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Original Article

Vitamin D Deficiency and Bone Turnover in People Living With HIV Switching to Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir Versus Continuing Nonnucleoside Reverse Transcriptase Inhibitor or Protease Inhibitor Regimens in Thailand

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Abstract

Background: People living with HIV (PLWH) frequently have low bone mineral density, with vitamin D deficiency as a key risk factor. Recently, World Health Organization (WHO) and Thai national HIV guidelines recommend dolutegravir as first-line therapy, replacing nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Objectives: To compare vitamin D levels and bone changes in PLWH switching from NNRTI- or boosted protease inhibitor (PI)-containing regimens to DTG-based therapy versus those continuing NNRTI- or PI-based therapy.

Methods: This post hoc analysis used data from a randomized controlled trial (2020-2022) at Suddhavej Hospital, a university-affiliated tertiary care hospital in Maha Sarakham, Thailand. PLWH aged 18 years or older without virologic failure were randomized to either continue current NNRTI/boosted PI-containing combined antiretroviral therapy (control group, CG) or switch to tenofovir disoproxil fumarate/lamivudine/dolutegravir (TDF/3TC/DTG) (switch group, SG). The primary outcome was vitamin D deficiency at 48 weeks; secondary outcomes assessing changes in bone metabolism markers.

Results: Thirty-nine patients completed follow-up (20 CG, 19 SG). After 48 weeks, vitamin D deficiency prevalence increased in both groups (CG: 15% to 35%; SG: 15.8% to 31.6%) with no significant difference ($P = .905$). Osteocalcin increased in SG but decreased in CG ($P = .036$). Beta-crosslaps increased in both groups ($P = .461$ between groups). Procollagen type 1 amino-terminal propeptide showed a nonsignificant decrease in both ($P = .960$).

Conclusions: Switching to TDF/3TC/DTG had minimal impact on vitamin D status but was associated with increased osteocalcin, suggesting a possible positive effect on bone formation. No significant differences were seen in bone resorption or other formation markers.

Keywords: HIV, Dolutegravir, Vitamin D deficiency, Bone turnover, Bone resorption

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Introduction

In 2023, approximately 39.9 million people living with HIV (PLWH) worldwide included 1.4 million children and 38.6 million adults. An estimated 1.3 million new HIV infections occurred globally.[1] In Thailand, approximately 580 000 PLWH in 2023 represented a prevalence of about 1.1% among adults aged 15 to 49. Additionally, around 9100 new adult HIV infections

were reported in the same year.[1] As the population of PLWH continues to increase, so too does the prevalence of aging-related comorbidities, such as osteoporosis and fragility fractures. PLWH are at a significantly higher risk for fragility fractures — 35% to 68% greater than that of HIV-negative individuals.[2, 3] Concurrently, vitamin D deficiency is highly prevalent among PLWH, with rates reported as high as 80%, even in sun-rich regions.[2]

Although several studies have documented the high prevalence of vitamin D deficiency and low bone mineral density in PLWH, limited data are available on the burden of vitamin D deficiency specifically among those with confirmed fragility fractures.[3] Furthermore, while the impact of various antiretroviral therapies on bone health has been explored, the bone-specific effects of newer regimens — particularly those containing integrase strand transfer inhibitors (INSTIs) — remain inadequately characterized, especially in real-world settings.[3, 4] This lack of data poses a challenge for optimizing antiretroviral therapy (ART) regimens to minimize bone-related complications.

The etiologies of low bone mineral density in PLWH are multifactorial, involving the direct effects of HIV infection, traditional risk factors for osteoporosis, chronic illness (eg, malnutrition and low body weight), tobacco and alcohol use, vitamin D deficiency, and the effects of ART.[4-6] HIV infection itself may contribute to impaired bone health through chronic systemic inflammation and immune activation, which disrupt the balance between bone formation and resorption. Furthermore, certain ART agents — particularly efavirenz (EFV) and tenofovir disoproxil fumarate (TDF) — have been shown to interfere with vitamin D metabolism by enhancing catabolism via induction of cytochrome P450 enzymes and impairing renal tubular function, respectively, thereby contributing to lower serum vitamin D levels and altered bone turnover.

INSTIs have been recommended as the preferred backbone of combined antiretroviral therapy (cART) in international treatment guidelines.[7-9] Among these, dolutegravir (DTG) and bictegravir (BIC) have demonstrated efficacy equal to or greater than that of nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI)-based regimens in numerous randomized controlled trials (RCTs).[10-12] According to the 2020 Thai national HIV treatment guidelines, DTG in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) is recommended as first-line therapy for individuals newly diagnosed with HIV-1 infection, based on its well-established durability, efficacy, and safety.[13] The guidelines also support switching from older NNRTI-based fixed-dose combinations — such as TDF/lamivudine (3TC) or emtricitabine (FTC)/EFV — to the preferred DTG-based regimen.[13]

This study aimed to evaluate the clinical outcomes associated with the implementation of the national guideline recommending a switch to the TDF/3TC/DTG fixed-dose combination, with a particular focus on bone metabolism markers.

Methods

Study Design, Setting, and Participants

This study serves as a post hoc analysis of an open-label, RCT conducted at Suddhavej Hospital, Maha Sarakham, Thailand, from December 2020 to December 2022. The study included PLWH aged 18 years or older without evidence of virologic failure, recruited from the outpatient clinic. Following the provision of written informed consent, participants were randomly assigned in a 1:1 ratio to either switch to a regimen of TDF/3TC/DTG or continue their current cART, using a computer-generated block randomization method with a block size of 4. The current cART group (CG) consisted of patients who continued to receive an NNRTI

or boosted PI-containing regimen, while the switch group (SG) comprised patients who switched from an NNRTI or boosted PI-containing regimen to a fixed drug combination including 300 mg of TDF, 300 mg of 3TC, and 50 mg DTG. The exclusion criteria included: 1) women of childbearing age who intended to conceive within the next 52 weeks or refused contraception; 2) pregnant women; 3) presence of documented ART-resistant-associated mutations; 4) virologic failure, defined as an HIV viral load at least 200 copies/mL; 5) creatinine clearance less than or equal to 60 mL/min/1.73 m^2; 6) cirrhosis Child-Turcotte-Pugh score of B to C; 7) current antituberculous therapy; 8) current metformin use at a dose exceeding 1000 mg/day; 9) history of DTG hypersensitivity; 10) alanine aminotransferase (ALT) levels exceeding 5 times the upper limit of normal or total bilirubin levels exceeding 1.5 times the upper limit of normal; and 11) current use of vitamin D supplementation.

The study assessed 210 participants for eligibility, of whom 48 participants were included in the study. The remaining individuals were excluded because 130 did not meet the inclusion criteria, 17 declined to participate, 13 women of childbearing age declined contraception, and 2 were on antituberculous therapy. The 48 eligible participants were randomized, with 23 assigned to the TDF/3TC/DTG group and 25 assigned to the NNRTI or boosted-PI-containing regimen group. The intention-to-treat-exposed analysis included all participants in their assigned groups, while the per-protocol analysis included 19 participants in the TDF/3TC/DTG group and 20 in the NNRTI/boosted-PI group after accounting for discontinuations and loss to follow-up (Figure 1).

Outcomes

The primary outcome measure of this study was the proportion of patients with vitamin D deficiency, defined as a serum 25(OH) vitamin D level below 20 ng/mL at 48 weeks. Secondary outcomes included changes in biological markers of bone health assessed at the 48-week follow-up, specifically beta-crosslaps (bCTx), N-MID (N-midfragment) osteocalcin, and total procollagen type 1 amino-terminal propeptide (P1NP). Beta-crosslaps (bCTx), degradation products of type I collagen, serve as sensitive indicators of bone resorption and reflect the rate of bone turnover. N-MID osteocalcin, synthesized by osteoblasts during the bone mineralization process, is a marker of bone formation and indicative of osteoblastic activity. Total P1NP, another bone formation marker, reflects the synthesis of type I collagen, the principal structural protein in the bone matrix. Collectively, these markers provide insights into the dynamic balance between bone formation and resorption.

Demographic data and routine laboratory tests were also collected. Blood samples were obtained at baseline and at the 48-week follow-up to measure serum 25(OH)D and the aforementioned bone turnover markers. These samples were collected concurrently with routine blood chemistry evaluations, including renal and liver function panels, as part of the preliminary RCT protocol. All specimens were processed and analyzed in a certified central laboratory using standardized procedures.

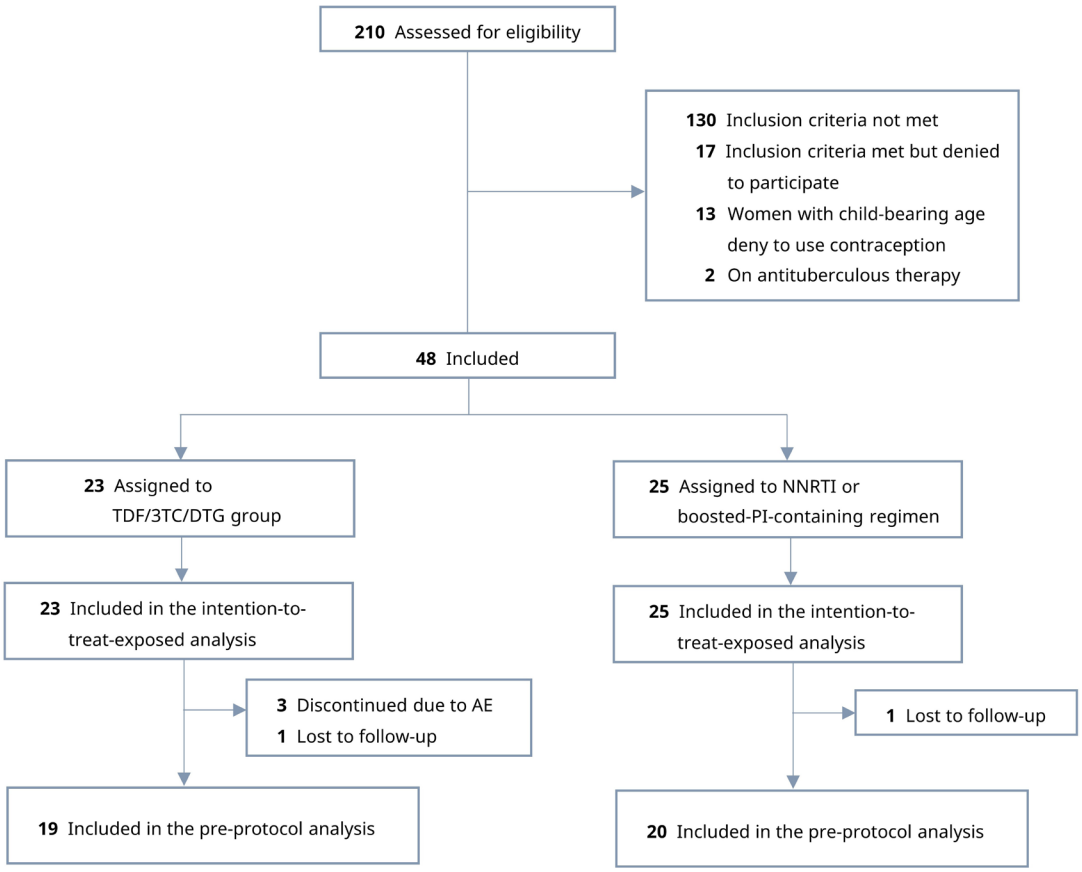
Statistical Analysis

Statistical analysis involved expressing categorical data as frequencies and percentages, which were compared using the chi-square test. If exceed 20% of expected cell counts were less than 5, Fisher exact test was used instead. Continuous variables were analyzed using Student's *t* test or the Wilcoxon rank sum test, depending on data distribution. A mixed model was used to analyze changes in bone turnover markers between groups. The McNemar test was applied to categorical dichotomous data. The primary outcome of the study was

achieving a viral load of less than 50 copies/mL at the end of week 24 (with a 4-week window on either side) in the intention-to-treat population, which included all patients who received at least 1 dose of the trial medication. Patients with missing RNA results at week 24 were considered as not having reached an undetectable level of plasma HIV-1 RNA for the primary efficacy measure.

Sample size was calculated based on a noninferiority assumption to demonstrate that the new treatment is not clinically inferior to the standard therapy within a prespecified margin, ensuring adequate power to confirm comparable efficacy. To determine the noninferior efficacy of the DTG-based regimen compared to the standard-of-care regimen, we estimated a sample size of 75 patients per group, providing 80% power. The calculations were based on a noninferiority margin of -10 percentage points and an assumed efficacy of 79% in the standard-of-care group. The analysis also included a minimum of 20 patients per group from the pilot study. Statistical analyses were conducted using SPSS version 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; 2016) with a significance level set at $P \leq .05$ (2-sided). The efficacy and safety results of the main pilot study were published in an abstract presented at IDWeek 2023.[14]

Figure 1. Flow Diagram of Eligible Patients



Abbreviations: AE, adverse event; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF/3TC/DTG, tenofovir disoproxil fumarate/lamivudine/dolutegravir.

Results

The study population consisted of 48 PLWH, with 25 patients in the CG (continuing their current ART, either NNRTI or boosted-PI regimen) and 23 patients in the SG who had switched to the DTG-based regimen. All baseline characteristics were similar between groups (Table 1).

A total of 39 patients completed the 48-week follow-up period (20 in the CG and 19 in the SG). The prevalence of vitamin D deficiency in this population was 33.33% (13 out of 39 at the final follow-up). The proportion of patients with vitamin D deficiency showed a tendency to increase in both groups after the 48-week follow-up period (from 15.78% to 31.58% in the SG and from 15% to 35% in the CG; *P* = .268 and .186, respectively). However, there was no statistical difference between the 2 groups (*P* = .428). In the SG, mean serum 25(OH) vitamin D levels tended to minimally decrease from baseline at the final follow-up period, but the difference was not statistically significant (*P* = .321). Conversely, in the CG, mean serum 25(OH) vitamin D levels remained steady (*P* = .983). Furthermore, there was no statistical difference between the 2 groups (*P* = .505) (Table 2).

At 48 weeks, after switching to DTG, the osteocalcin level significantly increased (mean [SD], 23.85 [13.92] to 30.21 [13.92]; *P* = .025). In the CG, which maintained the NNRTI or boosted PI-containing regimen, there was a slight but insignificant decrease from 23.95 (7.58) to 22.74 (8.15) (*P* = .570). There was a significant difference in osteocalcin level changes between the 2 groups, corresponding to a 7.57 ng/mL difference in the SG compared to the CG (*P* = .036). Beta-crosslaps significantly increased in both groups (mean [SD], 0.48 [0.34] to 0.73 [0.34]; *P* = .019 in the switch group and from 0.45 [0.25] to 0.61 [0.27]; *P* = .030 in the current cART group). However, there was no statistical difference between the 2 groups (*P* = .461). Total P1NP showed a tendency to decrease in both groups after the 48-week follow-up, but there was no statistical difference between the 2 groups (*P* = .960) (Figure 2).

Table 1. Baseline Characteristics and Laboratory Markers in the 2 Groups

Baseline Characteristic	No. (%)	
	DTG-Based Regimen (n = 19)	NNRTI or Boosted-PI-Containing Regimen (n = 20)
Age, mean (SD), y	28.94 (11.20)	29.45 (9.57)
Sex		
Male	16 (84.21)	17 (85.00)
Female	3 (15.78)	3 (15.00)
Body weight, mean (SD), kg	60.67 (12.97)	63.06 (10.19)
Waist circumference, mean (SD), cm	76.44 (10.60)	78.82 (8.88)
Body mass index, mean (SD), kg/m^2	21.46 (3.55)	21.85 (3.32)
Duration since HIV diagnosis, median (IQR), mo	24 (10.00-47.00)	22 (18.00-39.50)
Nadir CD4, median (IQR), %	407 (168.50-562.00)	337 (219.00-449.00)

Table 1. Baseline Characteristics and Laboratory Markers in the 2 Groups (Continued)

Baseline Characteristic	No. (%)	
	DTG-Based Regimen (n = 19)	NNRTI or Boosted-PI-Containing Regimen (n = 20)
Preswitch ART		
TDF + FTC + EFV	12 (63.15)	15 (75.00)
TDF + 3TC + EFV	4 (21.05)	4 (20.00)
TDF + 3TC or FTC + RPV	2 (10.52)	1 (5.00)
TDF + 3TC or FTC + LPV-r	1 (5.26)	0
Laboratory profiles		
Vitamin D deficiency*	3 (15.78)	3 (15.00)
Serum 25(OH) vitamin D, mean (SD), ng/mL	30.75 (10.80)	26.79 (8.10)
N-MID osteocalcin, mean (SD), ng/mL	23.85 (13.92)	23.95 (7.58)
Beta-crosslaps , mean (SD), ng/mL	0.48 (0.34)	0.45 (0.25)
Total P1NP, mean (SD), ng/mL	66.04 (24.47)	57.35 (15.77)
CD4, mean (SD), cells/mm^3	518.78 (191.76)	506.25 (229.70)
CD4, mean (SD), %	21.94 (7.52)	21.52 (8.32)

Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; LPV-r, lopinavir-ritonavir; N-MID, N-midfragment; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; P1NP, procollagen type 1 amino-terminal propeptide; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

* Vitamin D deficiency referred to serum 25(OH) vitamin D level less than 20 ng/mL.

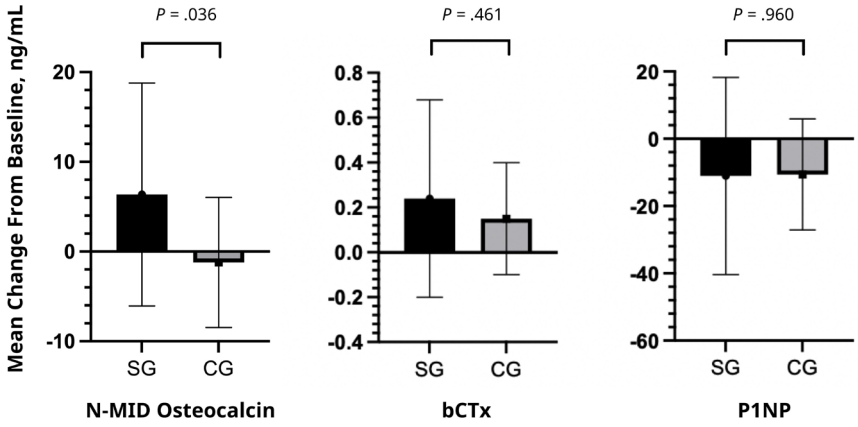
Table 2. Laboratory Markers After 48-Week Follow-Up Period in the 2 Groups

Laboratory Profile	DTG-Based Regimen (n = 19)			NNRTI or Boosted-PI-Containing Regimen (n = 20)		
	Baseline	48-Week	*P* Value	Baseline	48-Week	*P* Value
Vitamin D deficiency, No. (%)*	3 (15.78)	6 (31.58)	.268	3 (15.00)	7 (35.00)	.186
Serum 25(OH) vitamin D, mean (SD), ng/mL	30.75 (10.80)	28.46 (14.13)	.321	26.79 (8.10)	26.74 (11.93)	.983
N-MID osteocalcin, mean (SD), ng/mL	23.85 (13.92)	30.21 (13.92)	.025	23.95 (7.58)	22.74 (8.15)	.570
Beta-crosslaps, mean (SD), ng/mL	0.48 (0.34)	0.73 (0.34)	.019	0.45 (0.25)	0.61 (0.27)	.030
Total P1NP, mean (SD), ng/mL	66.04 (24.47)	54.98 (24.47)	.100	57.35 (15.77)	46.73 (17.11)	.029

Abbreviations: DTG, dolutegravir; N-MID, N-midfragment; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; P1NP, procollagen type 1 amino-terminal propeptide.

* Vitamin D deficiency referred to serum 25(OH) vitamin D level less than 20 ng/mL.

Figure 2. Bone Markers Change After 48-Week Follow-Up Period



Abbreviations: CG, current cART group; bCTx, beta-crosslaps; N-MID, N-midfragment; P1NP, procollagen type 1 amino-terminal propeptide; SG, switch group.

Discussion

Low vitamin D levels, defined as a serum 25(OH) vitamin D level below 30 ng/mL, have been reported to range from 60% to 75% in the literature.[15, 16] The prevalence of vitamin D deficiency in PLWH in Thailand has been reported to be between 10% and 25%,[17, 18] whereas in this study, it was 33%. There was a tendency for the proportion of vitamin D deficiency to increase in both groups at the 48-week follow-up, but this difference was not statistically significant. Interestingly, low vitamin D levels, vitamin D insufficiency, and vitamin D deficiency showed different effects in this population.

Occupational factors likely influence vitamin D status, as individuals working indoors or night shifts have reduced sunlight exposure, limiting cutaneous vitamin D synthesis. In contrast, outdoor workers may have higher serum vitamin D levels due to greater sun exposure.[19] In this study, the majority of participants in both treatment groups were young adult males (84%-85%) with a mean age of approximately 29 years. As most participants were of working age, it is likely that a significant proportion engaged in the indoor work, limiting their UVB exposure and consequently their vitamin D synthesis. This finding aligns with previous studies indicating that occupational sun exposure is a key determinant of vitamin D status, even in the tropical regions.[19] These differences suggest that occupation should be considered a relevant factor when evaluating vitamin D status in PLWH.

Switching to the DTG-containing regimen led to a nonsignificant increase in the proportion of individuals with low vitamin D levels, while those who received NNRTI or boosted PI-containing regimens showed a nonsignificant decrease. It is worth noting that there was a difference in the proportions of low vitamin D levels between the 2 groups at baseline, rendering the interpretation of these changes invalid. These findings align with the results from a larger observational study, which demonstrated a significant increase in bone mineral density of the lumbar spine (+1.6%) after approximately 2 years of DTG-based ART, particularly among participants with baseline osteopenia or those receiving vitamin D supplementation.[20] These data support the potential favorable effect

of DTG-containing regimens on the bone health in PLWH. Additionally, low vitamin D levels may occur in the general population without significant clinical implications; however, factors such as the use of sunblock lotion — which reduces UVB radiation needed for cutaneous vitamin D synthesis — may further contribute to lower serum vitamin D levels, particularly in individuals with limited sun exposure.[19] It is noteworthy that the CG had persistently lower baseline vitamin D levels compared to the SG. This can be explained by the mediation of EFV through cytochrome P24 (CYP24) induction. Upregulation of CYP24, a 25-hydroxyvitamin D3-24-hydroxylase, may accelerate the catabolism of vitamin D, thereby decreasing the level of 25(OH) vitamin D.[21]

Initiation of ART induces a significant loss of bone mineral density by 2% to 6%, regardless of the choice of ART.[8, 22, 23] Underlying pathogenesis includes HIV-related inflammation after immune reconstitution and ART-related toxicity.[21, 22] Tenofovir (TNV), a NRTI, may indirectly affect bone health through proximal renal tubulopathy, leading to renal phosphate wasting and increased bone resorption, commonly known as renal osteomalacia.[24] However, chronic renal phosphate loss from TNV-induced proximal renal tubulopathy can result in osteoporosis and subsequent fractures.[23] EFV and PIs may also indirectly affect bone metabolism through vitamin D metabolism.[25-27] Boosted PIs can increase TNV exposure and the risk of renal and bone adverse events.[22, 23] In a rat model, EFV was shown to have a negative effect on bone tissue by affecting bone microarchitecture and impairing biomechanical properties.[24]

In terms of clinical evidence, switching to a TDF-sparing DTG-based regimen has previously been associated with increased bone turnover rates, manifesting as reductions in bone formation markers (P1NP, osteocalcin) with minimal changes in bone resorption markers (beta-crosslaps).[28] In contrast, this study demonstrated a significant increase in N-MID osteocalcin in the SG compared to the CG, with no significant differences in P1NP or bCTx between groups. Interestingly, total P1NP was significantly reduced only in the CG. These findings suggest enhanced bone formation activity following the switch to the DTG-based regimen. This observation appears more pronounced than what was reported in the STRIIVING trial, which also observed increased bone turnover and formation after switching to a DTG-based regimen, even when TDF remained a part of the regimen.[27] Regarding bone metabolism, this data supports the phase-out strategy endorsed by the 2020 Thai national HIV guidelines, which advocate switching to TDF/3TC/DTG. Given that NNRTI- or PI-based regimens remain widely used in the resource-limited settings, and with the increasing availability of fixed-dose combination TDF/3TC/DTG, transitioning to DTG-based regimens may mitigate long-term bone toxicity.

PLWH with compromised bone health should be managed with a comprehensive care strategy incorporating routine screening, lifestyle optimization, ART regimen selection, and nutritional support. Improved dietary intake of calcium-, vitamin D-, and protein-rich foods — such as dairy products, fortified cereals, eggs, fatty fish, and leafy green vegetables — along with safe sun exposure and regular weight-bearing exercise, may enhance bone metabolism and lower fracture risk.

However, several limitations must be acknowledged. The small sample size may have reduced the statistical power to detect significant differences across some parameters. Additionally, the study population primarily comprised of young male PLWH, limiting generalizability to the older individuals and postmenopausal women, who are at greater risk of bone-related complications. This study was limited by its relatively short follow-up period and modest sample size. Moreover, bone mineral density was not assessed using

dual-energy x-ray absorptiometry, the gold standard for evaluating bone health and diagnosing osteoporosis. Future studies with larger, more diverse populations and longitudinal assessment are essential to clarify the long-term skeletal effects of DTG-based regimens in PLWH.

Conclusions

In this study, switching to TDF/3TC/DTG had a minimal impact on vitamin D status. Bone turnover markers indicated an increase in bone formation compared to continuing NNRTI or PI-based cART. These findings suggest a potential beneficial effect of the TDF/3TC/DTG regimen on bone metabolism within the 48-week follow-up period.

Further research with longer-term follow-up is necessary to assess the impact of switching to TDF/3TC/DTG on bone mineral density and fracture incidence, particularly in aging populations of PLWH. Such studies would provide more comprehensive insights into the clinical implications of bone metabolism changes observed in this study.

Additional Information

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Ethics Approval: The study protocol received approval from the Ethics Committee of Mahasarakham University (No. 264-157/2564) on 20 July 2021, in Mahasarakham, Thailand. Written informed consent was obtained from all recruited patients.

Clinical Trial Consideration: The study was registered in the Thai Clinical Trials Registry (TCTR20210409003) and received approval on 24 December 2020.

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Formal Analysis: All authors
Funding Acquisition: Pakawas Praisarnti
Methodology: All authors
Visualization: All authors
Writing – Original Draft: Pakawas Praisarnti
Writing – Review & Editing: Samadhi Patamatamkul

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