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ORIGINAL ARTICLE

Longitudinal Evaluation of Bone Safety in Children and Adolescents With HIV-1 Starting Tenofovir Alafenamide-Containing Antiretroviral Therapy

Eva Natukunda[1,*]; Aditya H. Gaur[2]; Jaime Gerardo Deville[3]; Pope Kosalaraksa[4]; Renate Strehlau[5]; Elizabeth Castaño[6]; Afaaf Liberty[7]; Susanne Crowe[8]; Ramesh Palaparthy[9]; Vinicius Adriano Vieira[10,*]; Kathryn Kersey[11]; Natella Rakhmanina[12,13,14]; Catherine M. Gordon[15]

[1]Department of Pediatrics, Joint Clinical Research Centre, Kampala, Uganda; [2]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, United States; [3]Mattel Children's Hospital, University of California, Los Angeles, Los Angeles, CA, United States; [4]Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [5]VIDA Nkanyezi Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa; [6]Department of Medicine, Hospital del Niño, Panama City, Panama; [7]Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Johannesburg, South Africa; [8]Biostatistics, Clinical Data Science, Gilead Sciences, Inc., Foster City, CA, United States; [9]Clinical Pharmacology, Gilead Sciences, Inc., Foster City, CA, United States; [10]Virology Clinical Development, Gilead Sciences, Inc., Foster City, CA, United States; [11]Clinical Development, Gilead Sciences, Inc., Foster City, CA, United States; [12]Division of Infectious Diseases, Children's National Hospital, Washington, DC, United States; [13]Department of Pediatrics, School of Medicine and Health Sciences, The George Washington University, Washington, DC, United States; [14]Technical Strategies and Innovation, Elizabeth Glaser Pediatrics AIDS Foundation, Washington, DC, United States; [15]Section on Adolescent Bone Health and Body Composition, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, United States

[*]Corresponding authors: Eva Natukunda, MMed, Department of Pediatrics, Joint Clinical Research Centre, Entebbe Road, 10005 Kampala, Kampala, Uganda (enatukunda@jcrc.org.ug) and Vinicius Adriano Vieira, PhD, Gilead Sciences, Inc., North Dock Two, 93–94 North Wall Quay, Dublin D01 V8Y6, Ireland (vinicius.adrianovieira@gilead.com).

Background: Adult participants taking tenofovir alafenamide (TAF) in clinical trials had a better bone safety profile than those taking tenofovir disoproxil fumarate. Herein, we report medium- to long-term effects of TAF-containing regimens on bone health in children and adolescents with human immunodeficiency virus (HIV).

Methods: This *post hoc* pooled analysis of data from 2 phase 2/3 clinical studies (NCT01854775 and NCT02285114) evaluated the pharmacokinetics, safety, and efficacy of TAF-based regimens in children and adolescents with HIV-1. Participants were categorized into group 1 (aged 12 to < 18 years, weighing ≥ 35 kg), group 2 (aged 6 to < 12 years, weighing ≥ 25 kg), and group 3 (aged ≥ 2 years, weighing 14 to < 25 kg). Evaluations included virologic suppression, height Z-score, Tanner stage, bone mineral density (BMD) of the spine and total body less head (TBLH; absolute and height-for-age Z-score adjusted [HAZ-adjusted] for both), bone serum markers, bone-related adverse events, and pharmacokinetic assessments.

Results: Overall, 169 participants were enrolled and treated (78, 61, and 30 in groups 1, 2, and 3, respectively). Median (range) exposure to study drug was 320.3 (8.3-492.3), 290.1 (24.0-393.9), and 168.3 (9.0-193.0) weeks in groups 1, 2, and 3, respectively. Virologic suppression (HIV-1 RNA < 50 copies/mL) rates were high across all groups. Spine and TBLH absolute BMD increased over time in all groups, and spine and TBLH HAZ-adjusted BMD Z-scores increased or remained stable in all groups. There were no significant changes in bone serum markers, and no treatment-related fractures or bone-related adverse events.

Conclusions: TAF-based regimens demonstrated acceptable medium- to long-term bone safety in children and adolescents with HIV.

Key words: Human immunodeficiency virus; tenofovir alafenamide; bone health; antiretroviral therapy; pediatric.

Lay summary

This pooled analysis of 2 phase 2/3 studies demonstrated acceptable bone safety of TAF-based regimens in children and adolescents with HIV-1 over medium- to long-term exposure (median: 168.3-320.3 weeks). Bone mineral density increased over time and was consistent with developmental stage.

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INTRODUCTION

In 2023, an estimated 2.4 million children aged 0-19 years were living with human immunodeficiency virus (HIV) worldwide.[1] The availability of effective antiretroviral therapies (ARTs) means that life expectancy among people with HIV is now approaching that of the general population.[2] Consequently, children and adolescents with HIV may encounter an increased risk of comorbidities associated with long-term exposure to HIV and some ARTs, including fractures and osteoporosis[3];

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therefore, there is a need to identify safer ART alternatives for long-term use in this population.

Human immunodeficiency virus is associated with reduced bone mineral density (BMD), and people with HIV have a lower BMD than age-matched people without HIV.[4–6] The reduced BMD is multifactorial and due in part to the effects of HIV viral proteins and T-cell activation on osteoblast and osteoclast activity, as well as traditional risk factors such as diet and physical activity.[7,8] Some ARTs, including tenofovir disoproxil fumarate (TDF)-based regimens, can also lead to a reduction in BMD,[9,10] although findings have been conflicting.[11] This is of particular concern in children and adolescents with HIV who are exposed to lifelong ART, as bone undergoes profound changes throughout childhood development.[7,12,13]

Tenofovir alafenamide (TAF) is a plasma-stable tenofovir (TFV) prodrug that is selectively hydrolyzed to TFV intracellularly and results in 90% lower TFV plasma levels compared with TDF.[14] TAF has a better bone safety profile in adults than TDF,[14-16] and TAF-based regimens are guideline-recommended treatments for children and adolescents with HIV and/or hepatitis B virus in the United States and Europe.[17-19] However, medium- to long-term data on the impact of TAF-based regimens on bone safety in children and adolescents with HIV are limited.[20]

Studies 0106 and 1269 are ongoing phase 2/3, open-label, multicohort studies evaluating the efficacy, safety, and pharmacokinetics (PK) of TAF-based regimens in children and adolescents aged 2 to < 18 years and weighing ≥ 14 kg.[21-24] The main phases of the studies have been completed and participants who remained in the studies are now in optional extension phases. Here we examined the medium- to long-term effects of TAF-based regimens on efficacy and bone safety among children and adolescents in these studies.

METHODS

Study Design and Participants

This *post hoc* pooled analysis included data from 2 phase 2/3, open-label, multicohort studies—studies 0106 and 1269—in children and adolescents with HIV-1.

Study 0106 (GS-US-292-0106; NCT01854775) is being conducted in South Africa, Thailand, Uganda, the United States (all cohorts), and Zimbabwe (cohort 3 only).[22-24] Study 1269 (GS-US-311-1269; NCT02285114) is being conducted in Panama, South Africa, and the United States.[21] Detailed methods for only study 0106 have been described previously.[23,24]

Study 0106 consisted of 3 cohorts. Cohort 1 included treatment-naïve (ie, had not received ART before study entry) adolescents aged 12 to < 18 years, weighing ≥ 35 kg. Cohort 2 included virologically suppressed children on ART aged 6 to < 12 years, weighing ≥ 25 kg. Cohort 3 included virologically suppressed children on ART aged ≥ 2 years, weighing 14 to < 25 kg. Study 1269 consisted of 2 cohorts. Cohort 1 included virologically suppressed adolescents on ART aged 12 to < 18 years, weighing ≥ 35 kg. Cohort 2 included virologically suppressed children on ART (group 1: aged ≥ 6 to < 12 years and weighing ≥ 25 kg and group 2: aged ≥ 2 to < 12 years and weighing < 25 kg).

In this *post hoc* pooled analysis, participants from studies 0106 and 1269, enrolled between May 2013 and May 2023, were categorized into 3 groups according to age and weight: group 1, aged 12 to < 18 years and weighing ≥ 35 kg; group 2, aged 6 to < 12 years and weighing ≥ 25 kg; and group 3, aged ≥ 2 years and weighing 14 to < 25 kg.

Eligibility criteria are detailed in the supplement. Protocols of both studies were approved by independent review boards and ethics committees (details provided in Supplementary Methods Tables S1 and S2) and conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines, or country laws and regulations. Parents or guardians provided written informed consent for all participants; where applicable, participants also provided age-appropriate assent.

Study Treatments

In study 0106, eligible participants received once-daily elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed-dose combination with food. Participants weighing ≥ 25 kg received E/C/F/TAF 150/150/200/10 mg and those weighing 14 to < 25 kg received E/C/F/TAF 90/90/120/6 mg. In study 1269, eligible participants received once-daily emtricitabine/tenofovir alafenamide (F/TAF) plus a boosted protease inhibitor or other third antiretroviral (ARV) agent. F/TAF was administered at doses dependent on weight and whether the third ARV agent was boosted or unboosted (cohort 1: 200/25 mg for unboosted and 200/10 mg for boosted third ARV agent; cohort 2: 200/25 mg for group 1 or 120/15 mg for group 2, regardless of the third ARV). Whether F/TAF was administered with or without food depended on the third ARV agent. The doses were selected to provide expected plasma PK exposures in the pediatric population comparable to those associated with safety and efficacy in adults. Treatments in both studies were administered for 48 weeks, followed by an optional open-label extension phase.

Procedures

Efficacy, bone safety, and PK were assessed in each group. Plasma HIV-1 RNA levels were measured at all visits using TaqMan 2.0 or cobas 6800 (from January 2023 onward) (Roche Diagnostics, Pleasanton, CA, USA). Virologic suppression was defined as HIV-1 RNA < 50 copies/mL.

Anthropometry was measured at each visit. The development of secondary sexual characteristics, as assessed by Tanner

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stage, was monitored at baseline and then every 12 weeks (every 48 weeks during the extension phase of study 0106) for participants aged ≥ 6 years until they reached Tanner stage 5. Spine and total body less head (TBLH) BMD were assessed using dual-energy X-ray absorptiometry.

Bone serum markers including bone-specific alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were measured at screening (study 0106 cohort 3 only), day 1, and regular intervals throughout both studies, and analyzed according to the laboratory manual and in accordance with LabCorp (Burlington, NC, USA) guidance.

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA v23.0). Fracture events were defined based on the standardized MedDRA query of osteoporosis/osteopenia and high-level group term of fractures. The relation of a fracture to the study drug was determined by the study investigators based on the assessment of whether the fracture was traumatic and aligned with the mechanism of injury.

In study 0106, blood samples for intensive PK sampling were collected at prespecified intervals at week 4 for cohorts 1 and 2, and week 2 for cohort 3. In study 1269, samples for intensive PK sampling were collected at multiple timepoints at week 2 for cohort 1, and week 2 or 4, or within 7 days of completion of the week 2 or 4 visit for cohort 2. Plasma TFV concentrations were measured using validated high-performance liquid chromatography–tandem mass spectrometry (QPS, Newark, DE, USA). Tenofovir area under the plasma drug concentration-time curve over the dosing interval (AUC_{tau}) and maximum observed plasma concentration (C_{max}) were determined.

Statistical Analyses

We present pooled virologic suppression at week 48 by the US Food and Drug Administration (FDA)-defined Snapshot algorithm and missing = excluded analysis (where participants with missing data at week 48 were excluded from the analysis), and bone safety data through week 288 (group 1), week 240 (group 2), or week 144 (group 3) for participants who received TAF-based regimens in studies 0106 and 1269. Due to low participant numbers at week 144, data for bone serum markers in group 3 are shown through week 96. Correlation between change from baseline in HAZ-adjusted spine and TBLH BMD Z-scores (extrapolated) at week 48 and plasma TFV AUC_{tau} and C_{max} was measured using Pearson correlation coefficient. No participant was excluded from the analysis based on follow-up time. For all analyses, participants were grouped based on their age/weight at screening. Full details of the statistical analyses are included in the supplement.

RESULTS

Baseline Demographics and Disease Characteristics

Overall, 170 participants were enrolled across both studies before the data cutoff date of May 22, 2023 (129 participants in study 0106, and 41 participants in study 1269) (Figure S1). One participant in study 1269 was enrolled but was not treated and consequently, 169 participants were included in this analysis. Seventy-eight participants were assigned to group 1 (aged 12 to <18 years, weighing ≥ 35 kg), 61 to group 2 (aged 6 to < 12 years, weighing ≥ 25 kg), and 30 to group 3 (aged ≥ 2 years, weighing < 25 kg). Baseline demographics and disease characteristics are shown in Table 1.

Median (range) exposure to study drug was 320.3 (8.3-492.3), 290.1 (24.0-393.9), and 168.3 (9.0-193.0) weeks in groups 1, 2, and 3, respectively.

Efficacy

At week 48, 91% (71/78) of participants in group 1, 95% (58/61) in group 2, and 93% (28/30) in group 3 had virologic suppression (by US FDA-defined Snapshot algorithm). Five participants in group 1 and 1 participant in group 3 had HIV-1 RNA ≥ 50 copies/mL. No virologic data were available in the 48-week window for 2 participants in group 1, 3 participants in group 2, and 1 participant in group 3. These participants were included in the denominator for this analysis. Virologic suppression rates using missing = excluded analysis were 94.7%, 100.0%, and 96.6% in groups 1, 2, and 3, respectively.

Anthropometry and Sexual Maturation

At baseline, median (interquartile range [IQR]) height Z-scores were −0.96 (−1.84, 0.03) in group 1, −0.73 (−1.28, 0.13) in group 2, and −0.44 (−1.36, 0.19) in group 3. Median (IQR) height Z-scores increased from baseline at week 288 in group 1 (0.32 [−0.05, 0.70]), decreased at week 240 in group 2 (−0.30 [−0.78, 0.34]), and were relatively stable at week 144 in group 3 (−0.05 [−0.40, 0.15]) (Table S1).

The proportion of male and female participants with available data in late puberty (maximum Tanner stages 4 and 5) increased in group 1, from approximately 50% at baseline to 100% (22/22 and 24/24, respectively) at week 288 (Table S1). In group 2, the proportion increased from 0% at baseline to 65% (11/17) of male participants, and to 100% (21/21) of female participants at week 240. In group 3, the proportion of participants in late puberty (maximum Tanner stages 4 and 5) increased from 0% at baseline to 13% (2/15) of female participants at week 144; all male participants (6/6) remained in early to mid-puberty (maximum Tanner stages 1-3).

Bone Safety

Absolute spine and TBLH BMD increased across all groups; HAZ-adjusted BMD Z-scores generally increased or were stable during follow-up (Table 2, Figures 1 and 2, Figure S2, and Table S2), with the exception of a decrease in median (IQR) spine HAZ-adjusted BMD Z-score from −0.81 (−1.03, −0.18) at baseline to −1.01 (−1.71, −0.40) at week 240 in male participants in group 2, TBLH HAZ-adjusted BMD Z-score from −0.63 (−0.88, −0.32) at baseline to −1.09 (−1.57,

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Table 1. Baseline Demographics and Disease Characteristics (Safety Analysis Set)

		Group 1 12 to < 18 years, ≥ 35 kg (*n* = 78)[a,b]	Group 2 6 to < 12 years, ≥ 25 kg (*n* = 61)[a]	Group 3 ≥2 years, 14 to < 25 kg (*n* = 30)[a]
Age, years, median (IQR)		14 (13–16)	10 (9–11)	7 (4–8)
Female, *n* (%)		40 (51)	35 (57)	19 (63)
Race, *n* (%)				
Black		56 (72)	41 (67)	26 (87)
Asian		7 (9)	13 (21)	3 (10)
White		3 (4)	2 (3)	0
Other		12 (15)	5 (8)	1 (3)
Hispanic or Latino ethnicity, *n* (%)		14 (18)	5 (8)	1 (3)
Maximum Tanner stage, *n* (%)[c]				
Male	Stages 1–3	19 (50)	26 (100)	4 (100)
	Stages 4–5	19 (50)	0 (0)	0 (0)
Female	Stages 1–3	18 (46)	35 (100)	15 (100)
	Stages 4–5	21 (54)	0	0
HIV positive at birth, *n* (%)		56 (72)	61 (100)	28 (93)
HIV-1 RNA < 50 copies/mL, *n* (%)		27[d] (35)	61 (100)	30 (100)
CD4 count, cells/μL, median (IQR)		563 (407–863)	925 (760–1133)	1057 (897–1315)
CD4, %, median (IQR)		30 (20–35)	38 (34–41)	37 (32–40)
Prior ART, *n* (%)				
Any		28 (36)	61 (100)	30 (100)
Containing TDF		20 (26)	5 (8)	1 (3)
None		50 (64)	0	0

[a]Participant enrollment by country (all enrolled analysis set; *n* = 170): group 1 (*n* = 79): *n* = 12 from Panama, *n* = 13 from South Africa, *n* = 6 from Thailand, *n* = 30 from Uganda, and *n* = 18 from the United States; group 2 (*n* = 61): *n* = 6 from Panama, *n* = 13 from Thailand, *n* = 27 from Uganda, and *n* = 15 from the United States; group 3 (*n* = 30): *n* = 1 from Panama, *n* = 17 from South Africa, *n* = 1 from Thailand, *n* = 8 from Uganda, and *n* = 3 from the United States. Location information is based on all enrolled individuals (*n* = 170); table data are from treated population (*n* = 169).

[b]Group 1 included treatment-naïve participants from study 0106 (cohort 1; *n* = 50), and treatment-experienced virologically suppressed participants from study 1269 (cohort 1; *n* = 28).

[c]Tanner stage assessed for participants ≥ 6 years of age at the time of visit; 11 participants in group 3 < 6 years of age at baseline and 1 participant in group 1 with missing data were excluded from the percentage.

[d]One participant was virologically suppressed at screening but had an HIV-1 RNA ≥ 50 copies/mL at day 1 (baseline).

ART, antiretroviral therapy; CD, cluster of differentiation; HIV, human immunodeficiency virus; IQR, interquartile range; TDF, tenofovir disoproxil fumarate.

−0.12) at week 240 in male participants in group 2, and TBLH HAZ-adjusted BMD Z-score from −1.02 (−1.69, −0.54) at baseline to −1.45 (−1.90 to −0.95) at week 144 in female participants in group 3 (Table S3). Multivariable linear regression analysis indicated that changes from baseline in maximum Tanner stage, age/weight group, and sex at birth were associated with changes from baseline in spine and TBLH BMD (Table S4). No clear difference was observed across studies despite potential variations in the study population and ART regimen.

One participant in group 2 had a ≥ 4% decrease from baseline in spine absolute BMD at week 240 (HAZ-adjusted Z-score of −1.88). No other participants had a ≥ 4% decrease from baseline in spine or TBLH absolute BMD at weeks 288, 240, and 144 in groups 1, 2, and 3, respectively.

Two participants in group 2 (2/32; 6%) had a shift in spine HAZ-adjusted BMD Z-score from > −2 at baseline to ≤ −2 at week 240 (one of them had a simultaneous shift in TBLH HAZ-adjusted BMD Z-score from > −2 at baseline to ≤ −2). In addition, 5 participants had a shift in TBLH HAZ-adjusted BMD Z-score from > −2 at baseline to ≤ −2 at follow-up: 1/27 (4%) in group 1 at week 288; 2/35 (6%) in group 2 at week 240; and 2/21 (10%) in group 3 at week 144. All 6 participants with a shift in spine or TBLH HAZ-adjusted BMD Z-score from > −2 at baseline to ≤ −2 increased their absolute BMD values relative to baseline at weeks 288, 240, and 144 in groups 1, 2, and 3, respectively.

No clinically relevant changes from baseline were seen in any of the evaluated bone metabolism markers at weeks 288, 240, and 96 for groups 1, 2, and 3, respectively (Figure S3).

There were no treatment-related bone AEs. Three participants in group 1, 4 in group 2, and none in group 3 had bone fractures, none of which were considered study drug related. All fractures were sport related or other traumatic injuries, except in the case of 1 participant in group 1, who had a right forearm fracture of unspecified cause. Of the 6 participants with a shift in spine or TBLH HAZ-adjusted BMD Z-score from > −2 at baseline to ≤ −2, only 1 had a bone fracture event (right-hand index finger fracture), which was trauma related.

Pharmacokinetic Analysis

No statistically significant correlations were observed between change from baseline in HAZ-adjusted BMD Z-scores of spine

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Table 2. Absolute BMD and HAZ-Adjusted Z-Scores Over Time (Spine and TBLH DXA Analysis Sets)

		Group 1		Group 2		Group 3	
		Baseline	**Week 288**	**Baseline**	**Week 240**	**Baseline**	**Week 144**
Absolute BMD, g/cm^2	*n*	73	44	57	33	30	25
	Spine, median (Q1, Q3)	0.778 (0.677, 0.927)	0.945 (0.885, 1.022)	0.625 (0.548, 0.676)	0.869 (0.712, 0.941)	0.457 (0.412, 0.492)	0.505 (0.482, 0.594)
	P-value[a]		<.0001		<.0001		<.0001
	n	71	41	59	36	30	24
	TBLH, median (Q1, Q3)	0.847 (0.749, 0.923)	0.928 (0.895, 0.993)	0.668 (0.641, 0.709)	0.831 (0.791, 0.885)	0.501 (0.443, 0.549)	0.596 (0.559, 0.654)
	P-value[a]		<.0001		<.0001		<.0001
HAZ-adjusted BMD Z-score	*n*	73	31	57	33	30	25
	Spine, median (Q1, Q3)	−0.48 (−1.55, 0.39)	−0.41 (−1.13, 0.58)	−0.58 (−1.00, 0.22)	0.04 (−1.02, 0.75)	−1.51 (−2.02, −0.68)	−1.35 (−1.67, −0.55)
	P-value[a]		<.0001		.2441		.0455
	n	71	28	59	36	30	24
	TBLH, median (Q1, Q3)	−0.57 (−1.40, 0.25)	−0.48 (−1.28, 0.28)	−0.80 (−1.17, −0.31)	−0.82 (−1.38, −0.16)	−1.44 (−1.81, −0.83)	−1.47 (−1.77, −1.19)
	P-value[a]		.1514		.9509		.0951

For all analyses, participants were grouped based on their age/weight at screening. [a]Calculated using a Wilcoxon signed-rank test for difference in median scores at baseline and week 288 (group 1), week 240 (group 2), or week 144 (group 3).

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HAZ, height-for-age Z-score; IQR, interquartile range; Q, quartile; TBLH, total body less head.

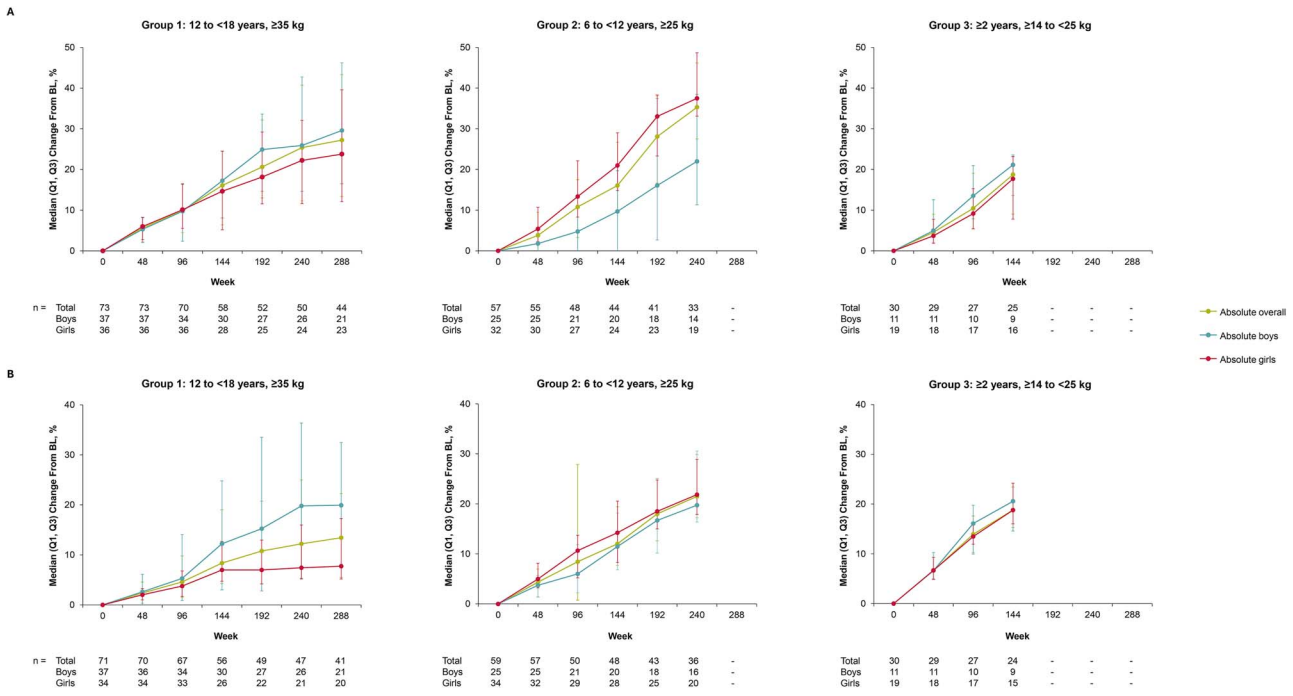


Figure 1. Change From Baseline in BMD Over Time for Spine (A) and TBLH (B) (Spine and TBLH DXA Analysis Sets). For all analyses, participants were grouped based on their age/weight at screening. BL, baseline; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; TBLH, total body less head; Q, quartile.

or TBLH at week 48 versus TFV AUC_{tau} or C_{max} (Table S5 and Figure S4).

DISCUSSION

Human immunodeficiency virus is associated with reduced BMD and thus the protection of bone health is paramount in children and adolescents, as peak bone mass is attained during the second to third decade of life.[5,6] The risk of later-life osteoporosis may therefore be influenced by changes in BMD during childhood and adolescence.[5,25,26] This is of particular importance in children with HIV, since malnutrition is prevalent, particularly in sub-Saharan Africa,[27,28] and calcium and vitamin D are vital for bone health.[29] ARV treatments

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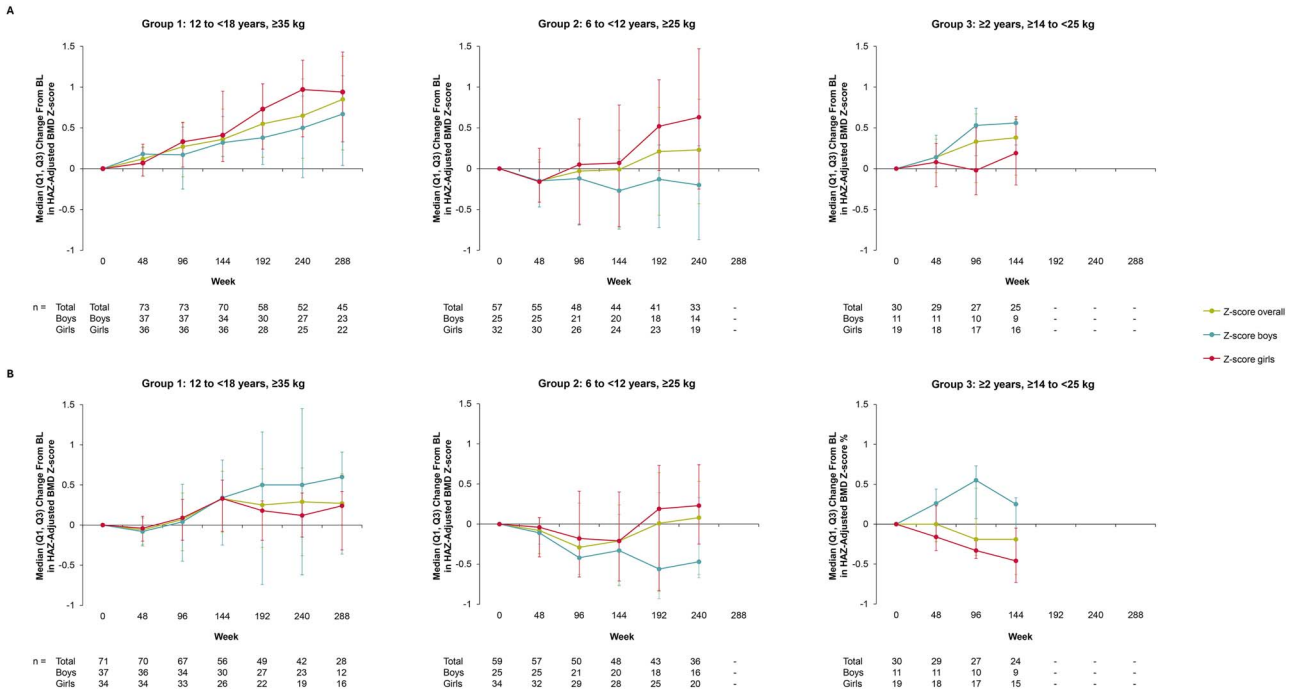


Figure 2. Change From Baseline in HAZ-Adjusted BMD Z-Scores Over Time for Spine (A) and TBLH (B) (Spine and TBLH DXA Analysis Sets). For all analyses, participants were grouped based on their age/weight at screening. BL, baseline; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HAZ, height-for-age Z-score; TBLH, total body less head; Q, quartile.

that are not detrimental to bone health are therefore needed to prevent exacerbating the negative effects of malnutrition and HIV. Findings from previous studies on the impact of TDF on BMD in children and adolescents are conflicting and have been reviewed in detail elsewhere[30]; overall, further long-term high-quality studies are needed to quantify the potential impact. In this study, we show that medium- to long-term treatment with TAF-based regimens (median exposure 168.3-320.3 weeks) resulted in high rates of sustained virologic suppression and no clinically significant impact on bone safety in children and adolescents with HIV aged ≥ 2 years and weighing ≥ 14 kg. Our study reports the longest follow-up data published to date in this population.

Changes in height Z-scores over time varied between groups, with a decrease in height Z-score observed in group 2 (participants aged 6 to < 12 years and weighing ≥ 25 kg) and an increase observed in group 1 (participants aged 12 to < 18 years and weighing ≥ 35 kg). Around two-thirds of participants in group 1 were treatment naïve, and as such, the increase in height Z-score in group 1 may represent a "return to health," similar to the weight gain associated with initiation of ART.[31] This may be particularly pronounced in group 1 due to the relatively late initiation of ART in a population in which the majority had HIV infection at birth.[32] The increase in height Z-score may also reflect a catch-up growth effect usually observed in this population, whereby reaching the reference population height is delayed due to late puberty. The numerical decrease in height Z-score observed in group 2 can be associated with delayed growth spurts and puberty typically seen in children with HIV. This also explains the numerical decrease observed in spine and TBLH HAZ-adjusted BMD Z-scores in male participants in group 2 and in TBLH HAZ-adjusted BMD Z-score in female participants in group 3. This delay can have a greater impact on children aged 6 to < 12 years weighing ≥ 25 kg (group 2 data) based on Z-scores compared with the general population (mean age of puberty is reported to be 12-13 years for children with HIV versus 9-10 years in the general population).[33-35] The developmental stage of children in groups 2 and 3 showed delayed pubertal onset compared with the general population of the same chronological age. Puberty starts earlier in girls, which would mainly affect girls in group 3, considering that the decrease is observed at weeks 96-144 (3 years on study drug) and the median age at baseline was 8 years. Conversely, puberty starts later in boys, and this trend is more apparent in group 2 for boys, which continues beyond week 144 and the median age at baseline was 10 years. In group 2, the girls in our studies would have reached puberty and (partially) caught up with the reference population. Puberty is a period of rapid growth and bone mineral accrual,[12,13] and the observed delays are likely to reflect reduced bone mineral accrual and height increases compared with the reference population. Indeed, in our multivariable analysis, change in Tanner stage, sex at birth, and group (partially characterized by chronological age) were overall associated with change in BMD. In contrast to groups 2

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and 3, the older participants in group 1 may have had the chance to catch up with the reference population that stabilized their growth and bone accrual at a younger age. Longer-term follow-up will help determine if participants in groups 2 and 3 will also show increased height Z-score in later adolescence. In addition, traditional risk factors, such as malnutrition, contribute to differences in height,[36] and, particularly among African children, may outweigh those specifically associated with HIV.

Lower BMD is common among children and adolescents with HIV and with use of some ARVs, including TDF.[5,6,9,10,26] Previous studies examining TAF-based treatments have shown that HAZ-adjusted BMD Z-scores remained stable during 48 weeks of follow-up.[20] In this analysis, spine and TBLH absolute BMD increased over time during treatment with TAF-based regimens and were similar to increases observed in a pediatric population without HIV.[37,38] Spine and TBLH HAZ-adjusted BMD Z-scores also generally increased over time, with no treatment-related fracture events. One participant from group 2 had a $\geq 4\%$ decrease from baseline in absolute spine BMD at week 240, although the clinical significance of this is unclear. Furthermore, no statistically significant correlations were observed between change from baseline in HAZ-adjusted BMD Z-scores of spine or TBLH at week 48 versus TFV AUC_{tau} or C_{max}. This suggests that changes in BMD are not related to PK exposure levels of TFV, supportive of TAF's neutral effect on BMD.

Bone biomarker levels may be influenced by various factors, including puberty stage (ie, advanced Tanner stages 4 and 5), sex, and growth rate, and levels are typically high in children and adolescents and therefore more difficult to interpret than in adults.[39] Adding to those challenges, 1,25-hydroxyvitamin D has a short half-life and is difficult to measure.[40] The fluctuations in bone biomarkers measured in the present population were consistent with the effects of growth and skeletal size expected in children in the age range studied. No clinical relevance was derived from the changes from baseline in any of the bone biomarkers at weeks 288, 240, and 144 for groups 1, 2, and 3, respectively.

Our study was subject to limitations, including being a *post hoc* pooled analysis that combined 2 different studies without a comparator. Height-for-age Z-score-adjusted BMD Z-scores have drawbacks due to the differences between the study and reference populations, for example, race,[41] nutritional status, HIV infection, and puberty onset.[33] Participants were recruited from various geographic regions, with different socioeconomic conditions and nutrition, which could have affected the timing of puberty in children. Thus, a child with late normal puberty would be less likely to be misclassified as short if pubertal status were not considered. In addition, vitamin D deficiency/insufficiency could affect the timing of puberty, but data related to the use of vitamin D supplements were not collected consistently across the sites and thus its analysis was not available for this study. It should be noted that Tanner stage assessments may have been performed by different assessors between visits, leading to some variation in reported stage. However, Tanner stage was used to assess the onset of puberty and understand more broadly the growth stage of participant groups overall; therefore, variations between visits may be of minimal relevance. Although adherence has not been directly described in this *post hoc* pooled analysis, the high rates of virologic suppression indicate good adherence to the study drugs. Finally, the participant numbers in group 3 and the study timeframe may not be adequate to identify rare bone-related AEs, assess the effect of longer-term TAF exposure on bone health, and evaluate if switching from a different regimen to a TAF-based regimen affects bone health.

Overall, the BMD data collected over 3-5 years of continued treatment with TAF-based regimens demonstrated acceptable bone safety in children and adolescents with HIV.

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Author contributions

S.C., V.A.V., and K.K. designed the study. E.N., J.G.D., R.S., and S.C. contributed to the collection of data. J.G.D., S.C., V.A.V., and K.K. have verified the underlying data reported in the manuscript. C.M.G. contributed to data interpretation. All authors had full access to all the data in the study, contributed to drafting or revising the article, and had final responsibility for the decision to submit for publication.

Supplementary material

Supplementary material is available at *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

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Conflicts of interest

A.G. reports research grants from Gilead Sciences, Inc. and ViiV Healthcare, payments for expert advisory board participation and serving as a webinar panelist from ViiV Healthcare. J.G.D. and P.K. report research funding paid to their institution from Gilead Sciences, Inc. R.S. reports research funding paid to their institution from Gilead Sciences, Inc., GSK, Merck, and Penta; consulting fees from GSK and ViiV Healthcare; and travel support from Enanta Pharmaceuticals and Gilead Sciences, Inc. S.C. is an employee of Gilead Sciences, Inc., and holds stocks/shares in Alcon, Gilead Sciences, Inc., Novartis, and Sandoz. R.P., V.A.V., and K.K. are employees of and hold stock in Gilead Sciences, Inc. N.R. reports research funding paid to their institution from Gilead Sciences, Inc., GSK, Merck, and Penta; travel support from Gilead Sciences, Inc.; and payments

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for expert advisory boards and expert testimony from ViiV Healthcare. C.M.G. reports serving as a paid consultant for Gilead Sciences, Inc., while employed at Baylor College of Medicine. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Data availability

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflicts of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to DataSharing@gilead.com.

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