± SD	Z-score ≤ −2.0, n (%)
Lumbar spine	1.00 ± 0.09	−0.70 ± 0.81	14 (5.1)
Total hip	0.95 ± 0.09	−0.27 ± 0.93	9 (3.3)
Femoral neck	0.84 ± 0.09	−0.42 ± 0.95	14 (5.1)
Any skeletal site	—	—	21 (7.7)

Note. Reduced BMD was defined as a Z-score ≤ −2.0 at one or more sites.

Association Between ART Duration and Bone Mineral Density

The frequency of reduced BMD differed across ART duration categories. No participants in the group receiving ART for less than two years had reduced BMD. Seven participants (5.0%) in the two-to-less-than-five-year group and 14 participants (14.3%) in the five-year-or-longer group had reduced BMD.

A negative correlation was observed between ART duration and lumbar spine Z-score (Spearman's $\rho = -0.279$, $p < 0.001$). Longer ART duration was associated with lower lumbar spine Z-scores in the dataset. TDF exposure was not significantly associated with the binary reduced-BMD outcome (Fisher's exact $p = 0.234$).

Table 3. Bone Mineral Density According to ART Duration

ART duration	Total n	Reduced BMD, n (%)	Lumbar Z-score, mean ± SD
6 to less than 24 months	35	0 (0.0)	−0.32 ± 0.79
24 to less than 60 months	141	7 (5.0)	−0.62 ± 0.77
60 months or longer	98	14 (14.3)	−0.96 ± 0.80
Total	274	21 (7.7)	—

Note. ART duration was negatively correlated with lumbar spine Z-score (Spearman's $\rho = -0.279$, $p < 0.001$).

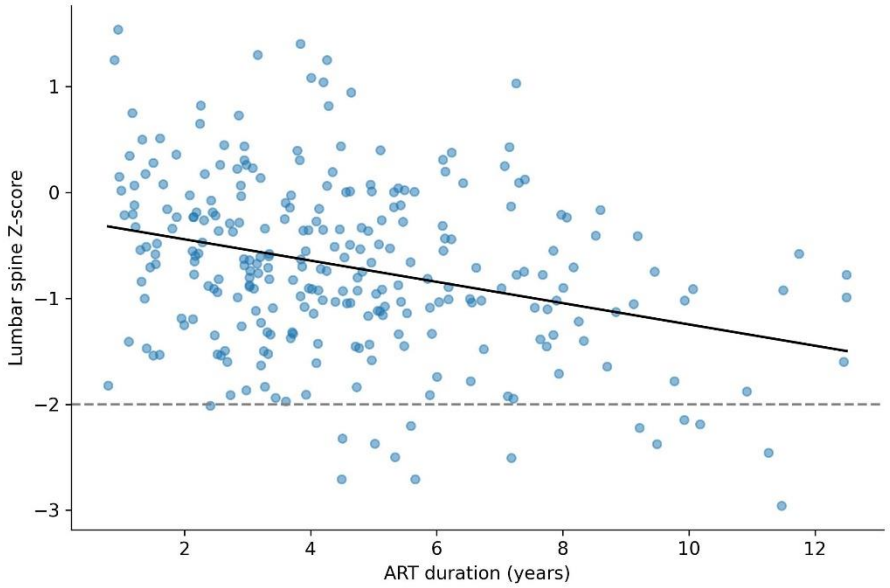


Figure 3. Association between ART duration and lumbar spine Z-score

Vitamin D Status and Bone Mineral Density

The mean serum vitamin D concentration among participants with reduced BMD was 21.15 ± 9.03 ng/mL, compared with 22.58 ± 8.72 ng/mL among participants whose bone density was within the expected range for age. This difference was not statistically significant ($p = 0.494$).

A weak positive correlation was observed between serum vitamin D concentration and lumbar spine Z-score ($\rho = 0.135$, $p = 0.026$). Thus, higher vitamin D values were associated with slightly higher lumbar spine Z-scores, although the relationship was small.

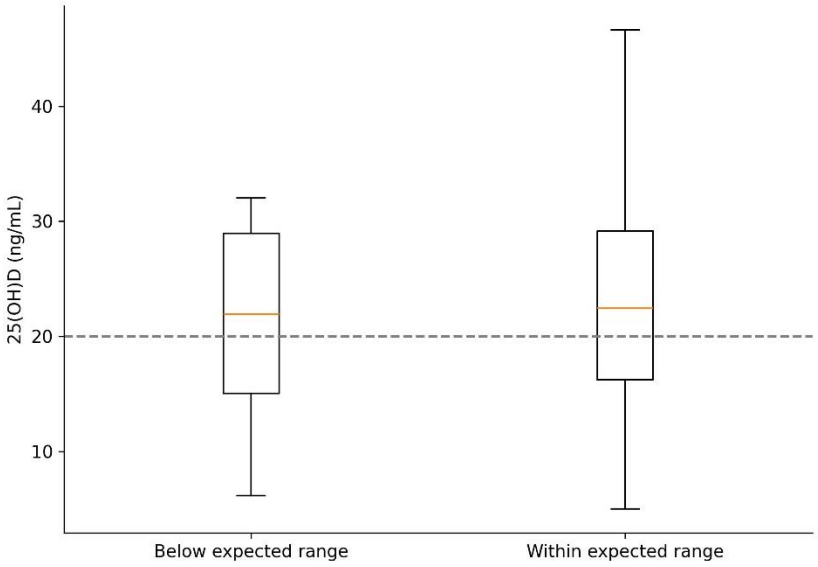


Figure 4. Serum vitamin D concentrations according to bone density status

Inflammatory Markers and Bone Mineral Density

The median CRP concentration was 2.6 mg/L (IQR: 1.8–4.8) among participants with reduced BMD, compared with 2.4 mg/L (IQR: 1.4–4.0) among those with BMD within the expected range.

The difference between groups was not statistically significant ($p = 0.328$). Similarly, the correlation between CRP and lumbar spine Z-score was weak and not statistically significant ($\rho = -0.068$, $p = 0.259$).

Nutritional Status and Bone Mineral Density

Participants with reduced BMD had a lower mean BMI than those with BMD within the expected range (19.67 ± 3.04 versus 22.63 ± 3.48 kg/m², $p < 0.001$).

A moderate positive correlation was found between BMI and lumbar spine Z-score ($\rho = 0.407$, $p < 0.001$). Higher BMI was associated with higher lumbar spine Z-scores.

Skeletal Complications

A previous fracture was reported in 12 participants (4.4%). Four of the 21 participants with reduced BMD (19.0%) reported a previous fracture, compared with eight of the 253 participants (3.2%) whose BMD was within the expected range. The difference was statistically significant (Fisher's exact $p = 0.009$).

Persistent bone pain was reported by 46 participants (16.8%). Its association with reduced BMD was not statistically significant ($p = 0.763$).

The fracture variable represented previous fracture history and was not restricted to verified low-trauma fractures.

Table 4. Comparison of Participants With and Without Reduced BMD

Variable	Reduced BMD (n = 21)	Expected BMD (n = 253)	p-value
Age (years), mean ± SD	31.10 ± 5.97	29.10 ± 6.79	0.158
BMI (kg/m²), mean ± SD	19.67 ± 3.04	22.63 ± 3.48	<0.001
ART duration (months), median (IQR)	67.9 (53.9–113.9)	48.2 (31.7–66.3)	<0.001
Vitamin D (ng/mL), mean ± SD	21.15 ± 9.03	22.58 ± 8.72	0.494
CRP (mg/L), median (IQR)	2.6 (1.8–4.8)	2.4 (1.4–4.0)	0.328
CD4 count (cells/mm³), median (IQR)	415.3 (349.9–521.9)	482.2 (373.7–588.6)	0.225
TDF exposure, n (%)	11 (52.4)	168 (66.4)	0.234
Previous fracture, n (%)	4 (19.0)	8 (3.2)	0.009

Note. p-values were calculated using Welch's t-test, Mann–Whitney U test, or Fisher's exact test as appropriate.

Multivariable Logistic Regression Analysis

A multivariable logistic regression model was used to examine factors independently associated with reduced BMD. Because only 21 participants met the reduced-BMD definition, the adjusted model was restricted to three explanatory variables: age, BMI, and ART duration.

After adjustment, longer ART duration was associated with higher odds of reduced BMD (adjusted odds ratio [aOR] = 1.41 per additional year; 95% CI: 1.18–1.69; $p < 0.001$).

Higher BMI was associated with lower odds of reduced BMD (aOR = 0.73 per kg/m²; 95% CI: 0.62–0.86; $p < 0.001$). Age did not show a statistically significant independent association (aOR = 1.08 per year; 95% CI: 1.00–1.17; $p = 0.067$).

Table 5. Adjusted Logistic Regression for Reduced BMD

Variable	Adjusted OR	95% CI	p-value
Age (per year)	1.08	1.00–1.17	0.067
BMI (per kg/m²)	0.73	0.62–0.86	<0.001
ART duration (per year)	1.41	1.18–1.69	<0.001

Note. OR = odds ratio; CI = confidence interval. The model contains three predictors and 21 outcome events.

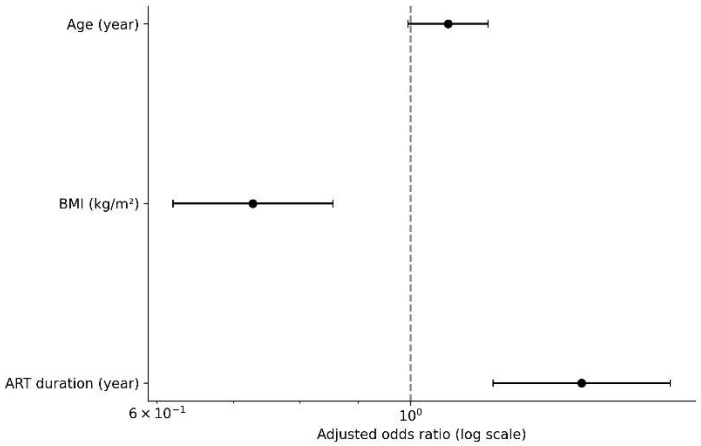


Figure 5. Adjusted associations with reduced bone mineral density

DISCUSSION

The present study examined bone mineral density (BMD) and its associated clinical and biochemical factors among 274 young adults living with HIV and receiving antiretroviral therapy (ART) in Lahore, Pakistan. The findings indicate that reduced bone density is a relevant health concern even among younger individuals undergoing HIV treatment. Overall, 7.7% of participants had BMD below the expected range for age, defined by a Z-score of −2.0 or lower at one or more skeletal sites. Longer ART duration and lower body mass index (BMI) were independently associated with reduced BMD, whereas vitamin D concentrations and C-reactive protein (CRP) levels showed comparatively weak or statistically non-significant relationships. These findings provide insight into the factors associated with skeletal health in a population where HIV-related bone complications have received relatively limited research attention.

Prevalence of Reduced Bone Mineral Density

The prevalence of reduced BMD in the present study was 7.7%, with abnormalities observed at the lumbar spine, femoral neck, and total hip. Reduced Z-scores were more frequent at the lumbar spine and femoral neck, each affecting 5.1% of participants, compared with 3.3% at the total hip. These findings suggest that skeletal changes may not occur uniformly across anatomical sites, highlighting the importance of assessing more than one region when evaluating bone health.

Previous research has consistently identified an increased burden of skeletal abnormalities among individuals living with HIV. Brown and Qaqish (2006), in their meta-analysis, demonstrated that low bone density and osteoporosis were more common among HIV-positive individuals than among HIV-negative populations. Similarly, Starup-Linde et al. (2020) reported reduced BMD at important skeletal sites among people living with HIV. Although these studies support the broader association between HIV infection and

compromised bone health, direct comparisons of prevalence should be made cautiously because of differences in age distribution, treatment history, study populations, and diagnostic criteria.

An important distinction in the present study is the use of Z-scores rather than T-scores to identify bone density below the expected range for age. This approach is particularly appropriate because the participants were between 18 and 40 years of age. Brown et al. (2015) emphasized the importance of age-appropriate interpretation of DXA findings, particularly among younger men and premenopausal women. Therefore, the reduced BMD observed in this study should not automatically be interpreted as a diagnosis of osteoporosis. Nevertheless, the presence of low bone density during early adulthood deserves clinical attention, as individuals affected at this stage may enter later life with a reduced skeletal reserve.

Association Between ART Duration and Bone Mineral Density

One of the most important findings was the association between longer ART duration and lower bone mineral density. The proportion of participants with reduced BMD increased across treatment-duration categories, from 0% among those receiving ART for less than two years to 5.0% among those treated for two to less than five years and 14.3% among those receiving treatment for at least five years. ART duration also demonstrated a significant negative correlation with lumbar spine Z-score ($\rho = -0.279$, $p < 0.001$).

This relationship remained significant after adjustment for age and BMI. Each additional year of ART exposure was associated with 41% higher odds of reduced BMD (aOR = 1.41; 95% CI: 1.18–1.69). The persistence of this association in the adjusted analysis suggests that treatment duration is an important clinical characteristic when evaluating skeletal health among young adults living with HIV.

These findings are consistent with earlier evidence indicating that changes in bone metabolism can accompany ART initiation and exposure. McComsey et al. (2010) described reductions in BMD following the commencement of antiretroviral treatment, particularly during the initial years of therapy. McComsey et al. (2011) further demonstrated that the extent of bone loss may differ according to the antiretroviral regimen used.

However, the association observed in the present study should not be interpreted as evidence that prolonged ART directly causes progressive bone loss. Longer treatment duration may also reflect a longer history of HIV infection, cumulative exposure to different antiretroviral drugs, or other clinical and nutritional influences. Because BMD was measured at a single point, changes in individual bone density over time could not be determined. Nevertheless, the findings suggest that patients with longer treatment histories may benefit from closer assessment of skeletal risk factors as part of routine HIV follow-up.

Tenofovir Exposure and Bone Health

Tenofovir disoproxil fumarate (TDF) has received considerable attention because of its potential effects on bone and mineral metabolism. In the current study, 65.3% of participants had a history of TDF exposure.

However, no statistically significant association was identified between TDF exposure and reduced BMD ($p = 0.234$).

This finding differs from some earlier investigations. McComsey et al. (2011) reported differences in bone density changes between antiretroviral regimens, while Gupta et al. (2017) examined reductions in BMD following TDF initiation alongside changes in renal phosphate handling. These studies indicate that the skeletal effects of antiretroviral treatment may depend on the specific medications involved.

The absence of a significant association in the present study does not necessarily indicate that TDF has no influence on bone health. Participants were classified according to exposure history, which may not fully represent cumulative dose, duration of individual drug use, previous regimen changes, or the timing of exposure relative to bone density assessment. Moreover, only 21 participants met the study definition of reduced BMD, limiting the ability to identify some treatment-specific associations.

The results therefore support a cautious interpretation. While overall ART duration was independently associated with reduced BMD, the findings were insufficient to establish a separate relationship between TDF exposure and the binary bone density outcome. Larger studies incorporating detailed treatment histories may help clarify whether particular regimens contribute differently to skeletal changes among young adults receiving HIV care in Pakistan.

Nutritional Status and Bone Mineral Density

Nutritional status emerged as another important factor associated with skeletal health. Participants with reduced BMD had a significantly lower mean BMI than those whose bone density remained within the expected range for age (19.67 ± 3.04 versus 22.63 ± 3.48 kg/m², $p < 0.001$). BMI was also positively correlated with lumbar spine Z-score ($\rho = 0.407$, $p < 0.001$), indicating that higher BMI was associated with better age-adjusted lumbar bone density.

The multivariable analysis supported this relationship. Each one-unit increase in BMI was associated with 27% lower odds of reduced BMD (aOR = 0.73; 95% CI: 0.62–0.86). Among the variables examined, BMI therefore represented a particularly relevant correlate of skeletal health.

Several explanations may account for this finding. Lower body weight can be associated with reduced mechanical loading on the skeleton, while insufficient nutritional intake may limit the availability of nutrients needed for maintaining bone tissue. Changes in muscle mass and overall body composition may also influence skeletal health. Guimarães et al. (2022) examined lean mass and sarcopenia among people living with HIV, highlighting the importance of body composition in this population. Similarly, Biver (2022) discussed the multiple metabolic and clinical factors that may contribute to bone fragility in individuals with HIV infection.

Although BMI is a useful and easily obtainable clinical measurement, it cannot distinguish between muscle mass and fat mass or provide a complete assessment of nutritional health. Consequently, the observed

association should not be interpreted as evidence that increasing body weight alone would necessarily improve BMD. Instead, it emphasizes the need to consider nutritional adequacy, physical condition, and body composition when assessing patients at risk of skeletal complications.

Vitamin D Status and Bone Health

Vitamin D deficiency was common among the participants, with 40.9% having serum concentrations below 20 ng/mL. Despite this relatively high frequency, mean vitamin D levels did not differ significantly between participants with reduced BMD and those with bone density within the expected range ($p = 0.494$). A weak positive correlation was nevertheless observed between vitamin D concentration and lumbar spine Z-score ($\rho = 0.135$, $p = 0.026$).

These findings suggest that vitamin D may have a modest relationship with continuous measures of bone density, although its association with clinically classified low BMD was not demonstrated in this sample.

Vitamin D plays an essential role in calcium absorption and bone mineralization. Siddiqee et al. (2021) documented the substantial burden of vitamin D deficiency among South Asian adults, supporting the relevance of assessing vitamin D status in populations such as Pakistan. Ahmed et al. (2023) also discussed the importance of metabolic and nutritional factors in the management of bone health among people living with HIV.

The relatively weak relationship identified in the present study may reflect the multifactorial nature of reduced BMD. Bone density is influenced by several interacting factors, including nutritional status, hormonal regulation, physical activity, chronic infection, and medication exposure. A single serum vitamin D measurement may not adequately represent long-term vitamin D status or cumulative skeletal effects.

Therefore, while vitamin D deficiency was common and remains clinically relevant, the present findings do not establish it as an independent predictor of reduced BMD. Further studies could investigate whether sustained vitamin D insufficiency, dietary calcium intake, or supplementation history explains additional variation in bone health.

Inflammatory Markers and Bone Mineral Density

Chronic inflammation has been proposed as one of the mechanisms linking HIV infection with altered bone metabolism. Persistent immune activation may affect the balance between bone formation and resorption, potentially contributing to reductions in skeletal density. Biver (2022) and Jadzic et al. (2024) have discussed the complex biological pathways through which HIV-related changes may influence bone structure and fragility.

In the present study, CRP concentrations were slightly higher among participants with reduced BMD, but the difference was not statistically significant ($p = 0.328$). Similarly, the correlation between CRP and lumbar spine Z-score was weak and non-significant ($\rho = -0.068$, $p = 0.259$).

These findings indicate that CRP, as measured in this study, was not strongly associated with reduced bone density. However, CRP is a general marker of systemic inflammation and does not directly reflect all the immune processes involved in bone remodeling. The inflammatory pathways affecting skeletal metabolism may involve mechanisms that are not adequately captured by a single CRP measurement.

Accordingly, the absence of a statistically significant relationship should not be taken as evidence against an inflammatory contribution to HIV-related bone changes. Future investigations using more specific inflammatory biomarkers and repeated measurements may provide a clearer understanding of this relationship.

Skeletal Complications and Fracture History

Previous fractures were reported by 4.4% of participants. Importantly, fracture history was more common among individuals with reduced BMD than among those with bone density within the expected range for age (19.0% versus 3.2%, $p = 0.009$).

This finding is clinically relevant because it suggests that participants with lower bone density were more likely to report previous skeletal injuries. Shiau et al. (2013), through a systematic review and meta-analysis, identified an increased incidence of fractures among individuals living with HIV. Collin et al. (2009) also investigated long-term fracture occurrence and associated risk factors among treated HIV-positive adults. Together, these studies support the importance of considering fracture history when evaluating skeletal health in HIV care.

Nevertheless, the fracture findings in the present study require careful interpretation. The recorded outcome represented a history of previous fractures and was not restricted to confirmed low-trauma fractures. Therefore, the observed relationship cannot establish that the reported fractures resulted from osteoporosis or skeletal fragility.

Persistent bone pain was reported by 16.8% of participants but showed no significant association with reduced BMD ($p = 0.763$). This finding suggests that bone pain alone may not reliably distinguish individuals with reduced bone density from those with measurements within the expected range. Clinical assessment should therefore incorporate relevant risk factors and fracture history rather than relying solely on musculoskeletal symptoms.

Clinical Implications

The findings of this study have practical implications for the long-term management of young adults living with HIV in Pakistan. Although ART remains essential for maintaining viral suppression and improving survival, the results suggest that skeletal health deserves attention alongside conventional indicators of treatment success.

Longer ART duration and lower BMI were the two principal factors independently associated with reduced BMD. Both variables can be identified through routine clinical records and basic physical assessment, making them potentially useful when deciding which patients warrant further evaluation.

Brown et al. (2015) recommended a structured approach to assessing and managing bone disease in people living with HIV. The present findings support consideration of a similar risk-based approach in local clinical practice, with particular attention to nutritional assessment, previous fractures, prolonged treatment exposure, and other established skeletal risk factors.

Where clinically indicated and resources permit, DXA assessment may help identify patients requiring more detailed evaluation. Exercise and nutritional interventions may also be relevant components of comprehensive care, although their effectiveness was not tested in this study. Lopes et al. (2024) reviewed the effects of exercise training on bone health among adults living with HIV, providing a basis for further consideration of physical activity as part of supportive management.

CONCLUSION

The study identified bone mineral density below the expected range for age in 7.7% of young adults living with HIV and receiving ART in Lahore. Longer ART duration and lower BMI were independently associated with reduced BMD, while vitamin D and CRP showed limited or non-significant associations with the primary outcome. Previous fracture history was also more frequent among participants with reduced BMD.

These findings suggest that skeletal health should be considered during the long-term clinical management of younger adults receiving HIV treatment. Attention to treatment history, nutritional status, and fracture risk may facilitate earlier recognition of individuals who require additional bone health assessment. Further longitudinal research is needed to establish whether these associations represent progressive skeletal changes and to identify effective prevention strategies in the Pakistani healthcare setting.

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