Markers of Maternal Bone and Renal Toxicity Through 50 Weeks Postpartum: IMPAACT 2010 (VESTED) Trial

Gaerolwe Masheto, MD,[a,b] Sean S. Brummel, PhD,[b] Lauren Ziemba, MS,[b] John Shepherd, PhD,[c] Tapiwa Mbengeranwa, MD, MBA,[d] Laarni Igawa, MPH,[c] Anne Coletti, MS,[e] Dorinda Mukura, MSc,[d] Lindie Rossouw, MD,[f] Gerhard Theron, MD,[g] Chelsea Krotje, MPH,[h] Patrick Jean-Philippe, MD,[i] Nahida Chakhtoura, MD,[j] Haseena Cassim, MBChB,[k] Sisinyana Ruth Mathiba, MBChB,[k] Joel Maena, MBChB, MPH,[l] William Murtaugh, MPH,[m] Lee Fairlie, MBChB,[n] Judith Currier, MD,[m] Risa Hoffman, MD,[m] Lameck Chinula, MD,[o] Paul E. Sax, MD,[p,q] Lynda Stranix-Chibanda, MBChB,[d,r] and Shahin Lockman, MD, MSc,[a,b,p,q] for the IMPAACT 2010/VESTED Study Team and Investigators

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Background: Safety data from randomized trials of antiretrovirals in pregnancy are scarce. We evaluated maternal bone and renal data from the International Maternal Pediatric Adolescent AIDS Clinical Trials Network 2010 trial, which compared the safety and efficacy of 3 antiretroviral therapy regimens started in pregnancy: dolutegravir + emtricitabine/tenofovir alafenamide (DTG + FTC/TAF), dolutegravir + emtricitabine/tenofovir disoproxil fumarate (DTG + FTC/TDF), and efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF).

Methods: A subset of participants underwent dual-energy X-ray absorptiometry scans at postpartum week 50 only. Maternal bone mineral density (BMD) Z-scores were compared between arms. Maternal creatinine was measured at enrolment and periodically through week 50 postpartum, and by-arm differences in average weekly change in estimated creatinine clearance were compared.

Results: Six hundred forty-three participants were randomized to DTG + FTC/TAF (N = 217) or DTG + FTC/TDF (N = 215) or EFV/FTC/TDF (N = 211). Median age = 27 years (IQR 23, 32), median CD4 count = 466 cells/mm^3 (IQR 308, 624); 564 (88%) women enrolled in Africa and 479 (74%) breastfed. Week 50 postpartum dual-energy X-ray absorptiometry results from 154 women were included in the analysis. Hip and spine BMD was on average higher in women in the DTG + FTC/TAF and lower in the DTG + FTC/TDF and EFV/FTC/TDF arms, but no significant differences in BMD Z-scores were observed between treatment groups. The weekly rate of change in estimated creatinine clearance differed among treatment groups during the antepartum period, but not over the full study follow-up.

Conclusions: Markers of bone and renal toxicity did not differ significantly through week 50 postpartum among women randomized to start DTG + FTC/TAF or DTG + FTC/TDF or EFV/FTC/TDF in pregnancy.

Key Words: HAART, renal, bone, pregnant, women, postpartum

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From the [a]Botswana Harvard Health Partnership, Gaborone, Botswana; [b]Center for Biostatistics in AIDS Research, Harvard TH Chan School of Public Health, Boston, MA; [c]University of Hawai'i Cancer Center, Honolulu, HI; [d]University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe; [e]FHI 360, Durham, NC; [f]Family Centre for Research with Ubuntu (FAMCRU), Stellenbosch University, Cape Town, South Africa; [g]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [h]Frontier Science & Technology Research Foundation, Inc, Amherst, NY; [i]National Institute of Allergy and Infectious Diseases, Rockville, MD; [j]National Institute of Child Health and Human Development, Bethesda, MD; [k]Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa; [l]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda; [m]David Geffen School of Medicine, University of California, Los Angeles, CA; [n]Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [o]UNC Project–Malawi, Lilongwe, Malawi; [p]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA; [q]Harvard Medical School, Boston, MA; and [r]Child and Adolescent Health Unit, Faculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

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Correspondence to: Gaerolwe Masheto, MD, Botswana Harvard Health Partnership, Plot 1836, North Ring Road, Princess Marina Hospital, Gaborone, Botswana (e-mail: gmasheto@bhp.org.bw).

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INTRODUCTION

An estimated 1.3 million people living with HIV-1 become pregnant annually.[1] Antiretroviral therapy (ART) during pregnancy is important for maternal health and

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prevention of vertical HIV-1 transmission. However, high-quality renal and bone safety data are scarce for most antiretrovirals during pregnancy and lactation. In 2018, World Health Organization guidelines replaced efavirenz (EFV) with dolutegravir (DTG) in first-line, second-line, and possibly third-line ART regimens for treating adults with HIV-1 (including in pregnancy).[2] Tenofovir disoproxil fumarate (TDF) remains a component of WHO-recommended first-line ART, in combination with either lamivudine (3TC) or emtricitabine (FTC). TDF, a prodrug of the active form tenofovir (TFV), can have toxic renal and bone effects, which are positively correlated with plasma TFV concentrations.[3–6] Tenofovir alafenamide (TAF), a TFV prodrug that is as efficacious as TDF in treating HIV, leads to 90% lower plasma TFV levels than TDF (but higher intracellular TFV).[7] TAF thus has a more favorable renal and bone safety profile than TDF in adults starting ART, as reflected by biomarkers[8,9] and pooled analyses of clinical data,[10] although clinical significance of differences in bone density is not entirely clear. Little is known about the renal or bone safety profile of TAF during pregnancy and breastfeeding. Bone mass declines during breastfeeding (and possibly to a lesser extent during pregnancy),[11–17] which could be exacerbated with concomitant TDF use.

We evaluated markers of maternal renal and bone toxicity in pregnant and postpartum participants in the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2010 trial, in which pregnant women living with HIV were randomized to start ART with DTG + FTC/TAF or DTG + FTC/TDF or EFV/FTC/TDF and were followed with renal monitoring through (and dual-energy X-ray absorptiometry [DXA] scan at) 50 weeks postpartum.

METHODS

Study Design, Participants, and Treatment

The IMPAACT 2010 trial (or "VESTED: Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG") was a Phase 3 open-label randomized trial conducted at 22 clinical research sites in 9 countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the United States, and Zimbabwe). Detailed trial design and primary study results through delivery and week 50 postpartum have been published.[18] We enrolled pregnant women 18 years or older who had confirmed HIV-1 infection and were between 14 and 28 weeks of gestation. Participants were ART-naive with the following exceptions permitted: up to 14 days of ART use during the current pregnancy, prior TDF or TDF/FTC pre-exposure prophylaxis, or ART during prior pregnancies if the last dose was taken 6 months or more before study entry. We excluded individuals whose screening ultrasound revealed multiple gestation or fetal anomaly. We also excluded individuals with hospitalization or acute significant illness in the preceding 14 days and individuals with active tuberculosis, estimated creatinine clearance (eCrCl) <60 mL/min (or creatinine >1.8 times the upper limit of normal), or serum alanine aminotransferase or aspartate aminotransferase ≥ 2.5 times the upper limit of normal. Mothers and infants were followed through 50 weeks postpartum.[18]

Eligible participants were randomly assigned (1:1:1) to receive either DTG + FTC/TAF, DTG + FTC/TDF, or EFV/FTC/TDF, open-label, with dosing per package inserts.

Study Procedures

After randomization, participants had regular study visits through 50 weeks postpartum. Maternal HIV-1 RNA (Abbott RealTime m2000 HIV-1 Viral Load assay; Abbott Molecular, Des Plaines, IL), alanine aminotransferase, aspartate aminotransferase, and creatinine concentrations were measured before randomization and at antepartum weeks 4, 12, and 24; delivery; and postpartum weeks 14, 26, and 50. Creatinine clearance was estimated using the Cockcroft–Gault formula.[19]

Maternal DXA was performed only at the final week 50 postpartum study visit in a subset of women at selected sites. The prespecified sample size for participation in DXA scans was 213 (71 per arm) of 639 total planned participants in IMPAACT 2010, which provides at least 80% power to detect ≥ 0.5 SD difference in bone mineral density (BMD) between any 2 arms, which was deemed to be clinically relevant (difference of approximately 0.07 g in adult lumbar spine DXA). Seven sites in 3 countries (Zimbabwe, South Africa, and Uganda) had the capacity to perform DXA scans and did so in sequential participants until the target number of participants had completed DXA scans.

Lumbar spine and whole hip scans were performed according to standardized procedures, and images were transmitted electronically to the University of Hawaii Cancer Center once a month for centralized reading. Quality control procedures were used to monitor the performance of the scanners throughout the course of the study, including longitudinal monitoring of each site's accuracy and stability and a cross-calibration phantom scan to assess scanner differences between the sites. Hologic DXA longitudinal quality control procedures consisted of a Hologic Spine phantom scan either daily or no less than 3 times per week and by performing a Table Top Radiographic Uniformity Test (Airscan) once a week for the duration of the study.

Trial Ethics and Oversight

Each participating research site received approval from the appropriate local research ethics authorities. All participating women provided written informed consent. The study was monitored by an independent data and safety monitoring board and was registered with ClinicalTrials.gov, NCT03048422.

Role of the Funding Source

Overall support for the IMPAACT was provided by the National Institute of Allergy and Infectious Diseases with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the National Institutes of Health, under Award Numbers UM1 AI068632 (IMPAACT LOC), UM1 AI068616 (IMPAACT

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Statistical Analysis

Study Outcomes

The objectives of this analysis were to evaluate whether the following differed between participants in each of the 3 study arms, for any pairwise between-arm comparison: (1) maternal renal function and renal adverse events through 50 weeks postpartum and (2) BMD density at week 50 postpartum.

Analyses presented here are intention-to-treat. Differences between treatment arms were considered statistically significant if the corresponding *P*-value was <0.05. Non-statistically significant results were described as "no apparent difference"; however, conclusions were primarily based on the estimated treatment effect and uncertainty described by the 95% confidence interval (CI). No adjustments were made for multiple comparisons of different outcome measures.

DXA Outcomes

For the primary analysis, only DXA results obtained within the allowable week 50 visit window ($\pm$6 weeks) were included. A sensitivity analysis included the results of all DXA scans obtained. Mean hip and spine BMD Z-scores were computed. The two-sample *t* test with unequal variance was used to compare average BMD Z-scores.

Renal Outcomes

By-arm differences in the average weekly change in eCrCl in all study participants were estimated and tested using generalized estimating equations with an identity link and an exchangeable working correlation matrix. To account for differences in eCrCl measurements between groups at time zero (entry or delivery), an additional sensitivity analysis adjusting for eCrCl at time zero was performed.

We also summarized Grade 3 or higher adverse renal laboratory results (eCrCl <60 mL/min or creatinine >1.8 times the upper limit of normal) and renal events that prompted a change in study drug (creatinine and eCrCl were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, 2017, based on absolute creatinine/eCrCl values and not change from baseline).

RESULTS

Study Enrolment and Completeness of Assessments

A total of 643 pregnant individuals were enrolled in the VESTED study between January 2018 and February 2019, and participants were randomized to start DTG + FTC/TAF (N = 217), DTG + FTC/TDF (N = 215), or EFV/FTC/TDF (N = 211).

A total of 213 DXA scans were expected per the protocol, and 208 (98%) scans were completed (all women enrolling in Zimbabwe, South Africa, and Uganda), 154 (74%) of which were included in the primary DXA analysis (ie, had results available and obtained inside the $\pm$6 weeks window of the postpartum week 50 visit); see more details in Figure 1 and Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C318.

Overall, 639 participants were included in the results of renal outcomes. Creatinine clearance data were available for 605 (94%) of women at delivery and 574 (89%) at postpartum week 50.

DXA Outcomes

Most characteristics of the 154 women with DXA scans included in the main DXA analysis were similar in the 3 treatment arms (Table 1). Women took study ART for a mean of 66 weeks before their DXA scan. Most women (90%) with DXA results breastfed, for a mean duration of 44 weeks. Most women (62%) took medroxyprogesterone acetate contraceptives postpartum. No women had recent history of bone fracture, and only 3 had a positive hepatitis B surface antigen. Characteristics between women in the main DXA analysis and randomized women excluded from the DXA analysis were generally similar, with the exception of country (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C318). Table 3, Supplemental Digital Content, http://links.lww.com/QAI/C318 summarizes data availability for maternal DXA scans and results (Table 2).

Among women with a DXA scan taken in the analysis window, the mean (SD) hip BMD z-scores were -0.45 (0.71) in the DTG + FTC/TAF arm, -0.50 (0.73) in the DTG + FTC/TDF arm, and -0.57 (0.73) in the EFV/FTC/TDF arm. The mean (SD) spine BMD z-scores were -1.40 (1.08) in the DTG + FTC/TAF arm, -1.57 (1.07) in the DTG + FTC/TDF arm, and -1.64 (1.05) in the EFV/FTC/TDF arm. Thus, BMD z-scores were highest in women in the DTG + FTC/TAF arm and lower (and similar) in the DTG + FTC/TDF and EFV/FTC/TDF arms (Figure 2). However, there were no apparent differences in hip or spine BMD Z-scores between treatment groups (see Table 4, Supplemental Digital Content, http://links.lww.com/QAI/C318).

In a sensitivity analysis with all 208 available DXA results (including the 54 scans performed outside of the week 50 window), there were also no apparent differences in hip or spine BMD Z-scores between treatment groups (see Table 5, Supplemental Digital Content, http://links.lww.com/QAI/C318). A sensitivity analysis did not show substantially by-arm differences in BMD Z-scores in women with vs without postpartum medroxyprogesterone acetate exposure, as shown in Table 6, Supplemental Digital Content, http://links.lww.com/QAI/C318.

No bone fractures were reported to occur on study.

Renal Outcomes

Baseline characteristics for all 643 maternal participants and their renal outcomes are summarized in Tables 7 and 8,

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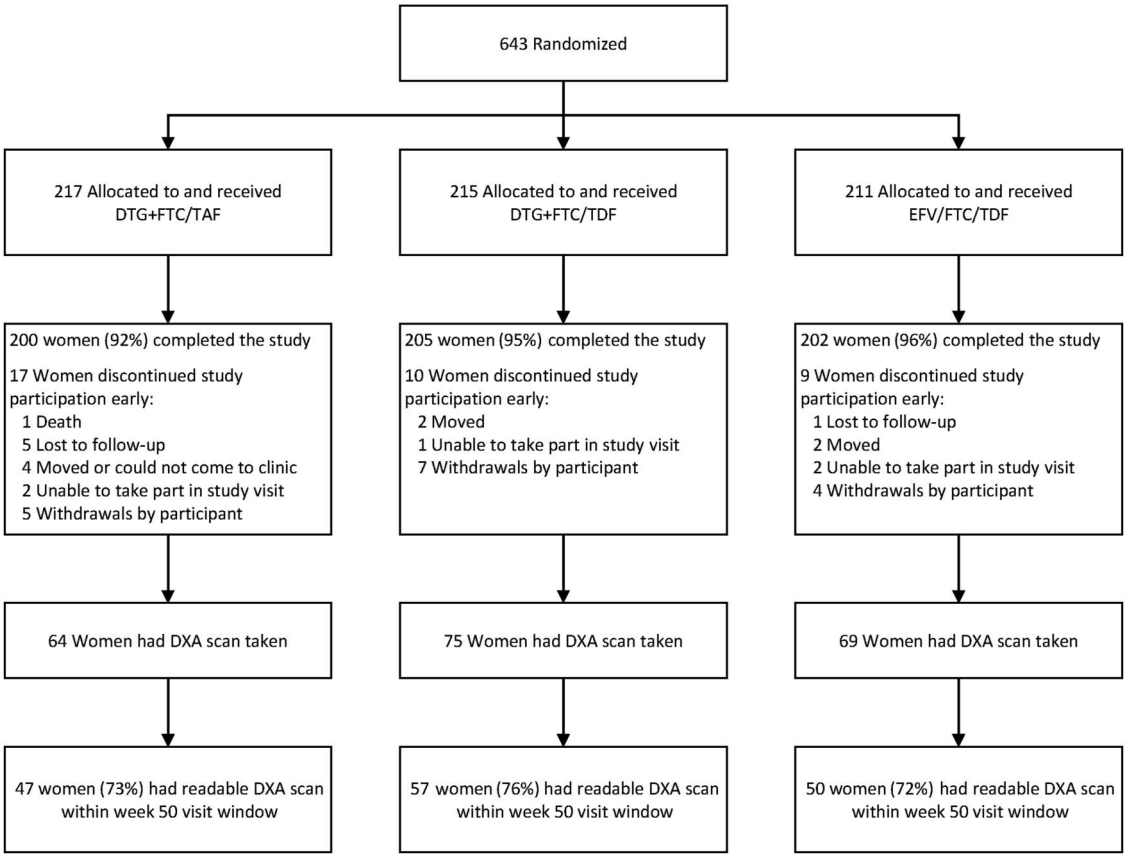

FIGURE 1. CONSORT diagram for DXA scan results.

Supplemental Digital Content, http://links.lww.com/QAI/C318, respectively. The median participant age was 27 years, and most women were enrolled in Zimbabwe (39%), South Africa (17%), and Uganda (17%). Most participants (90%) identified as Black or African. Thirteen women (2.0%) tested positive for hepatitis B.

The eCrCl data were available for 605 women (94%) at delivery and 574 (89%) at postpartum week 50. Grade 3 or

TABLE 1. Characteristics of Women With DXA Scan Results, by Randomized Treatment Arm

	DTG + FTC/TAF (N = 47)	DTG + FTC/TDF (N = 57)	EFV/FTC/TDF (N = 50)	Total (N = 154)
Age at enrolment, median, yr (Q1–Q3)	25 (20–30)	28 (24–33)	29 (25–33)	28 (23–32)
Country, n (%)				
South Africa	15 (32)	22 (39)	16 (32)	53 (34)
Uganda	2 (4)	4 (7)	1 (2)	7 (5)
Zimbabwe	30 (64)	31 (54)	33 (66)	94 (61)
Black African, n (%)	47 (100)	57 (100)	50 (100)	154 (100)
Gestational age at baseline, median, wk (Q1–Q3)	24 (21–26)	22 (19–25)	22 (19–26)	22 (19–26)
Body mass index at baseline, mean g/cm^2 (SD)	27 (6)	26 (5)	26 (4)	26 (5)
HIV-1 RNA<200 cp/mL (most recent before DXA), n (%)	47 (100)	54 (95)	50 (100)	151 (98)
CD4 cell count at baseline, median, cells/mm^3 (Q1–Q3)	546 (326–660)	468 (272–591)	439 (303–626)	459 (291–626)
Ever breastfed during study postpartum, n (%)	43 (92)	50 (88)	46 (92)	139 (90)
Duration of breastfeeding, mean, wk (SD)	44 (15)	44 (15)	43 (16)	44 (15)
Breast feeding at the time of DXA scan, n (%)	31 (66)	35 (61)	33 (66)	99 (64)
Duration of randomized ART through the time of scan, mean, wk (SD)	66 (10)	66 (9)	66 (7)	66 (9)
Medroxyprogesterone acetate used during the postpartum period, n (%)	32 (68)	35 (61)	28 (56)	95 (62)

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TABLE 2. Maternal Baseline Characteristics Among All VESTED Study Participants Who had eCrCl Performed, by Randomized Arm

	Randomized Treatment Arm			
	DTG + FTC/TAF (N = 217)	DTG + FTC/TDF (N = 215)	EFV/FTC/TDF (N = 211)	Total (N = 643)
Age, median, yr (Q1–Q3)	27 (22–32)	26 (22–31)	27 (23–32)	27 (23–32)
Country				
Botswana	16 (7%)	18 (8%)	17 (8%)	51 (8%)
Brazil	21 (10%)	19 (9%)	17 (8%)	57 (9%)
India	2 (1%)	1 (<1%)	0 (0%)	3 (<1%)
South Africa	37 (17%)	37 (17%)	37 (18%)	111 (17%)
Tanzania	15 (7%)	13 (6%)	15 (7%)	43 (7%)
Thailand	5 (2%)	4 (2%)	6 (3%)	15 (2%)
Uganda	37 (17%)	37 (17%)	36 (17%)	110 (17%)
United States	2 (1%)	2 (1%)	0 (0%)	4 (1%)
Zimbabwe	82 (38%)	84 (39%)	83 (39%)	249 (39%)
Race				
Asian	7 (3%)	5 (2%)	6 (3%)	18 (3%)
Black or African American	195 (90%)	196 (91%)	194 (92%)	585 (91%)
White	5 (2%)	7 (3%)	7 (3%)	19 (3%)
Other	10 (5%)	6 (3%)	4 (2%)	20 (3%)
Unknown	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Gestational age at enrolment, median, wk (Q1–Q3)	22 (18–25)	21 (18–25)	22 (18–25)	22 (18–25)
Weight, median, kg (Q1–Q3)	65 (57–77)	63 (56–72)	61 (55–71)	63 (56–73)
Hepatitis B status				
Missing	1	0	2	3
Negative	213 (99%)	209 (97%)	205 (98%)	627 (98%)
Positive	3 (1%)	6 (3%)	4 (2%)	13 (2%)
WHO clinical stage				
Stage 1	213 (98%)	211 (98%)	208 (99%)	632 (98%)
Stage 2	4 (2%)	4 (2%)	3 (1%)	11 (2%)
HIV-1 RNA, copies/mL				
Median (Q1–Q3)	781 (147–5733)	715 (128–4304)	1357 (198–5125)	903 (152–5183)
<200	62 (29%)	66 (31%)	53 (25%)	181 (28%)
CD4, cells/mm^3				
Median (Q1–Q3)	467 (324–624)	481 (332–642)	439 (300–616)	466 (308–624)
CD4, cells/mm^3, categorized				
Missing	2	0	3	5
50–349	64 (30%)	60 (28%)	73 (35%)	197 (31%)
350–499	56 (26%)	54 (25%)	50 (24%)	160 (25%)
500–750	68 (32%)	67 (31%)	59 (28%)	194 (30%)
>750	27 (13%)	34 (16%)	26 (13%)	87 (14%)

higher decrease in eCrCl occurred in 4 women in the DTG + FTC/TAF arm, 7 in the DTG + FTC/TDF arm, and 3 in the EFV/FTC/TDF arm. Two women (1 in each of the DTG + FTC/TAF and EFV/FTC/TDF arms) withdrew from study ART due to a renal adverse event assessed as related to treatment (1 woman in the DTG + FTC/TAF arm with eCrCl 50 mL/min and 1 woman in the EFV/FTC/TDF arm with eCrCl 61 mL/min).

The mean eCrCl at postpartum week 50 was 124 mL/min in the DTG + FTC/TAF arm, 118 mL/min in the DTG + FTC/TDF arm, and 131 mL/min in the EFV/FTC/TDF arm (Figure 3 and see Table 8, Supplemental Digital Content, http://links.lww.com/QAI/C318). Detailed results of comparison of change in eCrCl per week between arms (and change in eCrCl per week adjusted for time zero) are presented in Table 9, Supplemental Digital Content, http://links.lww.com/QAI/C318.

During the antepartum period, maternal eCrCl increased slightly in women in the DTG + FTC/TAF arm but decreased slightly in each of the other 2 arms (Figure 3); the difference in antepartum weekly eCrCl change between the DTG + FTC/TAF and DTG + FTC/TDF arms was +0.92 (95% CI: 0.21 to 1.63, P = 0.011) and the difference in weekly antepartum eCrCl change between the DTG + FTC/TAF and EFV/FTC/TDF arms was +0.66 (95% CI: −0.06 to 1.38, P = 0.072). In the postpartum period, the average adjusted difference in weekly eCrCl between the DTG + FTC/TDF and EFV/FTC/TDF arms was +0.15 (95% CI: 0.03 to 0.27, P = 0.015), with no apparent difference in the other 2 pairwise comparisons postpartum. Thus, in all study follow-up, the mean change in eCrCl per week was −0.98 mL/min in the DTG + FTC/TAF arm, −0.89 in the DTG + FTC/TDF arm, and −0.94 in the EFV/FTC/TDF arm, with no apparent

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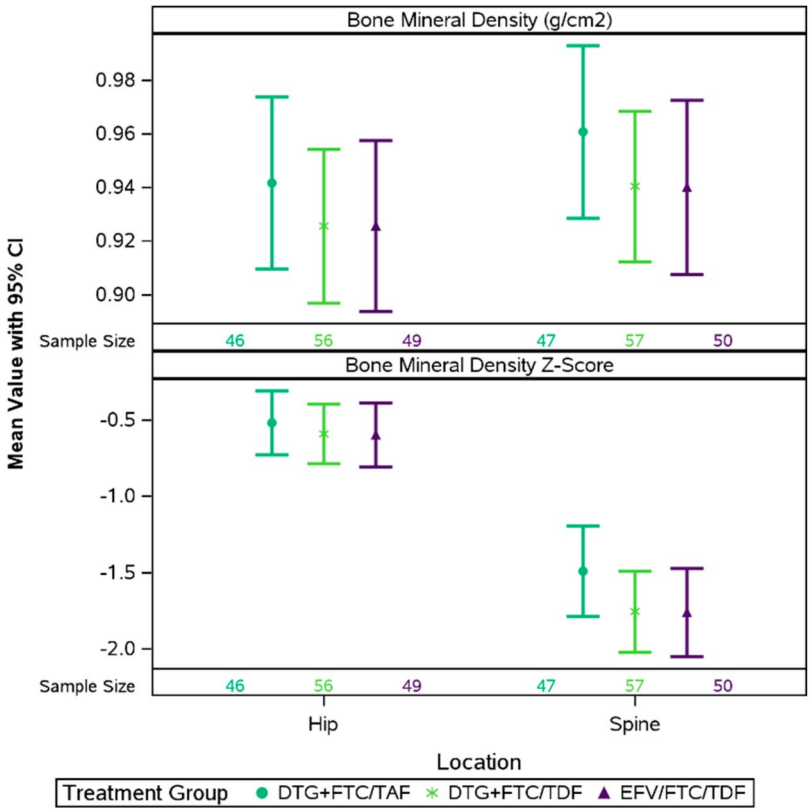

FIGURE 2. Maternal DXA results at the 50-week postpartum visit.

differences in change in eCrCl between treatment groups (see Table 10, Supplemental Digital Content, http://links.lww.com/QAI/C318).

DISCUSSION

In this randomized 3-arm trial comparing the safety and efficacy of DTG + FTC/TAF, DTG + FTC/TDF, and EFV/FTC/TDF started in pregnancy, we did not observe apparent differences between treatment groups in BMD Z-score nor changes in maternal renal function through 50 weeks postpartum.

BMD at week 50 postpartum did not differ significantly between study arms. However, women in both of the TDF arms had numerically lower BMD compared with women in the DTG/FTC/TAF arm. To the best of our knowledge, these

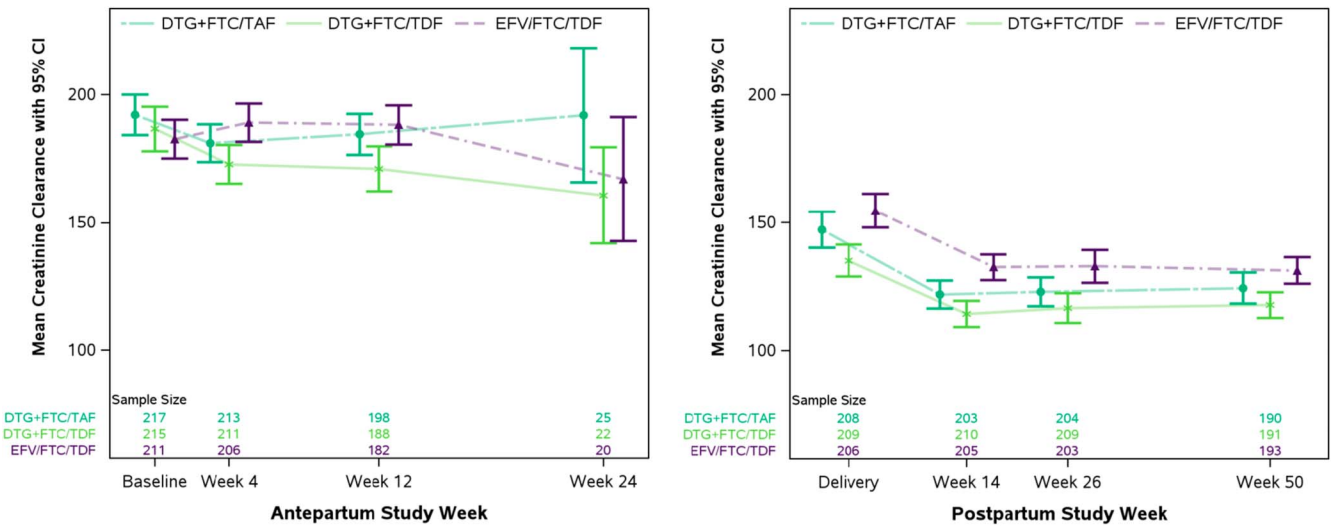

FIGURE 3. Maternal mean eCrCl over time by randomized study arm.

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are the first data on bone density in women taking TAF during pregnancy and/or breastfeeding. Some randomized trials in nonpregnant adults have demonstrated greater decrease in BMD in adults taking TDF-containing vs TAF-containing ART,[20] whereas others have not observed this difference, including the ADVANCE trial that randomized adults in South Africa to initiated ART with the same regimens that were used in the IMPAACT 2010 trial.[21]

We also found that, although mean eCrCl increased in women in the DTG + FTC/TAF arm and decreased most in the DTG + FTC/TDF arm (and decreased in the EFV/FTC/TDF arm) between enrolment and delivery, the overall change in eCrCl did not differ among arms when measured across the entire period from antepartum enrolment through the week 50 postpartum visit. Rates of clinically concerning changes in renal function were rare in our study. This is not surprising—previous studies have generally shown low rates of clinically concerning renal toxicity with TDF use in otherwise healthy persons starting ART, particularly in young populations.[3,4,6] Creatinine clearance increases during normal pregnancy due to glomerular hyperfiltration, and rates of drug-associated renal toxicity are not expected to be higher in pregnant or postpartum women[22] (unless accompanied by pregnancy complications such as preeclampsia). It is important to note that small increases (10%–20%) in serum creatinine are expected with DTG even in the absence of renal injury because DTG inhibits the renal transport and excretion of creatinine (hence leading to an artefactual decrease in eCrCl).

We previously published primary pregnancy and week 50 postpartum outcomes by arm in the IMPAACT 2010 participants.[18,23] Women randomized to start DTG + FTC/TAF had significantly fewer adverse pregnancy outcomes (preterm birth, small for gestational age, stillbirth, or neonatal death) compared with women in each of the other 2 study arms.[23] The results of our current analysis of markers of bone and renal toxicity do not change the overall finding from our trial that DTG + FTC/TAF seems to be safer in pregnancy than DTG + FTC/TDF or EFV/FTC/TDF.

The notable strengths of our study include the randomized design and the high proportion of completeness of follow-up and evaluation. Our study has some limitations. Our DXA sample size was modest; however, we designed the study to have 80% power to detect half of a SD (or more) in BMD between groups (a relatively small difference), and we were able to rule out moderate differences, as measured by the 95% CI: (eg, comparing DTG + FTC/TAF with DTG + FTC/TDF for hip BMD Z-score, the CI was [−0.24 to 0.33], ie, no more than 0.33 of 1 SD difference) with a very point estimate for the difference for BMD between arms (0.05 SD).

We also did not have baseline DXA measurements; other studies have evaluated change in BMD from baseline with standardized and calibrated DXA scanners (eg, use of a phantom), which might reduce intersubject variability. Finally, of the 213 week 50 DXAs expected per protocol, only 154 (72%) were available for the main analysis within the prespecified visit window. However, 208 of 213 participants had DXA results available outside the visit window (beyond window by median 3.3 weeks), and findings did not change substantially in sensitivity analyses including results from all 208 scans.

In summary, although DTG + FTC/TAF seems to be safer than DTG + FTC/TDF or EFV/FTC/TDF (when started in pregnancy) related to pregnancy outcomes, this study found no apparent differences in markers of bone or renal toxicity in women randomized to start DTG + FTC/TAF, DTG + FTC/TDF, or EFV/FTC/TDF in pregnancy, through week 50 postpartum.

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