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ORIGINAL RESEARCH

Bone Mineral Density Changes in People with HIV Who had Immediate Switch Versus Deferred Switch from Tenofovir Disoproxil Fumarate-Based Regimens to Bictegravir/Emtricitabine/Tenofovir Alafenamide: A Multicenter, Open-Label, Randomized Clinical Trial

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ABSTRACT

***Introduction*:** Tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy regimens remain one of the first-line treatments in many countries. We assessed the changes of bone mineral density (BMD) in people with HIV (PWH) who had early switch from TDF-based regimens to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

***Methods*:** This 48-week, multicenter, randomized, open-label clinical trial recruited adult PWH on TDF-based regimens with virological suppression for at least 24 weeks. Participants were randomly assigned (1:1) to immediately switch to B/F/TAF (immediate switch group) or switch after 24 weeks (deferred switch group). The primary endpoint was the median percentage change [interquartile range (IQR)] in BMD from baseline to week 48.

***Results*:** Between December 17, 2021 and February 21, 2023, 150 PWH were randomly

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assigned to immediate switch group (n = 75) or deferred switch group (n = 75). At week 48, no significant difference in BMD changes of the spine was observed at week 48 [3.30% (IQR 1.19, 5.47) vs. 2.84% (0.51, 5.00); P = 0.199]. The increase in hip BMD was greater in the immediate switch group than deferred switch group [median percentage change, 2.05% (0.20, 4.12) vs. 0.88% (– 0.52, 3.15); P = 0.035]. Viral suppression at week 48 was noted in 71 (94.6%) participants assigned to the immediate switch group and in 67 (89.3%) assigned to the deferred switch group. Similar rates and severity of adverse events were observed in both groups, with no serious adverse events reported.

Conclusions: While both immediate and deferred switch from TDF-based regimens to B/F/TAF maintained virological suppression, early switch resulted in better improvement of BMD in the hip joint.

Clinical Trials Registration: ClinicalTrials.gov (NCT05122754).

Keywords: Bone health; Osteopenia; Osteoporosis; Nucleotide reverse transcriptase inhibitor; Integrase strand-transfer inhibitor; Non-nucleoside reverse transcriptase inhibitor; Protease inhibitor

Key Summary Points

Why carry out this study?

The adverse effects of tenofovir disoproxil fumarate (TDF) on bone health in people with HIV (PWH) are well recognized.

However, bone data on the optimal timing of switching to tenofovir alafenamide (TAF)-based regimens remain limited, particularly in the Asia–Pacific region and among younger PWH without preexisting bone disease.

Previous studies have not clearly identified whether bone mineral density (BMD) improvement depends on the type of baseline antiretroviral regimen (e.g., PI- vs. NNRTI-based).

What was learned from the study?

We conducted a multicenter, open-label, randomized clinical trial evaluating changes in BMD among virologically suppressed PWH who switched from TDF-based antiretroviral regimens to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

Participants were randomized to immediate switching versus deferred switching after 24 weeks, with a 48-week follow-up.

Among 150 participants (predominantly young males without osteoporosis), early switching to B/F/TAF led to significant improvements in hip BMD, particularly in those whose baseline regimens contained protease inhibitors (PIs).

INTRODUCTION

People with HIV-1 (PWH) are prone to osteopenia and osteoporosis, due to complex interactions among aging, comorbidities, and traditional risk such as smoking [1], glucocorticoid use [2], low body mass index [3] and previous fractures and frailty [4]. Reduced bone mineral density (BMD) is common even in PWH who are under 50 years old, with the prevalence of reduced BMD as high as 22.80–39.4% [5, 6]. A meta-analysis demonstrates PWH had a higher prevalence of all fractures (4.08% vs. 0.44%) and fragility fractures (2.66% vs. 2.19%) compared with individuals without HIV infection [7]. In China, cross-sectional data have also documented a substantial prevalence of low BMD and identified lopinavir/ritonavir (LPV/r) exposure as important risk factors [8, 9].

Antiretroviral drugs, particularly tenofovir disoproxil fumarate (TDF) [10] and boosted protease inhibitors (PIs), such as LPV/r [11] also impact bone health [12]. However, TDF used to be the most commonly used backbone drug in many countries [13]. Several clinical studies have demonstrated a BMD benefit in virologically suppressed PWH switching to tenofovir alafenamide (TAF)-based regimens, such as coformulated elvitegravir, cobicistat, emtricitabine, and TAF (E/c/F/TAF) [14–17]. A small randomized controlled study has demonstrated that elderly PWH who switched from TDF to TAF exhibited reduced bone turnover levels [18]. Recently, coformulated bictegravir, emtricitabine(FTC), TAF (B/F/TAF) has replaced E/c/F/TAF owing to fewer drug–drug interactions and greater convenience [19], yet the bone data on the impact of switching from TDF to TAF on BMD of PWH are scarce in the Asia–Pacific region [20].

Therefore, we hypothesized that early switch from TDF- to TAF-based ART would result in a greater improvement in BMD over 48 weeks compared with deferred switch. The deferred-switch group was designed to reflect real-world clinical practice and to assess whether the skeletal benefits of B/F/TAF depend on the timing of regimen modification.

METHODS

Study Design

This randomized, open-label, multicenter, active-controlled study was conducted at three hospitals in China. Participants were randomly assigned in a 1:1 ratio to immediate switching to B/F/TAF (immediate switch group) or to continue their baseline TDF-based regimens for 24 weeks and then switch to B/F/TAF (deferred switch group). Stratified block randomization was performed with stratification according to the third drug at screening [LPV/r or nonnucleoside reverse transcriptase inhibitor (NNRTI)]. Neither investigators nor participants were masked to treatment assignment.

The study was approved by the independent ethics committee of Shanghai Public Health Clinical Center (number: 2020-S187-02) and conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. This study was registered with ClinicalTrials.gov (NCT05122754). All participants provided written informed consent.

Participants had been virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) for ≥ 24 weeks before screening, were aged 18 years or older, currently received a regimen containing TDF and lamivudine (3TC) plus a third drug (PI or NNRTI) for at least 24 consecutive weeks before screening. Participants with an estimated glomerular filtration rate (eGFR, by the CKD Epidemiology Collaboration formula) greater than 50 mL/(min/1.73m^2), and without TDF or thymidine analogue resistance-associated mutations based on historical genotype before screening were eligible. Participants with evidence of previous virological failure were excluded. Other key exclusion criteria included a new AIDS-defining condition diagnosed within the 30 days before screening, clinical evidence of decompensated cirrhosis, hypogonadism, and previous treatment for bone disease (including bisphosphonates and denosumab) or with drugs contraindicated with B/F/TAF (full inclusion and exclusion criteria are given in the Supplementary Material, pp 3).

Study Procedures

After screening, study visits occurred at day 1 and weeks 12, 24, 36, and 48. Dual-energy X-ray absorptiometry (DXA) scans (Lunar Prodigy; GE Healthcare, Chicago, IL, USA) to measure BMD of the spine and hip were carried out at screening and weeks 24 and 48 at each study center, using standardized procedures according to the manufacturer's manual. DXA technicians and the personnel performing BMD analyses were blinded to treatment assignment to minimize measurement bias. To make BMD measurements from the three centers comparable, the same European spine phantom (ESP-406; QRM, Möhrendorf, Germany; see Supplementary Material Figure S2) underwent ten scans, each

time being repositioned on different DXA scanners using an identical standardized scan protocol. At each center, a regression equation was established and BMD data from each site were adjusted using the regression equation separately (see Supplementary Material, Table S1).

Endpoints

The primary endpoints were the mean percentage change from baseline in spine and hip BMD at week 48. Secondary endpoints included the evaluation of spine and hip BMD at week 24, the proportion of participants who had increased or decreased spinal or hip BMD by more than 3% from baseline at weeks 24 and 48, the proportion of participants maintaining virological suppression at weeks 24 and 48 as defined by the US FDA snapshot algorithm, and the changes in CD4 cell count from baseline at weeks 24 and 48. The assessment of the overall safety and tolerability of B/F/TAF until week 48 was pre-specified as a secondary objective of the study.

Safety outcomes were incidence of adverse events and laboratory abnormalities, and change from baseline to week 48 in serum creatinine, renal function parameters, fasting lipid parameters and weight changes, coded with version 26.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were graded according to version 1.0 of the DAIDS AE Grading Table.

Statistical Analysis

Sample size and statistical power estimations are provided in the Supplementary Material (pp 3). Spine or hip DXA data were analyzed on all participants who were randomly assigned, received at least one dose of study drug (full analysis set), had no missing spine or hip BMD values at baseline, and at least one post-baseline visit. For the primary endpoint, the percentage changes from baseline in spine and hip BMD at week 48 were summarized by treatment group and compared using a non-parametric rank sum test.

For the secondary endpoint and safety profile were analyzed on full analysis set. Subgroup analysis, stratified by the third drug pre-switch, used a Bonferroni-corrected significance level ($P < 0.025$). Statistical analysis was conducted using SPSS 27.0 software (IBM Corp, Armonk, NY, USA), and graphs were generated using GraphPad 9.3.0 (La Jolla, CA, USA).

RESULTS

Disposition and Baseline Characteristics of the Participants

Between December 17, 2021, and February 21, 2023, a total of 150 participants were recruited across the three centers and were randomly assigned to either the immediate switch group ($n = 75$) or the deferred switch group ($n = 75$; Fig. 1 and Supplementary Material Figure S2). All participants received at least one dose of treatment, with the last visit occurring on January 23, 2024. During the study visits, three participants (4.0%) in the immediate switch group and five (6.7%) in the deferred switch group discontinued treatment before 48 weeks. Of these eight participants, four participants lost to follow-up, and two participants experiencing protocol violations.

Demographic and clinical characteristics of the two treatment groups at baseline were similar (Table 1). Participants had a mean age of 34 years (interquartile range [IQR] 29–40 years), with mostly males and an average weight of 67.48 kg (standard deviation [SD] 11.93) and BMI of 22 kg/m^2 (IQR 20–24). The median CD4 count in the immediate switch group was 594 cells/μL (IQR 447–836), and 585 cells/μL (IQR 455–737) in the deferred switch group. The mean CD4/CD8 ratio for both groups were 0.85 and their average duration of diagnosed HIV infection of 6.42 years (SD 0.31) prior to enrollment. Baseline BMD values were similar, with reduced BMD in 8 (10.7%) and 6 (8.0%) participants in immediate switch group and deferred switch group, respectively. The baseline regimen for most participants consisted of TDF plus 3TC, with efavirenz (EFV) as the third drug (Table 1).

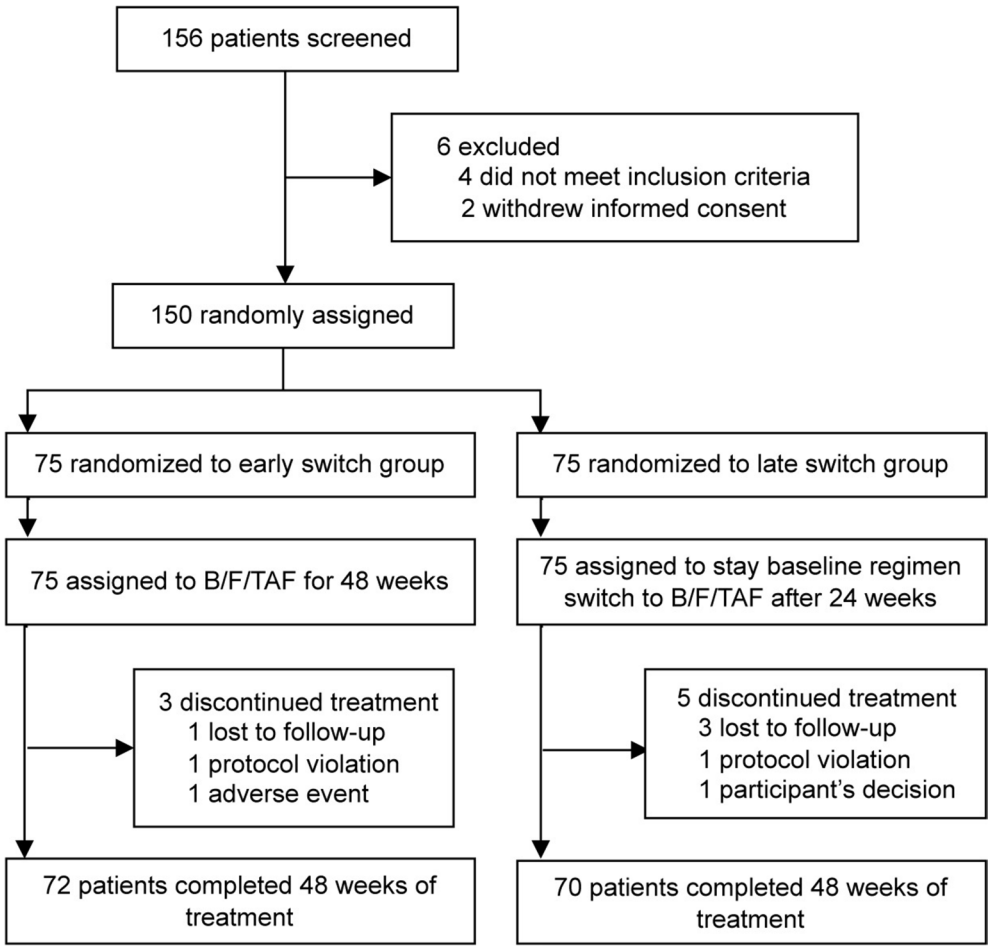

Fig. 1 Flowchart

Primary and Secondary Outcomes

All BMD data were calibrated using the cross-sectional calibration equations (see Supplementary Material, Table S1) before the start of analysis. At week 48, the median change in spine BMD relative to baseline were comparable in the immediate versus deferred switch group [3.30% (1.19, 5.47) vs. 2.84% (0.51, 5.00), $P = 0.199$). In contrast, the hip BMD showed a significantly greater increase in the immediate switch group compared to the deferred switch group [2.05% (0.20, 4.12) vs. 0.88% (– 0.52, 3.15), $P = 0.035$] at week 48. However, at week 24, the median change in spine BMD relative to baseline was 2.59% (1.03, 5.01) in the immediate switch group, which was significantly higher than that in the deferred switch group [0.25% (– 2.05, 2.17), $P < 0.001$; Fig. 2; Table 2]. Similarly, at week 24, the median increase in hip BMD was 1.75% (– 0.6, 3.45) and – 0.12% (– 1.47, 1.40) in the immediate switch and deferred switch group ($P = 0.015$), respectively.

In the subgroup analyses consisting of 95 participants who received NNRTI-based regimens, no significant differences in the changes of BMD at week 48 from baseline between immediate and deferred switch group [3.30% (0.84, 4.98) vs. 2.84% (1.40, 5.20), $P = 0.914$ in spine; 1.24% (– 1.44, 3.47) vs. 0.77% (– 0.82, 2.94), $P = 0.260$ in hip; Fig. 3A and B]. Similarly, there were no statistically significant differences at week 24 were observed in the mean percentage changes of spine [2.72% (0.79, 4.93) vs. 0.70% (– 1.70, 3.57), $P = 0.045$] and hip

Table 1 Baseline demographics and clinical characteristics

	Immediate switch group (*n* = 75)	Deferred switch group (*n* = 75)	Total (*n* = 150)
Mean age (years, IQR)	35 (29–42)	33 (30–40)	34 (29–40)
Sex			
Males	70 (93.3%)	67 (89.35%)	137 (91.3%)
Mean weight (kg, SD)	68.32 (12.76)	66.65 (11.06)	67.48 (11.93)
Body-mass index (kg per m^2, IQR)	22 (20,25)	22 (20,24)	22 (20,24)
Median CD4 count (cells/μL, IQR)	594 (447–836)	585 (455–737)	588 (450–796)
CD4 count (cells/μL)*			
< 50	0	0	0
50–199	3 (4.05%)	1 (1.35%)	4 (2.70%)
200–349	6 (8.10%)	8 (10.81%)	14 (9.46%)
350–499	19 (25.68%)	14 (18.92%)	33 (22.30%)
≥ 500	46 (62.17%)	51 (68.92%)	97 (65.54%)
CD4/CD8 ratio[a]	0.82 (0.05)	0·89 (0.05)	0·85 (0.03)
Time since diagnosis of HIV infection (years)	6.54 (3.75)	6.31 (3.86)	6·42 (0.31)
Mean spine BMD (g/cm^2)	0.996 (0.141)	0.969 (0.129)	0.982 (0.011)
Mean hip BMD (g/cm^2)	0.872 (0.018)	0.842 (0.013)	0.857 (0.011)
Normal BMD	67 (89.3%)	69 (92%)	132 (90.7%)
Below the expected range for age	5 (6.7%)	1 (1.3%)	6 (8%)
Osteopenia	2 (2.7%)	2 (2.7%)	4 (2.7%)
Osteoporosis	1 (1.3%)	3 (4%)	4 (2.7%)
Mean eGFR (mL per min per $1.73m^2$)	110.51 (19.33)	114.04 (20.28)	112.28 (1.62)
Comorbidities			
Hyperuricemia	16 (21.33%)	15 (20%)	31 (20.67%)
Baseline ART regimen (TDF + 3TC + third drug)			
NNRTI (EFV, NVP)	47 (62.67%)	48 (64%)	95 (63.33%)
PI (LPV/r)	28 (37.33%)	27 (36%)	55 (36.67%)

Data are *n* (%), mean (SD), or median (IQR) unless otherwise specified

3TC lamivudine, *ART* antiretroviral therapy, *BMD* bone mineral density, *EFV* efavirenz, *eGFR* estimated glomerular filtration rate, *IQR* interquartile range, *LPV/r* lopinavir/ritonavir, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *NVP* nevirapine, *PI* protease inhibitors, *SD* standard deviation, *TDF* tenofovir disoproxil fumarate

[a]One participant in immediate switch and deferred switch groups did not have baseline CD4 count test

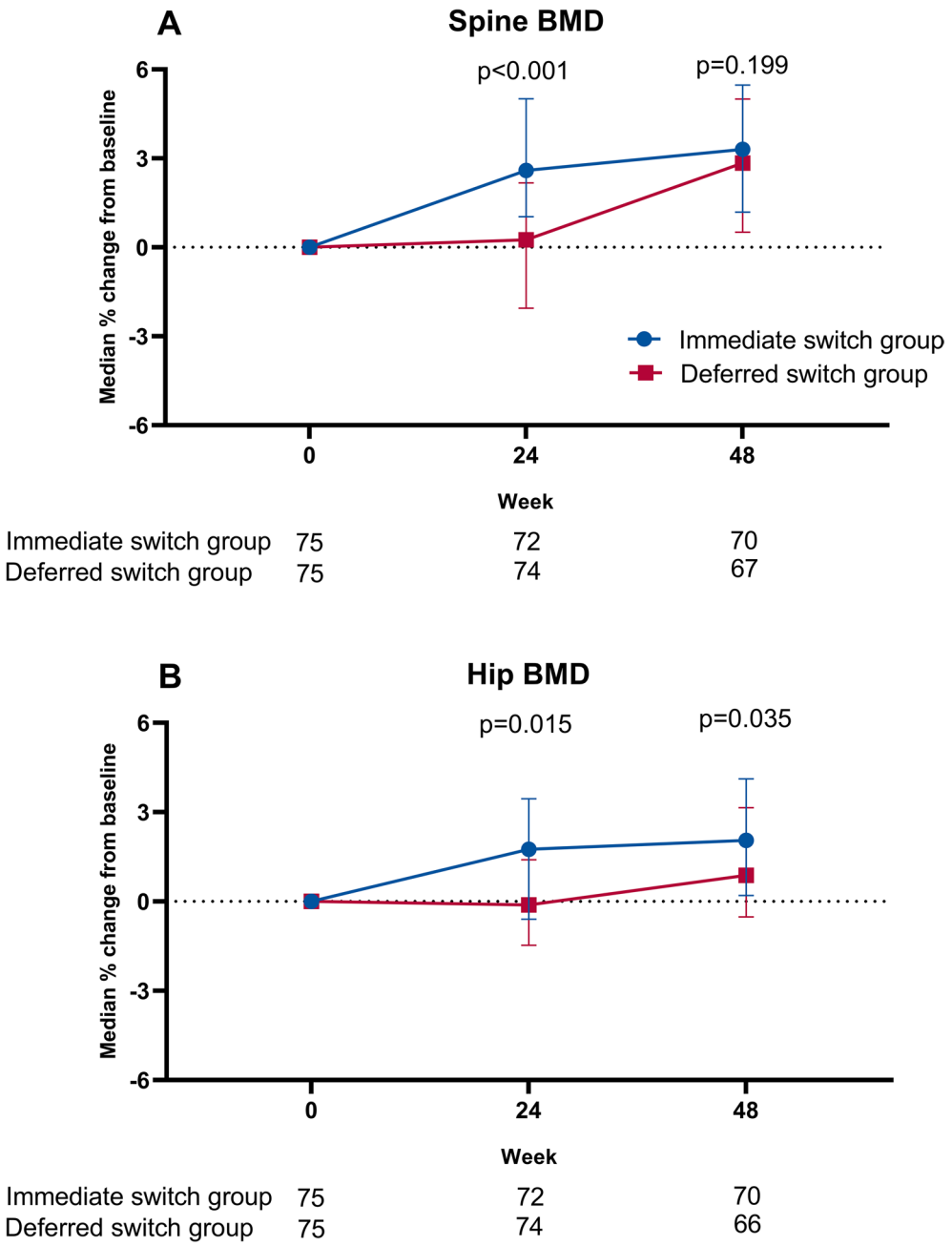

Fig. 2 Median percentage change from baseline in spine and hip BMD from baseline to week 48; *error bars* interquartile range

BMD [0.88% (– 1.40, 2.55) vs. 0.16% (– 1.52, 1.82), $P = 0.321$] compared to baseline between the two groups. Moreover, in the subgroup of 55 participants who received PI-based regimens, the median change in hip BMD relative to baseline at week 48 was 3.56% (0.83, 5.38) in the immediate switch group and 1.21% (0, 3.29) in the deferred switch group was significant ($P = 0.022$). The median change in spine BMD relative to baseline in the PI subgroup at week 48 was not statistically significantly different, with 3.36% (1.37, 6.55) in immediate

Table 2 BMD analyses at weeks 24 and 48

	Immediate switch group (*n* = 75)	Deferred switch group (*n* = 75)	*p* value	Difference (95% CI)
Week 24				
Spine BMD, median percentage change from baseline	2.59% (1.03,5.01); *n* = 72	0.25% (– 2.05,2.17); *n* = 74	< 0.001	2.56% (2.48, 2.94)
Hip BMD, median percentage change from baseline	1.75% (– 0.60,3.45); *n* = 72	-0.12% (– 1.47,1.40); *n* = 74	0.015	1.94% (1.40, 1.96)
Week 48				
Spine BMD, median percentage change from baseline	3.30% (1.19,5.47); *n* = 70	2.84% (0.51,5.00); *n* = 67	0.199	0.30% (0.13,0.63)
Hip BMD, median percentage change from baseline	2.05% (0.20,4.12); *n* = 70	0.88% (– 0.52,3.15); *n* = 66	0.035	0.94% (0.84,1.21)

Spine and hip BMD data include all participants who were randomly assigned, received at least one dose of study medication, did not lose spine or hip BMD values at screening (for baseline values), and had at least one post-baseline visit

BMD bone mineral density

switch group vs. 2.26% (– 2.53, 3.66) in the deferred switch group ($P = 0.030$). At week 24, the median changes in spine and hip BMD relative to baseline in the immediate switch group were 2.58% (1.32, 5.71) and 2.65% (0.18, 3.55), respectively, while in the deferred switch group, they were – 1.38% (– 3.57, 1.12) and – 0.18% (– 1.55, 0.81), with statistically significant differences observed between the groups for both sites ($P < 0.001$ for the spine; $P = 0.008$ for the hip).

At week 24, a significantly greater proportion of participants in the immediate switch group than in the deferred switch group had the spine [33/72 (45.8%) vs. 15/74 (20.2%), $P = 0.004$] and hip [23/72 (32%) vs. 11/74 (15%), $P = 0.029$] BMD increases of 3% or more (see Supplementary Material, Figure S3). However, at week 48, there were no significant differences observed in the proportion of participants with spine and hip BMD increase of 3% or more in the immediate switch group compared to the deferred switch group [spine, 37/70 (52.9%) vs. 29/67 (43.3%), $P = 0.159$; hip 28/70 (40.0%) vs. 17/66 (25.8%), $P = 0.202$].

At week 48, virological suppression was maintained in 71 (94.6%) of 75 participants in the immediate switch group, and 67 (89.3%) of 75 participants in the deferred switch group (Fig. 4). In both the immediate switch and deferred switch groups, minimal changes in the median CD4 cell count and increase in the median CD4/CD8 ratio from baseline were observed, but no statistically significant differences between the two groups at weeks 24 and 48.

Adverse Events

Table 3 summarizes the adverse events and laboratory abnormalities during the treatment period. Overall, there were 69 and 67 adverse events in the immediate switch and deferred switch group, respectively. Adverse events considered to be treatment-related occurred in 54 (72.0%) and 40 (53.3%) participants in the immediate switch group and deferred switch group, respectively. There were no reports of severe drug-related adverse events. Most adverse events were mild or moderate in severity, including 31 cases of moderate

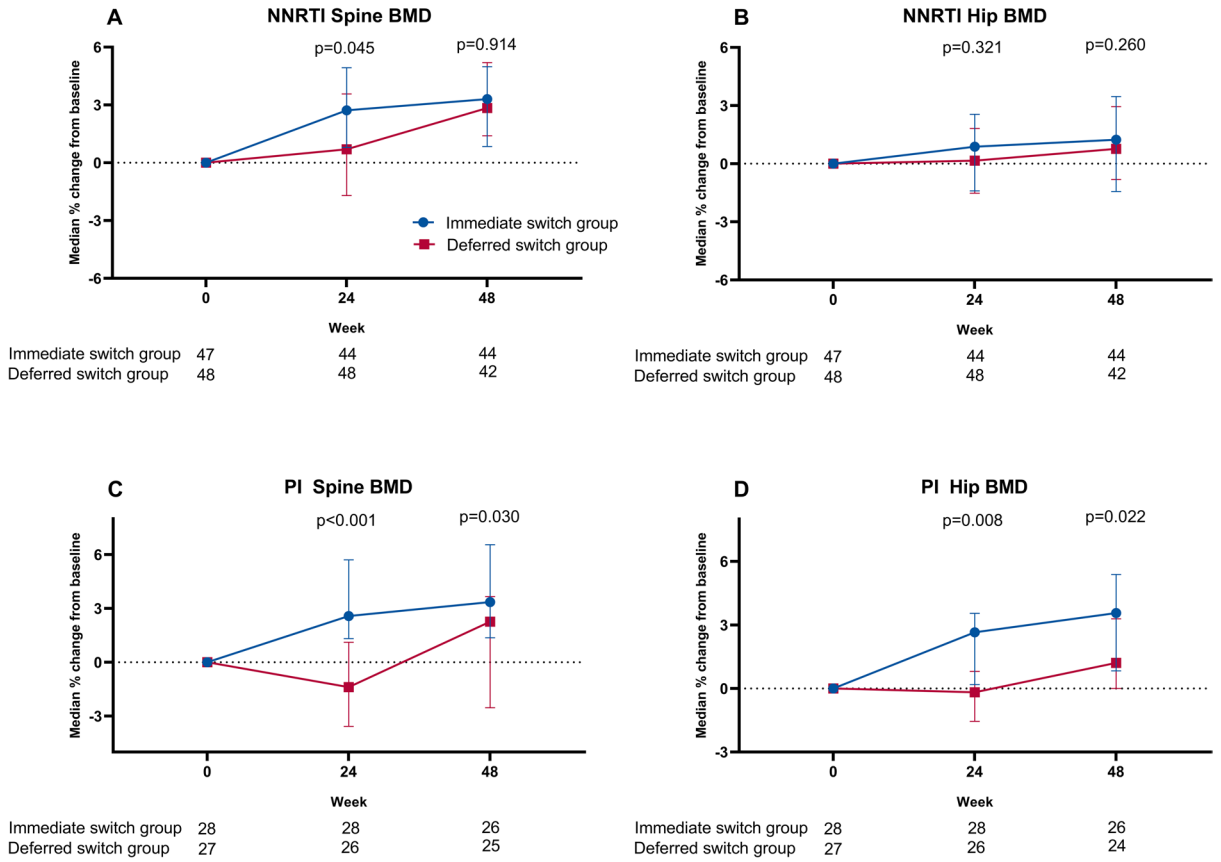

Fig. 3 Median percentage change from baseline to week 48 in spine and hip BMD for subgroups categorized according to ART regimen prior to switch. **A**, **B** NNRTI-containing regimens at baseline; **C**, **D** PI-containing regimens at baseline; *error bars* interquartile range. Subgroup analysis, stratified by the third drug pre-switch, used a Bonferroni-corrected significance level ($P < 0.025$)

adverse events, primarily weight gain in the immediate switch group and 27 cases in the deferred switch group (Table 3). Overall, all participants gained significantly more weight at week 24 [1.16 kg (– 2.84, 5.16), $P = 0.002$] and week 48 [2.25 kg (0, 5.00), $P < 0.001$] compared to baseline. At week 24, the median change in weight from baseline (IQR) was + 2.5 (0, + 3.0) kg in the immediate switch group and 0 (– 2.25, + 2.25) kg in the deferred switch group ($P < 0.001$). Post hoc exploratory analyses showed the difference was pronounced only in the NNRTI group (see Supplementary Material, Table S3). However, this difference disappeared at week 48 [3 kg (1, 6) in the immediate switch group vs. 2 kg (– 1,5) in the deferred switch group, $P = 0.095$]. Only one adverse event leading to premature discontinuation of B/F/TAF was observed, reported by a participant in the immediate switch group who experienced poor sleep after switching to B/F/TAF. We observed significantly higher uric acid levels in the immediate switch group compared to the deferred switch group [43.26 µmol/L (14.01, 91.63) vs. – 3.4 µmol/L (– 44.80, 57.66), $P < 0.001$] at 24 weeks (Table 4), and significantly higher uric acid levels in the overall population at both 24 and 48 weeks compared to baseline (see Supplementary Material, Table S2). Common lipid profile changes were not significantly different between the two groups throughout the study period (Table 4).

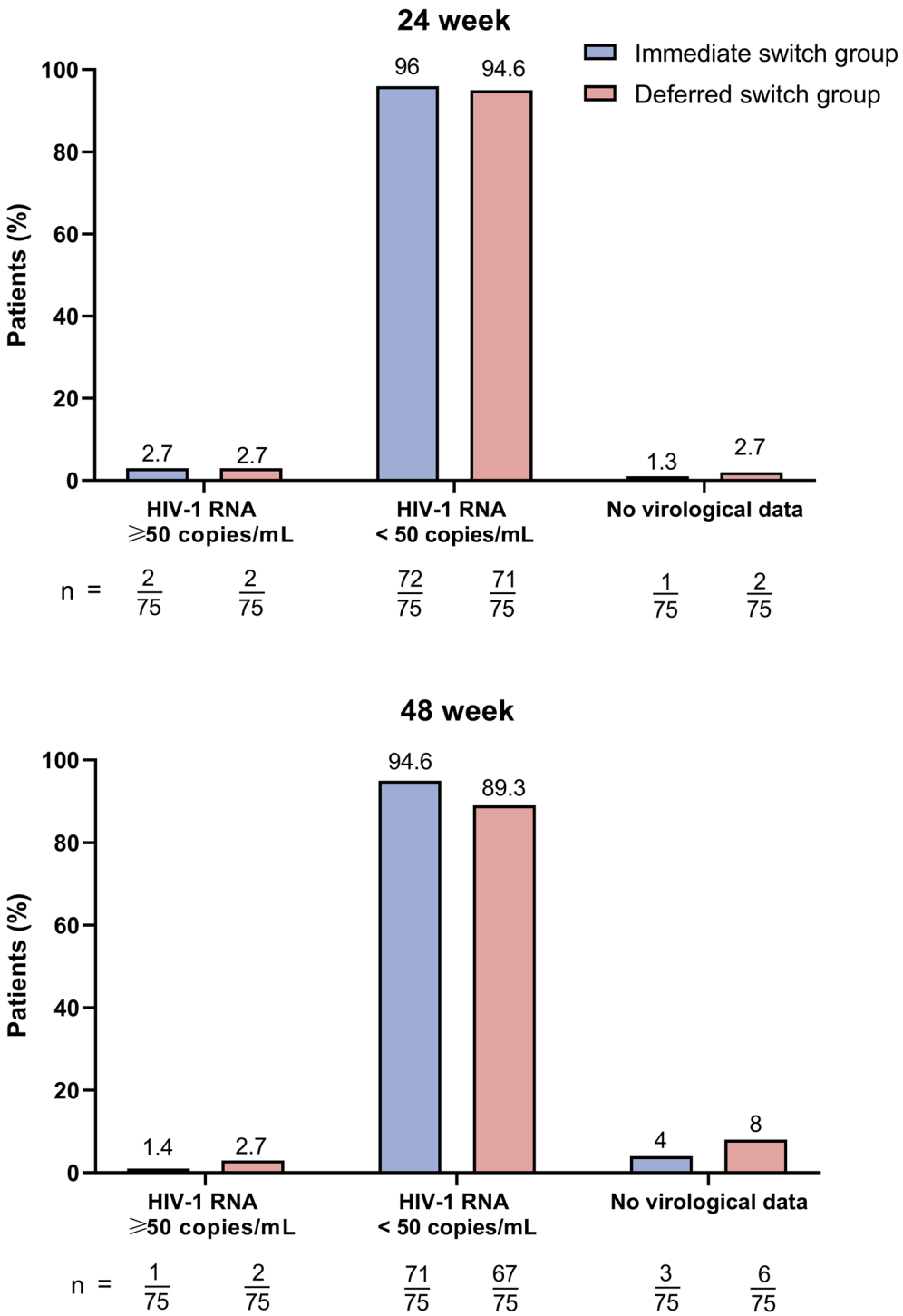

Fig. 4 Virological outcome at weeks 24 and 48 as defined by the US FDA snapshot algorithm. At week 24, missing virological data were attributed to discontinuations because of participant's decision (1 participant in the immediate switch group; 1 in the deferred switch group) and loss to follow-up (1, deferred group). At week 48, missing data resulted from participant decision (1 immediate, 1 deferred), loss to follow-up (1 immediate, 3 deferred), and protocol deviations (1 immediate and 3 deferred cases on study drug but lacked data within the week 48 window)

Table 3 Adverse events

	Immediate switch group ($n = 75$)	Deferred switch group ($n = 75$)	*P*
Grade			
Any AE, number of patients	69 (92%)	67 (90%)	0.414
Grade 1	32 (43%)	34 (45%)	0.742
Grade 2	31 (41%)	27 (36%)	0.502
Grade 3	6 (8%)	6 (8%)	> .999
Treatment-related adverse event	54 (72%)	40 (53%)	0.018
Adverse event leading to discontinuation of study drug	1 (1%)	0	> .999
Most common adverse events, number of patients			
Weight gain	35 (47%)	25 (33%)	0.096
Weight loss	5 (7%)	4 (5%)	0.731
Skin rash	1 (1%)	1 (1%)	> .999
Pain pharynx	2 (3%)	2 (3%)	> .999
Laboratory abnormalities, number of patients			
Impaired liver function	3 (4%)	2 (3%)	0.649
Raised serum uric acid	21 (28%)	9 (12%)	0.014
Increased serum creatinine	15 (20%)	10 (13%)	0.205
Cholesterol total increased	30 (40%)	22 (30%)	0.170
Hyper LDL cholesterolaemia	33 (44%)	36 (48%)	0.623
Raised triglycerides	1 (1%)	1 (1%)	> .999

The range of normal values for laboratory tests are as follows: (1) liver function: ALT 9–50 U/L; AST 15–40 U/L; (2) uric acid 200–420 μmol/L; (3) serum creatinine 57–97 μmol/L; (4) total cholesterol 0–5.18 mmol/L; (5) LDL cholesterol ≤ 3.37 mmol/L; (6) triglyceride:0–1.70 mmol/L. LDL = low-density lipoprotein

DISCUSSION

This randomized controlled study specifically investigated the impact of switching timing from TDF-based to B/F/TAF regimens on BMD in virologically suppressed PWH. While the beneficial effects of TAF compared to TDF on bone health are well established, our primary objective was to determine whether an immediate switch confers additional skeletal benefits compared with a deferred switch after 24 weeks of continued TDF exposure.

Switch from TDF-based regimens to TAF-based regimens may help prevent, reduce, and manage potential long-term adverse effects of ART regimens on bone and renal health [21–23]. Mechanistically, TDF may reduce BMD by inducing proximal tubular phosphate wasting, altering vitamin D metabolism, and affecting osteoblast/osteoclast function [24, 25]. These processes may explain the recovery of BMD after switching to TAF-based regimens. Evidence regarding the optimal timing of ART switching in relation to BMD recovery remains limited, particularly in younger PWH without pre-existing osteoporosis.

Table 4 Changes from baseline in metabolic laboratory parameters at weeks 24 and 48

Metabolic Assessment	Immediate switch group		Deferred switch group		*p* value
	n	Median or mean	*n*	Median or mean	
Total cholesterol (mmol/L)					
Baseline	75	4.83 (4.13,5.42)	75	4.69 (3.90,5.36)	0.205
Change at week 24	73	– 0.03 (– 0.52,0.32)	74	– 0.10 (– 0.42,0.30)	0.932
Change at week 48	69	0.23 (– 0.43,0.59)	68	0.09 (– 0.15,0.58)	0.726
Triglycerides (mmol/L)					
Baseline	75	2.12 (1.32,2.94)	75	1.62 (1.07,2.58)	0.14
Change at week 24	73	– 0.33 (– 0.95, – 0.06)	73	– 0.1 (– 0.62, – 0.06)	0.012
Change at week 48	71	– 0.25 (– 0.83,0.31)	68	– 0.09 (– 0.84,0.32)	0.778
High-density lipoprotein cholesterol (mmol/L)					
Baseline	75	1.04 (0.90.1.26)	75	1.09 (0.96,1.23)	0.151
Change at week 24	73	0.02 (– 0.11,0.12)	74	– 0.03 (– 0.12,0.09)	0.424
Change at week 48	71	0.03 (– 0.07,0.19)	67	0.08 (– 0.05,0.25)	0.116
Low-density lipoprotein cholesterol (mmol/L)					
Baseline	75	2.86 (0.82)	75	2.70 (0.81)	0.231
Change at week 24	73	0.15 (– 0.16,0.61)	74	0.07 (– 0.27,0.30)	0.090
Change at week 48	71	0.23 (0.75)	67	0.32 (0.52)	0.376
Uric acid (μmol/L)					
Baseline	75	356.42 (71.59)	75	341.23 (81.12)	0.226
Change at week 24	74	43.26 (14.01,91.63)	74	– 3.4 (– 44.80,57.66)	< 0.001
Change at week 48	73	54.00 (59.93)	71	38.30 (57.90)	0.112
eGFR (mL per min per 1.73 m^2)					
Baseline	75	110.51 (19.33)	75	114.04 (20.28)	0.276
Change at week 24	74	– 18 (11.85)	74	– 5.01 (15.61)	< 0.001
Change at week 48	73	– 17.95 (13.26)	71	– 17.34 (17.15)	0.812

In our study, an immediate switch to B/F/TAF showed a significantly greater gain in hip BMD at week 48 compared with a deferred switch, whereas spine BMD improvements were comparable. The discordant results between hip and spine BMD changes may relate to differences in bone composition. The hip, predominantly cortical bone, remodels more slowly than the trabecular spine [26, 27]. These findings suggest that the timing of switch plays a potential role, and the benefits of an immediate switch in hip cannot be fully achieved by a delayed change within the same period. Nevertheless, whether the additional BMD increase would persist or diminish with long-term follow-up remains unknown and warrants further investigation.

In subgroup analyses, the timing effect was most evident among participants receiving

PI-based regimens, who exhibited sustained increases in hip BMD after immediate switching. In contrast, participants on NNRTI-based regimens showed comparable BMD improvement regardless of switching time, suggesting that for people on TDF and NNRTIs (e.g., EFV, doravirine), deferred switch to B/F/TAF could gain similar improvement in BMD as immediate switch. However, the long-term implications of delayed switch from TDF should still be clarified.

In our study, people on a baseline regimen of LPV/r exhibited more pronounced hip BMD improvement at week 48 in the immediate switch group, compared to those with NNRTIs. Data from the first 24 weeks of our study also confirmed that the overall BMD benefit in the spine and hip was primarily driven by the subgroup receiving the boosted PI and TDF at baseline. A meta-analysis of studies suggests that the skeletal risks associated with TDF may be exacerbated when it is boosted by ritonavir or cobicistat [28]. Interestingly, the data from our study show that the 48-week BMD gain with switching to B/F/TAF appears to be higher than with previous E/c/F/TAF, which may be partly due to the fact that cobicistat increases plasma tenofovir concentrations by 24–30% [29, 30]. Moreover, in the study by Mills et al. [14], the subgroup with atazanavir as the baseline third drug also exhibited the most pronounced increase in BMD when switch to TAF-based regimens. A Japanese cohort study similarly found that longer duration of protease inhibitor use was associated with greater BMD loss at both the lumbar spine and femoral neck, and that discontinuation of PI therapy was linked with partial BMD recovery, supporting the notion that PI exposure contributes to skeletal deterioration and that switching off PI-containing regimens may facilitate bone recovery [31]. In large cohort studies such as the Veterans Aging Cohort Study, current use of protease inhibitors was found to be the only HIV-specific predictor of fragility fractures after adjustment for traditional risk factors, highlighting that PI exposure may independently contribute to skeletal fragility beyond its effects on BMD [32]. This underscores the potential long-term skeletal impact of PI beyond BMD changes alone, and supports the rationale for prioritizing earlier switches in patients on PI-based regimens.

During the 48-week treatment period, preserved virologic suppression and an acceptable safety profile are consistent with recent real-world cohort studies evaluating B/F/TAF, which have reported favorable virologic durability and safety at 12 months in large observational cohorts [33, 34]. Most fasting lipid parameters decreased upon switching to B/F/TAF which is similar to the results of the Asian cohort in the previous switch study [35]. Additionally, there was 2.25-kg gain in body weight in our cohort. Notably, this effect was more pronounced among participants switching from NNRTI-based regimens, which major previously on EFV. This finding suggests that weight gain following the switch to INSTI/TAF-based therapy may depend on the baseline regimen as EFV has been shown in the literature to have a weight-suppressive effect. Consequently, discontinuation of EFV may lead to a "rebound" increase in body weight. [36]. Persistent increase in uric acid levels throughout the trial period in the entire study population, and up to 20% of participants exhibited hyperuricemia, which is similar to reports of switching from TDF to TAF [37]. Although no metabolic events including gout event were observed, monitoring serum uric acid levels following TAF initiation may be clinically relevant, particularly in individuals with metabolic risk factors, as asymptomatic hyperuricemia may predict higher risks of cardiometabolic disorders such as hypertension, renal dysfunction, and metabolic syndrome in individual without comorbidities [38]. Despite the higher rate of moderate adverse events in the immediate switch group and a higher rate of treatment-related adverse events, no serious adverse events related to treatment were reported in either group.

Limitations of the study include the inability to assess BMD status before initiating TDF-based treatment regimens, thus precluding evaluation of whether switching to B/F/TAF restores BMD to pre-ART levels or further improves it. The second limitation is the short duration of 48 weeks of follow-up, which only allowed comparisons after 24 weeks of switching to B/F/TAF versus baseline regimens, or switching to B/F/TAF for 48 versus 24 weeks for the randomization arms, respectively. Additionally, the importance of

ART-related BMD reduction in subsequent fracture risk and the extent to which initiating or switching to "bone-protective" ART regimens can reduce the fracture risk in PWH remain unclear. We also recognize that the clinical significance of BMD gain within the normal range may be limited, due to most participants were relatively young, with normal BMD values or only mildly reduced BMD. Such individuals, with transient bone loss ranging from 2% to 6%, may not significantly increase bone fragility or notable fracture risk [39]. While objective endpoints such as DXA-measured BMD are unlikely to be affected by knowledge of treatment assignment, another potential bias is subjective safety outcomes due to the non-blinded study design and should be interpreted with caution. Lastly, because of limitation of sample size, subgroup analyses may be underpowered despite Bonferroni correction. Future studies should include longer follow-up and historical BMD comparisons to better understand both skeletal and virological outcomes.

CONCLUSIONS

This randomized study demonstrates that the timing of switching from TDF to B/F/TAF influences bone outcomes. An immediate switch provides additional hip BMD benefit at 48 weeks, particularly among those on PI-based regimens, supporting early switch to B/F/TAF for optimal bone health in PWH.

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Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Yueming Shao, Xinping Yang, Jianhua Yu, Xicheng Wang, Jiangrong Wang, Mei Liu, Zongxing Yang, Jie Han, Renfang Zhang, Li Liu, Yinzhong Shen, Meiyan Sun, Luling Wu, Zhihang Zheng, Yang Tang, Junyang Yang, Zhenyan Wang, Tangkai Qi, Shuibao Xu, Jingna Xun, Jianjun Sun, Wei Song, and Jun Chen declare that they have no competing interests. Jun Chen is an Editorial Board member of Infectious Diseases and Therapy. Jun Chen was not involved in the selection of peer reviewers

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Ethical Approval. The study was approved by the independent ethics committee of Shanghai Public Health Clinical Center (number: 2020-S187-02) and conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. This study was registered with ClinicalTrials.gov (NCT05122754). All participants provided written informed consent.

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