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Bone Mineral Content, Growth, and Renal Health of Infants With Perinatal Exposure to Maternal Dolutegravir Versus Efavirenz and Tenofovir Disoproxil Fumarate Versus Tenofovir Alafenamide: The Randomized IMPAACT 2010 (VESTED) Trial

Tapiwa G. Mbengeranwa, MD,[a] Lauren Ziemba, MS,[b] Sean S. Brummel, PhD,[b] Ben Johnston, BS,[c] Haseena Cassim, MD,[d] Gerhard Theron, MD,[e] Zukiswa Ngqawana, BSc,[f] Deo Wabwire, MD,[g] Katie McCarthy, MPH,[h] John Shepherd, PhD,[i] Shahin Lockman, MD,[b,j,k] Lameck Chinula, MD,[l] and Lynda Stranix-Chibanda, MD,[a,m] for the IMPAACT 2010/VESTED study team and investigators

Background: The impact on infant bone, growth, and renal health of in utero and breast milk exposure to contemporary antiretroviral treatment (ART) remains unclear.

Methods: Six hundred forty-three pregnant women with HIV in 9 countries in Africa, Asia, and the Americas were randomized to start ART with dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG + FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF between 14 and 28 weeks' gestation and continued for 50 weeks postpartum. Pairwise comparisons used 2-sample *t* tests of mean week 26 infant bone mineral content (BMC) assessed by dual-energy X-ray absorptiometry in a subset; mean infant z-scores for length-for-age z-score (LAZ), weight-for-age z-score (WAZ), and weight-for-length (WLZ) at 26 and 50 weeks; and mean infant creatinine and estimated creatinine clearance at birth and 26 weeks.

Results: Five hundred seventy-seven infants were included in the growth analysis, and 169 in the dual-energy X-ray absorptiometry analysis. Week 26 infant spine BMC was significantly lower in the EFV/FTC/TDF arm (133.5 g) than in the DTG + FTC/tenofovir alafenamide [143.4 g; mean difference (95% confidence intervals): 0.22 (0.02, 0.42) g] and DTG + FTC/TDF [137.4; mean difference (95% confidence interval): 0.20 (0.01, 0.40) g] arms. Mean LAZ and WAZ scores through week 50 were also significantly lower in the EFV/FTC/TDF versus DTG arms, but not WLZ. Infant obesity was rare (2%–4%) and similar between arms. There was no apparent by-arm difference in infant creatinine or estimated creatinine clearance through week 50 (P-values ≥ 0.18).

Conclusions: It is reassuring that maternal DTG-based ART during pregnancy and breastfeeding was associated with higher infant spine BMC, better growth, and less stunting than EFV/FTC/TDF.

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From the [a]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe; [b]Harvard TH Chan School of Public Health, Boston, MA; [c]Frontier Science Foundation, Inc., Amherst, NY; [d]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa; [e]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [f]UMLAZI Clinical Research Site, CAPRISA, Durban, South Africa; [g]Makerere University—Johns Hopkins University (MU-JHU), Kampala, Uganda; [h]FHI 360, Durham, NC; [i]National Institute of Child Health and Human Development, Bethesda, MD; [j]National Institute of Allergy and Infectious Diseases, Rockville, MD; [k]Botswana Harvard Health Partnership in Gaborone, Gaborone, Botswana; [l]University of North Carolina Project–Malawi, Lilongwe, Malawi; and [m]Child and Adolescent Health Unit, University of Zimbabwe Faculty of Medicine and Health Sciences, Harare, Zimbabwe.

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Correspondence to: Tapiwa Grace Mbengeranwa, MD, University of Zimbabwe Clinical Trials Research Centre, 15 Phillips Avenue, Belgravia, Harare, Zimbabwe (e-mail: tmbengeranwa@uz-ctrc.org).

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INTRODUCTION

Despite marked progress in reducing infant HIV acquisition with the rollout of universal maternal antiretroviral (ARV) therapy (ART),[1] little is known about the impact of exposure to contemporary ARVs in utero and through breast milk on infant bone density, growth, and renal function. Tenofovir disoproxil fumarate (TDF), an ARV widely used in ART regimens globally, causes proximal renal tubular dysfunction that lowers phosphorus levels available for bone mineralization.[2,3] Independent of any renal phosphate wasting, TDF in combination with efavirenz (EFV) is associated with increased bone turnover and reductions in bone mineral density (BMD).[4] Infants exposed to maternal TDF have been reported to have as much as 12% lower newborn mean bone mineral content (BMC) than TDF-unexposed newborns.[5,6] In adults, tenofovir alafenamide (TAF), a more recent prodrug of tenofovir, was shown to be less nephrotoxic and had a lower impact on BMC than TDF.[7] There is little information about whether exposure to TAF in utero will have similar infant bone effects as TDF.[8] EFV may affect BMD indirectly by interrupting vitamin D metabolism and thus inducing osteomalacia.[4,9,10] An association exists between BMD and child growth as reflected by weight-for-age and length-for-age z-scores (WAZ and LAZ) in older children.[11] A study of 53 infants exposed to TDF in utero did not find evidence of growth impairment; however, there is limited research on children younger than 18 months.[12] TDF use has also been associated with weight loss and low weight gain during pregnancy.[13,14] Adverse birth outcomes, including preterm delivery and infants who are small for gestational age, are common in women taking ART during pregnancy; this may be related to low gestational weight gain, among other factors.[15,16] Owing to the limited data available for infants, we sought to compare infant BMC, growth, and creatinine and creatinine clearance by maternal ART regimen in an analysis of the IMPAACT 2010 randomized trial that evaluated 3 ART regimens started during pregnancy.

MATERIALS AND METHODS

Study Population

IMPAACT 2010 (or "VESTED: Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG") was an open-label, phase 3 randomized study (NCT03048422) evaluating 3 ART regimens started during pregnancy, conducted in 22 sites across 9 countries in Africa, Asia, and the Americas.[17,18] Pregnant women with HIV enrolled between 14 and 28 weeks' gestation were randomly assigned 1:1:1 to start either dolutegravir (DTG) + emtricitabine (FTC)/TAF, DTG + FTC/TDF, or EFV/FTC/TDF. Women and infants were followed through 50 weeks postpartum (women received study ART from antepartum enrollment through week 50 postpartum) (see Figure 1, Supplemental Digital Content 1, http://links.lww.com/QAI/C472). Mothers chose infant feeding method after counseling (and infant postnatal ARV and cotrimoxazole prophylaxis were given) according to local standard of care.

The study was approved by the ethics committees and the institutional review boards at each of the participating sites and written informed consent was obtained for each mother–infant pair. The full protocol is available at https://www.impaactnetwork.org/studies/impaact2010.

Study Outcomes

The outcomes for this analysis were infant BMC, child anthropometry through 50 weeks, serum creatinine, and estimated creatinine clearance rate.

Infant Dual-Energy X-Ray Absorptiometry Scanning

Dual-energy X-ray absorptiometry (DXA) scans using Hologic systems were performed in a subset of IMPAACT 2010 participants at 7 sites in Africa that had this capacity (Fig. 1). Per the protocol, DXA scans from 213 infants (71 per arm) were planned to provide 80% power to detect at least 1 half a SD (0.40 g assumed in the protocol) difference between study arms, which the team assessed as clinically relevant.[19] Infants had whole-body and lumbar spine scans performed at 26 weeks of age (±6 weeks) to ensure the earliest practicable time point for performing high-quality infant DXA scans while minimizing infant radiation exposure. Scans were performed according to standardized procedures and scans were centrally read by a trained technologist.[20]

Infant Anthropometric Measurements

Infant length and weight were measured at each visit using standardized procedures to assess infant growth.[21] World Health Organization norms were applied to anthropometric measurements taken at 26 and 50 weeks of age (±6 weeks) to centrally calculate length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WLZ) z-scores (Fig. 1).

Infant Safety and Renal Health Assessment

Serum creatinine was measured at birth (birth through 14 days of life) in all infants, and at 26 weeks of age in breastfeeding infants (Fig. 1). Estimated creatinine clearance rate was centrally calculated using the Schwartz formula.[22]

Statistical Analysis

Mean infant BMC at week 26, growth z-scores at week 26 and week 50, and renal evaluations at week 26 were compared between arms using 2-sample *t* tests assuming unequal variance. The proportions of stunted infants (LAZ < -2) were compared between arms using a 2-sample test of binomial proportions. Wald 95% confidence intervals (CIs) and *P*-values were computed. SAS Version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

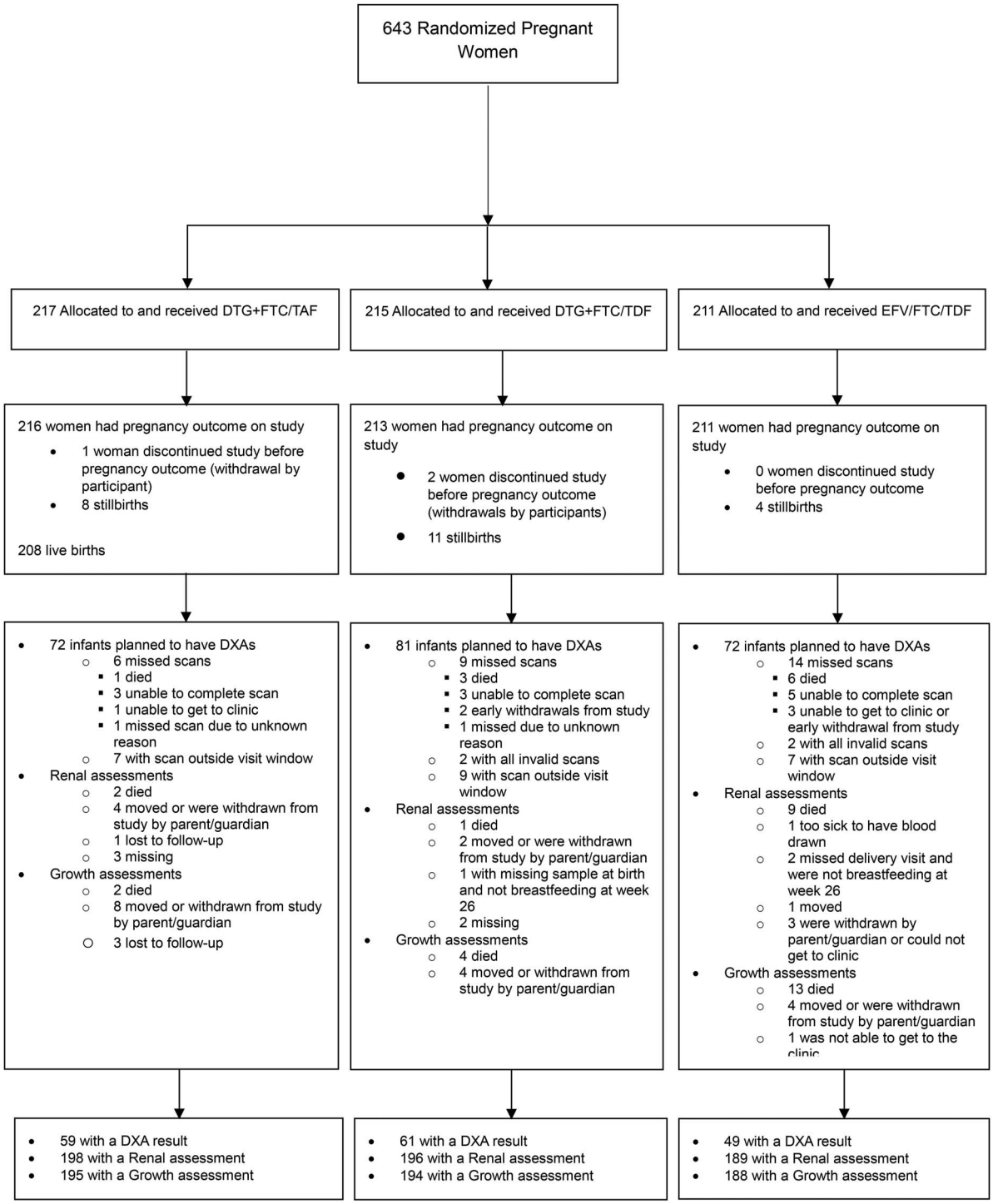

FIGURE 1. CONSORT diagram for results.

RESULTS

A total of 643 mother–infant pairs were enrolled at study sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe between January 2018 and February 2019.[23] A total of 617 infants were born on study and were predominantly breastfed [479/617 (77.6%)] for mean (SD) duration of 42.5 (15.6) weeks and median (Q1, Q3) duration of 49.9 (42.9, 50.7) weeks.

TABLE 1. Characteristics at Birth in All Liveborn Infants, and at Time of the DXA Scan in Subset of Infants With Valid DXA Result in 26-Week Visit Window

		Treatment Group			
		DTG+FTC/TAF	DTG+FTC/TDF	EFV/FTC/TDF	Total
Infant characteristics					
N Live born		208	202	207	617
Country	Botswana	15 (2.4%)	17 (2.8%)	17 (2.8%)	49 (7.9%)
	Brazil	21 (3.4%)	19 (3.1%)	16 (2.6%)	56 (9.1%)
	India	2 (0.3%)	1 (0.2%)	0 (0.0%)	3 (0.5%)
	South Africa	35 (5.7%)	33 (5.3%)	37 (6.0%)	105 (17.0%)
	Tanzania	15 (2.4%)	10 (1.6%)	15 (2.4%)	40 (6.5%)
	Thailand	5 (0.8%)	4 (0.6%)	6 (1.0%)	15 (2.4%)
	Uganda	35 (5.7%)	35 (5.7%)	36 (5.8%)	106 (17.2%)
	United States	2 (0.3%)	2 (0.3%)	0 (0.0%)	4 (0.6%)
	Zimbabwe	78 (12.6%)	81 (13.1%)	80 (13.0%)	239 (38.7%)
Sex	Female	97 (46.9%)	109 (54.0%)	101 (49.3%)	307 (50.0%)
Gestational age (wk)	Mean (SD)	39.6 (1.8)	39.5 (2.0)	39.1 (2.4)	39.4 (2.1)
Low birth weight	<2500 g	13 (6.4%)	19 (9.5%)	22 (12.0%)	56 (9.3%)
Breastfed on study	Breastfed	161 (77.4%)	158 (78.2%)	160 (77.3%)	479 (77.6%)
Breastfeeding duration (wk)	Mean (SD)	42.8 (16.2)	43.1 (14.3)	41.8 (16.4)	42.5 (15.6)
Infant characteristics among those with a DXA measurement					
N with DXA		59	61	49	169
Country	South Africa	17 (28.8%)	18 (29.5%)	13 (26.5%)	48 (28.4%)
	Uganda	2 (3.4%)	5 (8.2%)	2 (4.1%)	9 (5.3%)
	Zimbabwe	40 (67.8%)	38 (62.3%)	34 (69.4%)	112 (66.3%)
Sex	Female	27 (45.8%)	31 (50.8%)	27 (55.1%)	85 (50.3%)
Gestational age (wk)	Mean (SD)	40.0 (1.8)	39.5 (2.0)	39.1 (1.8)	39.5 (1.9)
Low birth weight	<2500 g	3 (5.3%)	6 (10.3%)	6 (12.2%)	15 (9.1%)
Age at scan (mo)	Mean (SD)	5.7 (0.6)	5.8 (0.6)	5.8 (0.5)	5.8 (0.6)
Breastfed on study	Breastfed	55 (93.2%)	58 (95.1%)	48 (98.0%)	161 (95.3%)
Breastfeeding status at scan	Breastfeeding	46 (78.0%)	50 (82.0%)	40 (81.6%)	136 (80.5%)
Breastfeeding duration (wk)	Mean (SD)	24.2 (6.9)	25.4 (6.1)	24.9 (6.8)	24.8 (6.6)

TAF, tenofovir alafenamide

TABLE 2. Mean and SDs for BMC, Renal, and Growth Outcomes

		Treatment Group					
		DTG + FTC/TAF		DTG + FTC/TDF		EFV/FTC/TDF	
Measurement	Study Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Bone mineral content							
Body (g)	Week 26	39	143.3 (31.0)	41	139.0 (30.7)	30	133.9 (28.6)
Body without head (g)	Week 26	39	73.3 (18.6)	41	70.1 (17.1)	30	69.3 (15.8)
Spine (g)	Week 26	57	2.9 (0.5)	56	2.8 (0.5)	49	2.6 (0.5)
Renal							
Creatinine (×ULN)	Birth	193	0.71 (0.38)	189	0.77 (0.46)	185	0.72 (0.51)
	Week 26	135	0.59 (0.20)	137	0.59 (0.15)	129	0.54 (0.14)
Creatinine clearance (mL/min)	Birth	190	52.7 (29.6)	186	53.1 (69.7)	182	49.0 (24.7)
	Week 26	132	125.9 (40.7)	134	123.6 (40.3)	128	135.0 (51.1)
Grade 3 or 4 blood creatinine increase	Birth through Week 50	208	0 (0%)	202	2 (1%)	207	1 (<0.5%)
WHO growth Z-score							
Length-for-age	Week 26	193	−0.65 (1.4)	193	−0.67 (1.4)	188	−1.04 (1.2)
	Week 50	179	−0.70 (1.6)	176	−0.58 (1.2)	170	−0.92 (1.3)
Weight-for-age	Week 26	193	−0.15 (1.2)	193	−0.12 (1.1)	188	−0.37 (1.2)
	Week 50	179	−0.14 (1.2)	176	−0.10 (1.2)	170	−0.44 (1.2)
Weight-for-length	Week 26	193	0.46 (1.3)	193	0.50 (1.4)	188	0.47 (1.3)
	Week 50	178	0.26 (1.1)	176	0.25 (1.3)	170	0.04 (1.3)
Stunting (%, <−2 LAZ)	Week 26	193	28 (14.5%)	193	28 (14.5%)	188	38 (20.2%)
	Week 50	179	24 (13.4%)	176	24 (13.6%)	170	35 (20.6%)
Obesity (%, >2 WAZ)	Week 26	193	8 (4.1%)	193	4 (2.1%)	188	6 (3.2%)
	Week 50	179	6 (3.4%)	176	5 (2.8%)	170	4 (2.4%)

TAF, tenofovir alafenamide; ULN, upper limit of normal

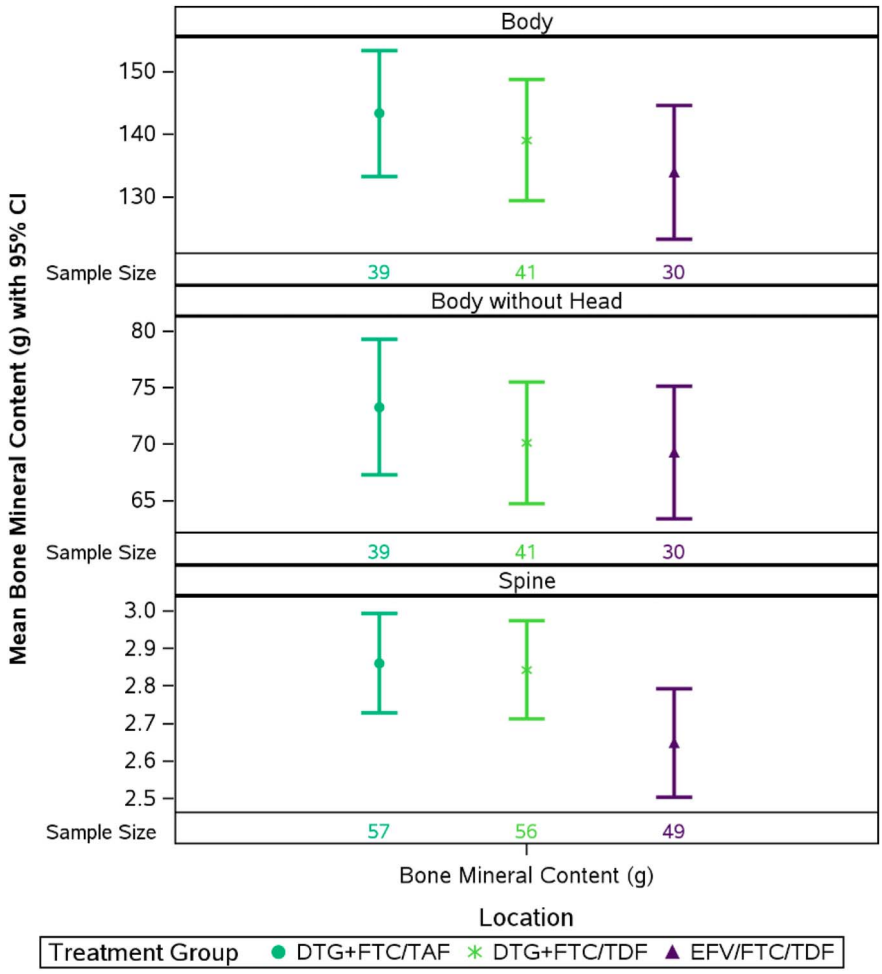

FIGURE 2. Infant BMD for the body, body without head, and spine.

Bone Mineral Content

DXA scans were performed at sites in Zimbabwe (112, 66%), South Africa (48, 28%), and Uganda (9, 5%). One hundred sixty-one (95.3%) infants taking part in the DXA component breastfed. Of the 225 planned participants with DXA scans, 191 (85%) whole-body and 190 (84%) spine scans were performed. Of the infant DXA scans done, 129 (68%) whole-body scans and 185 (97%) spine scans had valid results available, and of those results, 110 (85%) whole-body scans and 162 (88%) spine scans were taken within the 26-week analysis window. Hence, out of the total 225 participants expected, 110 (52%) whole-body and 162 (76%) spine week 26 results within the prespecified visit window were available for our primary infant DXA analysis. Common reasons for infants missing DXA scans were due to death (n = 10) or not able to complete the scan (n = 11). Most missing whole-body results were because of invalid scans (n = 31) or missing measurements (n = 36).

Birth characteristics were similar across arms among infants who had a DXA scan result (Table 1). Infants were on average 5.7 (SD 0.6) months of age at their DXA scan. Nearly all (161, 95%) were breastfed for some period, with 136 (81%) still breastfeeding at the time of their scan. Mean (95% CI) BMC by the randomized arm is given in Table 2 and Figure 2. Spine BMC was higher in the DTG + FTC/TAF arm than in the EFV/FTC/TDF arm [0.21g, (95% CI: 0.02, 0.41), $P = 0.032$] and was also higher in the DTG + FTC/TDF arm than in the EFV/FTC/TDF arm [0.20 g (95% CI: 0.00, 0.39), $P = 0.047$]. These mean differences were close to half of the observed SD (0.25 g). There was little difference observed for whole-body BMC and whole-body BMC without the head when comparing the EFV and DTG/TAF arms, with EFV having lower observed average BMC (Figure 2). A sensitivity analysis including all valid DXA results, even if the scan was conducted outside of the week 26 window, did not produce results appreciably different than the primary DXA analysis (see Table 1, Supplemental Digital Content 1, http://links.lww.com/QAI/C473).

Infant Growth

Five hundred seventy-seven liveborn infants were included in the growth analysis. Mean LAZ and WAZ were higher in the DTG arms than in the EFV/FTC/TDF arm; these differences were present from birth and persisted. Difference in mean (95%CI) LAZ between DTG + FTC/TDF and EFV/

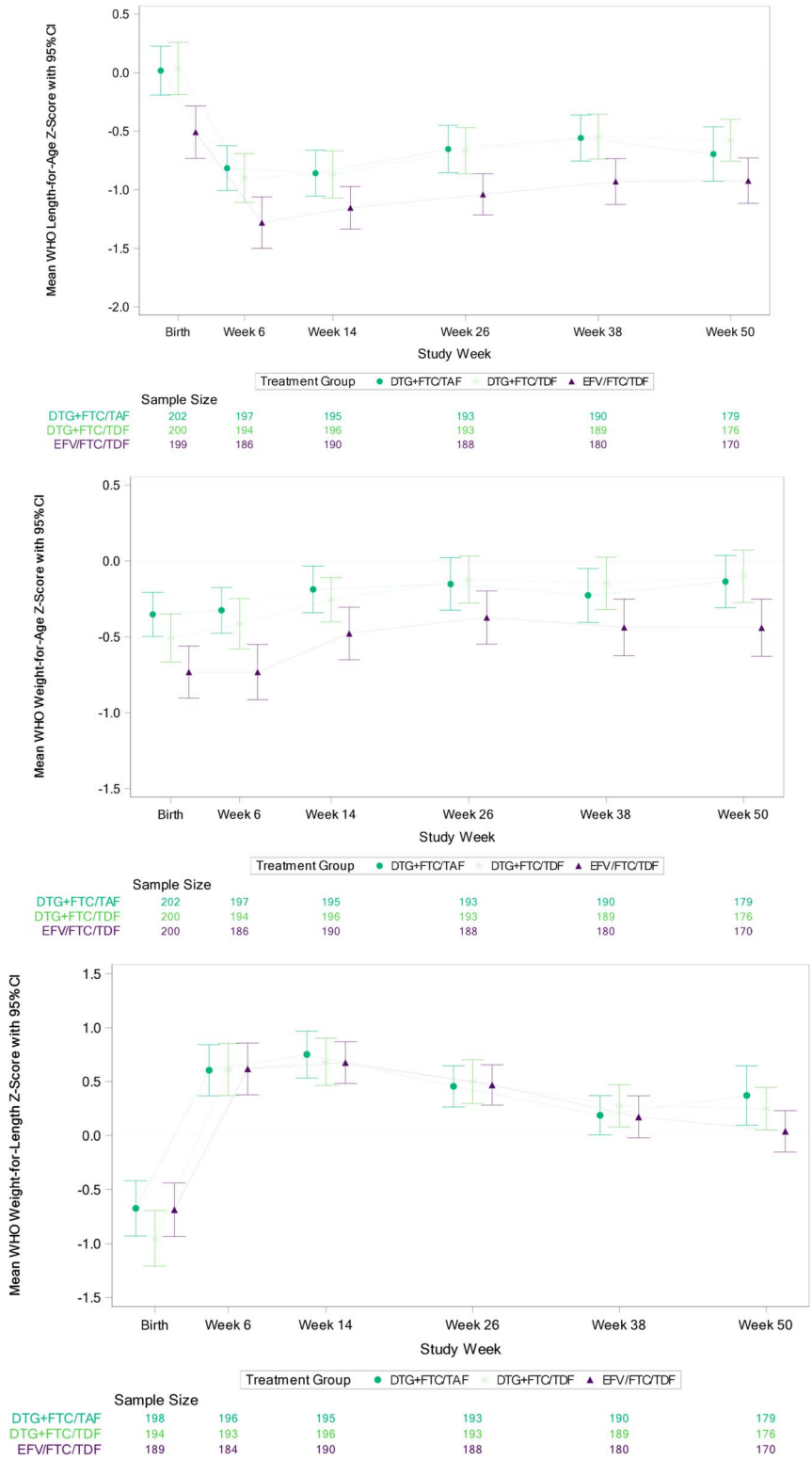

FIGURE 3. World Health Organization length-for-age, weight-for-age, and weight-for-length Z-score over time.

FTC/TDF arms was 0.4 (0.1, 0.6; $P = 0.0056$) at week 26 and 0.3 (0.1, 0.6; $P = 0.01$) at week 50. Mean WAZ difference (95% CI) between DTG + FTC/TDF and EFV/FTC/TDF arms was 0.3 (0.0, 0.5; $P = 0.035$) at week 26 and 0.3 (0.1, 0.6; $P = 0.0094$) at week 50. Mean LAZ and WLZ were similar between the DTG + FTC/TAF and DTG + FTC/TDF arms at week 26 or 50 (Fig. 3). A lower proportion of infants in the DTG-containing arms were stunted (LAZ below −2)

TABLE 3. Mean Difference Between Arms for BMC, Renal, and Growth Outcomes

		Mean Difference (95% CI) *P**		
Measurement	**Study Visit**	**DTG + FTC/TAF—DTG + FTC/TDF**	**DTG + FTC/TDF—EFV/FTC/TDF**	**DTG + FTC/TAF—EFV/FTC/TDF**
Bone mineral content				
Body (g)	Week 26	4.26 (−9.46, 17.99) 0.54	5.14 (−9.01, 19.29) 0.47	9.40 (−4.98, 23.79) 0.20
Body w/o head (g)	Week 26	3.17 (−4.79, 11.12) 0.43	0.86 (−6.99, 8.70) 0.83	4.02 (−4.24, 12.28) 0.33
Spine (g)	Week 26	0.02 (−0.17, 0.20) 0.85	0.20 (0.00, 0.39) 0.047	0.21 (0.02, 0.41) 0.032
Renal				
Creatinine (×ULN)	Delivery	−0.06 (−0.14, 0.03) 0.18	0.04 (−0.06, 0.14) 0.41	−0.02 (−0.11, 0.07) 0.71
	Week 26	0.00 (−0.04, 0.04) 0.90	0.05 (0.01, 0.08) 0.009	0.05 (0.01, 0.09) 0.020
Creatinine clearance (mL/min)	Delivery	−0.4 (−11.3, 10.5) 0.94	4.2 (−6.5, 14.9) 0.44	3.8 (−1.8, 9.3) 0.18
	Week 26	2.3 (−7.5, 12.1) 0.64	−11.4 (−22.6, −0.1) 0.048	−9.1 (−20.4, 2.2) 0.12
WHO growth Z-score				
Length-for-age	Week 26	0.01 (−0.27, 0.30) 0.92	0.37 (0.11, 0.64) 0.0056	0.39 (0.12, 0.65) 0.0047
	Week 50	−0.12 (−0.41, 0.17) 0.43	0.34 (0.08, 0.61) 0.010	0.23 (−0.07, 0.53) 0.14
Weight-for-age	Week 26	−0.03 (−0.26, 0.20) 0.80	0.25 (0.02, 0.48) 0.035	0.22 (−0.02, 0.47) 0.077
	Week 50	−0.03 (−0.28, 0.21) 0.78	0.34 (0.08, 0.59) 0.0094	0.30 (0.05, 0.56) 0.019
Weight-for-length	Week 26	−0.04 (−0.32, 0.23) 0.75	0.03 (−0.24, 0.31) 0.82	−0.01 (−0.28, 0.25) 0.92
	Week 50	0.01 (−0.25, 0.26) 0.94	0.21 (−0.06, 0.48) 0.13	0.22 (−0.03, 0.47) 0.086

*Tested with a 2-sample *t* test that assumes unequal variance. TAF, tenofovir alafenamide; ULN, upper limit of normal.

compared with the EFV/FTC/TDF arm: difference (95% CI) −5.7% (−13.3%, 1.9%) at week 26, and −7.2% (−15.0%, 0.7%) and −7.0% (−14.9%, 1.0%) at week 50, respectively. Between 2% and 4% of infants were obese at week 26 and week 50, with no evidence of an increased proportion of obese infants in the DTG + FTC/TAF arm (Table 2).

Infant Renal Outcomes

At birth, 558 (90%) infants had creatinine results. There was no apparent by-arm difference in infant creatinine or estimated creatinine clearance at birth (*P*-values ≥ 0.18, Table 3). The mean (SD) estimated creatinine clearance at birth was 53 (30) mL/min in the DTG + FTC/TAF arm, 53 (70) mL/min in the DTG + FTC/TDF arm, and 49 (25) mL/min in the EFV/FTC/TDF arm.

Among infants who were breastfed by their mothers at week 26 (N = 401), infants in the EFV/FTC/TDF arm had lower creatinine at week 26 than both of the DTG-containing arms: DTG + FTC/TAF with a mean difference (95% CI) of 0.05 (0.01, 0.09) × ULN (*P*-value = 0.020) and DTG + FTC/TDF with mean difference (95% CI) of 0.05 (0.01, 0.08) × ULN (*P*-value = 0.009). There was no observed difference in creatinine at week 26 between the DTG-containing arms. A total of 16 infants ever had a grade 3 or 4 elevated creatinine: 4 in the DTG + FTC/TAF arm, 8 in the DTG + FTC/TDF arm, and 4 in the EFV/FTC/TDF arm.

DISCUSSION

Infants whose mothers were randomized to EFV/FTC/TDF from pregnancy through 50 weeks postpartum had lower spine BMC, lower LAZ, WAZ, and more stunting (LAZ below −2) than infants whose mothers were randomized to either DTG + FTC/TAF or DTG + FTC/TDF. Infants whose mothers were in the EFV/FTC/TDF arm also had lower creatinine at week 26 than infants whose mothers were in the DTG-containing arms.

Estimated mean BMC in infants was highest in the DTG + FTC/TAF arm. This is consistent with findings from studies in adults that looked at the effect of TDF versus TAF regimens on BMD.[24–27] The effects of EFV on vitamin D metabolism and bone health are well known in adults,[4,28,29] however, there is little known about the effect of exposure to EFV on infant bone health. A study that assessed EFV-exposed breastfed infants did not observe significant growth, renal, or bone adverse outcomes.[30]

Infants born to mothers who started EFV/FTC/TDF during pregnancy had higher rates of stunting at 26 and 50 weeks of age than infants whose mothers started DTG-containing regimens. Although the difference in mean WHZ

scores seems modest, suboptimal nutritional status in the first 1000 days of life carries negative consequences for long-term health and survival.[31] The mechanisms of this difference remain unclear, potentially influenced by differential maternal weight gain during pregnancy and requiring extended follow-up to assess their persistence.[14] The growth differences observed at birth between study arms persisted through the study follow-up period. It is reassuring that not only was growth closer to optimal with maternal DTG (compared with EFV), including in combination with FTC/TAF, but also that rates of obesity through ~1 year of life did not differ between arms.

In infants exposed to TDF and TAF, there was no apparent by-arm difference in infant creatinine or creatinine clearance at birth, these findings are consistent with findings from the IMPAACT 1077BF (PROMISE) study where no infant renal safety concerns were observed on TDF exposure.[32] At week 26, there was significantly lower creatinine in the EFV arm than in the DTG-containing arms that could be because of the reversible nonpathologic inhibition of creatinine excretion by DTG.[33]

Limitations

The infant DXA sample size was smaller than planned resulting in increased variability to estimate differences (although some by-arm differences were nevertheless observed). In addition, we performed DXA scanning at only 1 time point so were not able to assess changes over time in infant BMC. An extended follow-up period could have benefitted the trial in adequately describing the growth patterns over time. Our results are only applicable to women who started ART in the second or third trimester of pregnancy, so our findings may not apply to women conceiving on ART. Most participants breastfed and enrolled primarily in Africa, hence results may not be generalizable to all settings.

CONCLUSIONS

It is reassuring that maternal DTG-based ART during pregnancy and breastfeeding was associated with higher infant spine BMC, better infant growth, and less stunting than EFV/FTC/TDF, and that these infant outcomes (and infant obesity) did not differ substantially between FTC/TAF versus FTC/TDF exposure (both in combination with DTG).

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REFERENCES

1. Unaids. *The Urgency of Now: AIDS at a Crossroads—2024 Global AIDS Update*; 2024. Available at: http://www.wipo.int/
2. Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. 2010;51:496–505.
3. Venter WDF, Fabian J, Feldman C. An overview of tenofovir and renal disease for the HIV-treating clinician. *South Afr J HIV Med*. 2018;19:817–818.
4. Hamzah L, Tiraboschi JM, Iveson H, et al. Effects on vitamin D, bone and the kidney of switching from fixed-dose tenofovir disoproxil fumarate/emtricitabine/efavirenz to darunavir/ritonavir monotherapy: a randomized, controlled trial (MIDAS). *Antivir Ther* 2016;21:287–296.
5. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis*. 2015;61:996–1003.
6. Van Dyke RB, Chadwick EG, Hazra R, et al. The PHACS SMARTT study: assessment of the safety of in utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199.
7. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606–2615.
8. Chen R, Zou J, Long L, et al. Safety and efficacy of tenofovir alafenamide fumarate in early-middle pregnancy for mothers with chronic hepatitis B. *Front Med (Lausanne)*. 2021;8:796901–796908.
9. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010;51:937–946.
10. Fabbriciani G, De Socio GVL. Efavirenz and bone health. *AIDS*. 2009;23:1181.
11. Kalkwarf HJ, Zemel BS, Yolton K, et al. Bone mineral content and density of the lumbar spine of infants and toddlers: influence of age, sex, race, growth, and human milk feeding. *J Bone Miner Res*. 2013;28:206–212.
12. Kinai E, Nguyen HDT, Do HQ, et al. Influence of maternal use of tenofovir disoproxil fumarate or zidovudine in Vietnamese pregnant women with HIV on infant growth, renal function, and bone health. *PLoS One*. 2021;16:e0250828.
13. Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? *AIDS*. 2021;35:S189–S195.
14. Hoffman RM, Brummel S, Ziemba L, et al. Weight changes and adverse pregnancy outcomes with dolutegravir- and tenofovir alafenamide fumarate–containing antiretroviral treatment regimens during pregnancy and postpartum. *Clin Infect Dis*. 2024;78:1617–1628.
15. Zash R, Caniglia EC, Diseko M, et al. Maternal weight and birth outcomes among women on antiretroviral treatment from conception in a birth surveillance study in Botswana. *J Int AIDS Soc*. 2021;24:e25763.
16. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis*. 2012;206:1695–1705.
17. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397:1276–1292.
18. Chinula L, Ziemba L, Brummel S, et al. Efficacy and safety of three antiretroviral therapy regimens started in pregnancy up to 50 weeks post partum: a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet HIV*. 2023;10:e363–e374.

19. Siberry G, Tierney C, Stranix-Chibanda L, et al. Impact of MaternalTenofovir use on HIV-exposed newborn bone mineral. *Conference on Retroviruses and Opportunistic Infections Boston, MA*. CROI; 2016: OA3-Feb 23, 2016.
20. Shepherd JA, Sommer MJ, Fan B, et al. Advanced analysis techniques improve infant bone and body composition measures by dual-energy X-ray absorptiometry. *J Pediatr*. 2017;181:248–253.e3.
21. WHO. *Training Course on Child Growth Assessment: WHO Child Growth Standards*. Geneva: World Health Organization; 2008:7.
22. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol*. 2009;4:1832–1843.
23. Lockman S, Chinula L, Coletti A. *IMPAACT 2010 Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants. "VESTED" Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG*; 2017:1–163.
24. Grant PM, Cotter AG. Tenofovir and bone health. *Curr Opin HIV AIDS*. 2016;11:326–332.
25. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606–2615.
26. Hill A, Hughes SL, Gotham D, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad*. 2018;4:72–79.
27. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16:43–52.
28. Wohl DA, Orkin C, Doroana M, et al. Change in vitamin D levels and risk of severe vitamin D deficiency over 48 weeks among HIV-1-infected, treatment-naive adults receiving rilpivirine or efavirenz in a Phase III trial (ECHO). *Antivir Ther*. 2014;19:191–200.
29. Welz T, Childs K, Ibrahim F, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS*. 2010;24:1923–1928.
30. Kapito-Tembo AP, Bauleni A, Wesevich A, et al. Growth and neurodevelopment outcomes in HIV-tenofovir-and efavirenz-exposed breastfed infants in the PMTCT option B+ program in Malawi. *J Acquir Immune Defic Syndr*. 2021;86:81–90.
31. Cusick SE, Georgieff MK. The role of nutrition in brain development: the golden opportunity of the "First 1000 Days". *J Pediatr*. 2016;175:16–21.
32. Vhembo T, Baltrusaitis K, Tierney C, et al. Bone and renal health in infants with or without breastmilk exposure to tenofovir-based maternal antiretroviral treatment in the PROMISE randomized trial. *J Acquir Immune Defic Syndr*. 2023;93:431–437.
33. McLaughlin MM, Guerrero AJ, Merker A. Renal effects of non-tenofovir antiretroviral therapy in patients living with HIV. *Drugs Context*. 2018;7:212519.