Bone Mineral Density in Children With HIV-1 Receiving TAF-Based Antiretroviral Therapy

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Conclusions

- Children and adolescents in the study who initiated a TAF-containing ART had baseline height Z-scores and spine and TBLH HAZ-adjusted BMD Z-scores below 0, consistent with those previously reported in children with HIV[1,2]
- In this pediatric population weighing ≥ 14 kg, the data do not raise concerns about bone safety associated with F/TAF-based regimens
  - There were no **treatment-related fractures**
  - **Spine and TBLH BMD** increased over time, similar to increases observed in a pediatric population without HIV[3-5]
  - **Spine and TBLH HAZ-adjusted BMD Z-scores** generally increased over time
- HAZ-adjusted BMD Z-scores have limitations due to the differences between the study and reference populations (eg, race, nutritional status, HIV infection, and puberty onset)
  - Delayed growth spurts and puberty normally seen in children with HIV[6] can have a greater impact on children aged 6 to < 12 years, weighing ≥ 25 kg (Group 2 data) based on Z-scores
- No statistically significant correlations were observed between change in HAZ-adjusted BMD Z-scores of spine or TBLH at Week 48 versus TFV AUC_{tau} or C_{max}
- Overall, these medium- to long-term BMD data demonstrated acceptable bone safety associated with F/TAF-based regimens in children and adolescents, aged 2 to 17 years and weighing ≥ 14 kg

Plain Language Summary

- HIV infection and some HIV medications can lower bone density (meaning a decrease in bone sturdiness), which can lead to bones breaking more easily
- This is especially concerning in children and adolescents as their bones are still developing
- HIV medications containing tenofovir alafenamide are associated with higher bone density compared with some other medications
- This poster shows the result of a bone density analysis from children with HIV aged 2 to 17 years who weighed at least 14 kg (about 31 lb) at screening and who had received HIV medications containing tenofovir alafenamide in HIV treatment studies
- The results of this analysis show that changes in bone density were in line with the typical changes for children of this age group
- This suggests that medications containing tenofovir alafenamide do not have a negative effect on bone development in this age group

Introduction

- Tenofovir alafenamide (TAF)–based regimens are guideline-recommended treatments for children and adolescents with HIV[7]
- TAF results in lower tenofovir (TFV) plasma levels than tenofovir disoproxil fumarate (TDF),[8,9] and has demonstrated a better bone safety profile[10-13]
- Two clinical studies – GS-US-292-0106 (NCT01854775)[14,15] and GS-US-311-1269 (NCT02285114)[16] – are evaluating the efficacy and safety of TAF-based regimens in children and adolescents aged 2 to < 18 years and weighing ≥ 14 kg
- Medium- to long-term data on the impact of TAF-based regimens on bone safety in children and adolescents with HIV aged ≥ 2 years and weighing ≥ 14 kg are limited[17]

Objective

- To examine the medium- to long-term (up to Week 288) effects of TAF–based regimens on efficacy and bone safety in children and adolescents with HIV aged ≥ 2 years and weighing ≥ 14 kg

Methods

Study Design

Clinical Studies Included in the Pooled Analysis

[a]A 3rd agent of the preexisting regimen may include boosted atazanavir, boosted lopinavir, boosted darunavir, efavirenz, dolutegravir, nevirapine, or raltegravir.
[b]n = 50 were TN and n = 28 were VS.
ART, antiretroviral therapy; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; F/TAF, emtricitabine/tenofovir alafenamide; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TN, treatment-naive; VS, virologically suppressed.

- BMD was assessed using dual-energy X-ray absorptiometry of the spine and total body less head (TBLH), and compared with age-matched bone mineral density (BMD) of children without HIV using adjusted Z-scores
  - Height-for-age Z-scores (HAZ) were derived from the Centers for Disease Control and Prevention's length and stature for age charts for children without HIV;[18] BMD Z-scores were then adjusted for HAZ

Results

Baseline Demographics and Disease Characteristics

	Group 1 12 to < 18 years, ≥ 35 kg (n = 78)[a]	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)
HIV-1 RNA < 50 c/mL, n (%)	27[b] (35)	61 (100)	30 (100)
CD4 count, cells/µL, median (IQR)	563 (407, 863)	925 (760, 1133)	1,057 (897, 1315)
CD4, %, median (IQR)	30 (20, 35)	38 (34, 41)	37 (32, 40)
Prior ART, n (%)	28 (36)	61 (100)	30 (100)
Containing TDF	20 (26)	5 (8)	1 (3)

[a]Group 1: n = 12 from Panama, n = 13 from South Africa, n = 6 from Thailand, n = 30 from Uganda, n = 18 from USA; Group 2: n = 6 from Panama, n = 13 from Thailand, n = 27 from Uganda, n = 15 from USA; Group 3: n = 1 from Panama, n = 17 from South Africa, n = 1 from Thailand, n = 8 from Uganda, n = 3 from USA. Location information is based on all enrolled individuals (n = 170); table data are from treated population (n = 169).
[b]One participant was VS at screening but had an HIV-1 RNA ≥ 50 c/mL at Day 1 (baseline).
ART, antiretroviral therapy; c, copies; TDF, tenofovir disoproxil fumarate; VS, virologically suppressed.

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 (HIV-1 RNA < 50 copies/mL by US Food and Drug Administration Snapshot analysis; no virologic data: n = 2 in Group 1, n = 3 in Group 2, and n = 1 in Group 3)

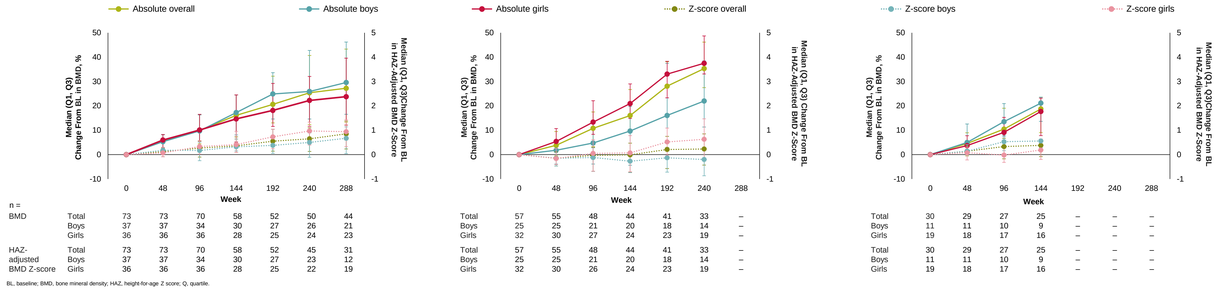
Bone-Related Adverse Events

- Three participants in Group 1, four participants in Group 2, and none in Group 3 had bone fracture (all were traumatic or sport related, and none of them were considered related to the study drug)

Height Z-Scores Over Time

- 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 by 0.32 (-0.05, 0.70) at Week 288 in Group 1, decreased by -0.30 (-0.78, 0.34) at Week 240 in Group 2, and were relatively stable at Week 144 in Group 3 (-0.05 [-0.04, 0.15])

Spine BMD and HAZ-Adjusted BMD Z-Score Over Time



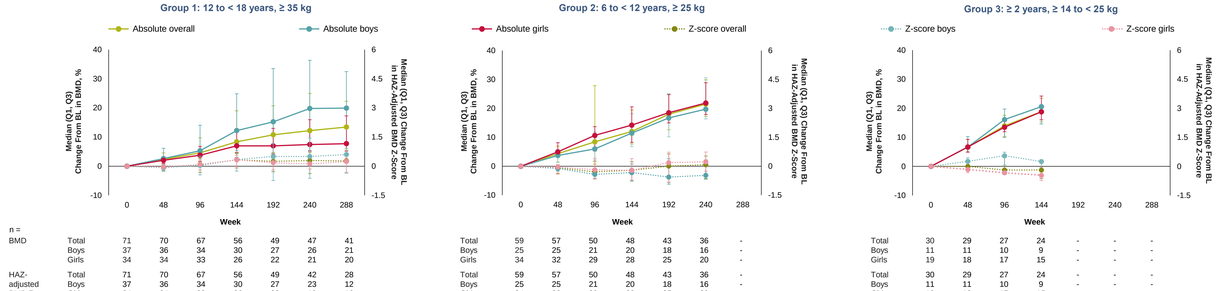
		Group 1					
n =							
BMD	Total	73	73	70	58	52	50	44
	Boys	37	37	34	30	27	26	21
	Girls	36	36	36	28	25	24	23
HAZ-adjusted BMD Z-score	Total	73	73	70	58	52	45	31
	Boys	37	37	34	30	27	23	12
	Girls	36	36	36	28	25	22	19

		Group 2					
n =							
BMD	Total	57	55	48	44	41	33	–
	Boys	25	25	21	20	18	14	–
	Girls	32	30	27	24	23	19	–
HAZ-adjusted BMD Z-score	Total	57	55	48	44	41	33	–
	Boys	25	25	21	20	18	14	–
	Girls	32	30	26	24	23	19	–

		Group 3					
n =							
BMD	Total	30	29	27	25	–	–	–
	Boys	11	11	10	9	–	–	–
	Girls	19	18	17	16	–	–	–
HAZ-adjusted BMD Z-score	Total	30	29	27	25	–	–	–
	Boys	11	11	10	9	–	–	–
	Girls	19	18	17	16	–	–	–

BL, baseline; BMD, bone mineral density; HAZ, height-for-age Z score; Q, quartile.

TBLH BMD and HAZ-Adjusted BMD Z-Score Over Time



		Group 1					
n =							
BMD	Total	71	70	67	56	49	47	41
	Boys	37	36	34	30	27	26	21
	Girls	34	34	33	26	22	21	20
HAZ-adjusted BMD Z-score	Total	71	70	67	56	49	42	28
	Boys	37	36	34	30	27	23	12
	Girls	34	34	33	26	22	19	16

		Group 2					
n =							
BMD	Total	59	57	50	48	43	36	-
	Boys	25	25	21	20	18	16	-
	Girls	34	32	29	28	25	20	-
HAZ-adjusted BMD Z-score	Total	59	57	50	48	43	36	-
	Boys	25	25	21	20	18	16	-
	Girls	34	32	29	28	25	20	-

		Group 3					
n =							
BMD	Total	30	29	27	24	-	-	-
	Boys	11	11	10	9	-	-	-
	Girls	19	18	17	15	-	-	-
HAZ-adjusted BMD Z-score	Total	30	29	27	24	-	-	-
	Boys	11	11	10	9	-	-	-
	Girls	19	18	17	15	-	-	-

BL, baseline; BMD, bone mineral density; HAZ, height-for-age Z score; Q, quartile; TBLH, total body less head.

BMD and HAZ-adjusted BMD Z-score

- Spine and TBLH BMD increased across all groups during the follow-up, with no participants with a decrease of > 4%
- HAZ-adjusted BMD Z-scores increased or were stable

Shift in HAZ-Adjusted BMD Z-Score to ≤ -2

Decrease from baseline, n/N		Group 1 at Week 288	Group 2 at Week 240	Group 3 at Week 144
Shift from > -2[a] at baseline to ≤ -2[a] at follow-up in HAZ-adjusted BMD Z-score	Spine	0/22	2/32	0/18
	TBLH	1/27	2/35	2/21

[a] -2 refers to -2 SD of the Z-score. BMD, bone mineral density; HAZ, height-for-age Z score; TBLH, total body less head.

- All participants with a shift in the spine or TBLH HAZ-adjusted BMD Z-score to ≤ -2 increased their absolute BMD values from baseline at Week 288 (Group 1), Week 240 (Group 2), and Week 144 (Group 3)
- Only one of these seven participants had a bone fracture adverse event (right-hand index finger fracture) which was trauma related

Absolute BMD and HAZ-adjusted BMD Z-Score

		Group 1		Group 2		Group 3	
		Baseline	Week 288	Baseline	Week 240	Baseline	Week 144
BMD	Spine	0.78 (0.68, 0.93)	0.95 (0.89, 1.02)	0.63 (0.55, 0.68)	0.87 (0.71, 0.94)	0.46 (0.41, 0.49)	0.51 (0.48, 0.59)
	TBLH	0.85 (0.75, 0.92)	0.93 (0.90,0.99)	0.67 (0.64, 0.71)	0.83 (0.79, 0.89)	0.50 (0.44, 0.55)	0.60 (0.56, 0.65)
HAZ-adjusted BMD Z-score	Spine	-0.5 (-1.6, 0.4)	-0.4 (-1.1, 0.6)	-0.6 (-1.0, 0.2)	0.0 (-1.0, 0.8)	-1.5 (-2.0, -0.7)	-1.4 (-1.7, -0.6)
	TBLH	-0.6 (-1.4, 0.3)	-0.5 (-1.3, 0.3)	-0.8 (-1.2, -0.3)	-0.8 (-1.4, -0.2)	-1.4 (-1.8, -0.8)	-1.5 (-1.8, -1.2)

Data shown as median (IQR). BMD, bone mineral density; HAZ, height-for-age Z score; TBLH, total body less head.

Analysis of Pharmacokinetic–Pharmacodynamic Correlations

- No statistically significant correlations were observed between change in HAZ-adjusted BMD Z-scores of spine or TBLH at Week 48 versus TFV area under curve (AUC) over the dosing interval (AUC_{tau}) or maximum concentration (C_{max})

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