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Bone and Renal Health in Infants With or Without Breastmilk Exposure to Tenofovir-Based Maternal Antiretroviral Treatment in the PROMISE Randomized Trial

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Background: We assessed bone and kidney outcomes in infants randomized postdelivery as mother–infant pairs within the IMPAACT PROMISE trial to maternal tenofovir disoproxil fumarate–based antiretroviral treatment (mART) or infant nevirapine prophylaxis (iNVP) to prevent breastfeeding HIV transmission.

Methods: Infants were coenrolled in the P1084s substudy on randomization day and followed through Week 74. Lumbar spine bone mineral content (LS-BMC) was assessed at entry (6–21 age days) and Week 26 by dual-energy x-ray absorptiometry. Creatinine clearance (CrCl) was calculated at entry; Weeks 10, 26, and 74. Student *t* tests compared mean LS-BMC and CrCl at Week 26 and mean change from entry between arms.

Results: Of 400 enrolled infants, the mean (SD; n) for entry LS-BMC was 1.68 g (0.35; n = 363) and CrCl was 64.2 mL/min/1.73 m^2 (24.6; n = 357). At Week 26, 98% of infants were breastfeeding and 96% on their assigned HIV prevention strategy. The mean (SD) Week 26 LS-BMC was 2.64 g (0.48) for mART and 2.77 g (0.44) for iNVP; mean difference (95% confidence interval [CI]) −0.13 g (−0.22 to −0.04), $P = 0.007$, n = 375/398 (94%). Mean absolute (−0.14 g [−0.23 to −0.06]) and percent (−10.88% [−18.53 to −3.23]) increase in LS-BMC from entry was smaller for mART than iNVP. At Week 26, the mean (SD) CrCl was 130.0 mL/min/1.73 m^2 (34.9) for mART vs. 126.1 mL/min/1.73 m^2 (30.0) for iNVP; mean difference (95% CI) 3.8 (−3.0 to 10.7), $P = 0.27$, n = 349/398 (88%).

Conclusion: Week 26 mean LS-BMC was lower in infants in the mART group compared with the iNVP group. However, this difference (~0.23 g) was less than one-half SD, considered potentially clinically relevant. No infant renal safety concerns were observed.

Key Words: infant, bone mineral content, renal health, tenofovir disoproxil fumarate

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INTRODUCTION

Breastfeeding provides short- and long-term health benefits for both mother and infant[1,2] and is increasingly practiced in diverse settings by women receiving antiretroviral treatment (ART) for HIV.[3–5] The effect on infant health of antiretroviral agents (ARVs) secreted in breastmilk on infant health should be considered when selecting regimens,[6,7] yet rigorous trial data are lacking. In particular, although it is well-established in adults that tenofovir disoproxil fumarate (TDF) is associated with 1%–3% greater loss in bone mineral density[8–10] and increased renal tubular dysfunction compared with non–TDF-containing ARV regimens,[11–14] scant experience of TDF use or exposure in infants limits the ability to estimate the likelihood of TDF-related bone and renal toxicity in infants.[15,16] Although breastfeeding infants are exposed to only 0.01%–0.04% of the recommended weight-adjusted therapeutic TDF dose,[8,17] the possibility of infant toxicity through direct exposure in breastmilk or mediated by potential TDF-related alterations in breastmilk[18] deserves evaluation given the wide use of TDF for HIV treatment and prevention.

The Postpartum (PP) Component of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Promoting Maternal and Infant Survival Everywhere (PROMISE) trial was a multicountry randomized open-label strategy trial comparing the efficacy and safety of maternal ART (mART) versus infant nevirapine prophylaxis (iNVP) without maternal ART throughout the breastfeeding period for the prevention of breastfeeding HIV transmission in women who did not meet ART initiation criteria for their own health at that time and their breastfeeding infants weighing at least 2 kg at birth. The Bone and Kidney Health substudy (P1084s) enrolled women without advanced HIV disease and no antepartum TDF exposure who intended to breastfeed to evaluate the effect of TDF-containing maternal ART on infant bone and renal function in the absence of the potential confounding effect on infant health of replacement feeding and maternal advanced HIV disease.[19–22] In this substudy, we compared infant lumbar spine (LS) bone mineral content (LS-BMC) at 26 weeks of life and creatinine clearance (CrCl) between infants randomized to mART or iNVP during breastfeeding.

MATERIALS AND METHODS

Study Population

The IMPAACT PROMISE randomized trial (NCT01061151) enrolled 3747 pregnant women living with HIV along with their infants in 15 countries across different health settings. Through sequential randomizations in pregnancy, PP, and after the risk for HIV transmission was over, PROMISE aimed to determine the optimal ARV strategy (medication, timing, and duration) to prevent vertical transmission of HIV and preserve maternal health and infant survival (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/C65). The PP Component randomized women living with HIV with high CD4 counts, who did not meet the criteria to initiate ART for their own health and intended to breastfeed, and their uninfected infants (negative HIV PCR from a specimen collected within 5 days of birth) weighing at least 2 kg at birth to receive either open-label mART (TDF/emtricitabine + lopinavir/ritonavir) or iNVP throughout the period of breastfeeding[19,23] The IMPAACT PROMISE study was conducted between the years 2011 and 2016, and at that time, universal ART was not yet standard for breastfeeding women. In 4 African countries with capacity for bone mineral evaluation (Malawi, South Africa, Uganda, and Zimbabwe), P1084s substudy offered PP coenrolment to a subset of 400 PROMISE women with no prior TDF exposure during pregnancy and their infants. This study was approved by the institutional review boards or ethics committee at each participating site, and written informed consent was obtained for each mother–infant pair (mothers provided permission for their infants' participation). The full protocol is available at https://www.impaactnetwork.org/P1084s.

Study Procedures

After obtaining substudy consent, P1084s entry occurred on the same day as PROMISE PP randomization on day 6–14 of life. Infants were assessed at entry and postnatal Weeks 10, 26, and 74 for medical and drug history, breastfeeding status, and adherence to assigned study ARV strategy. Anthropometric growth was measured by trained study staff according to standardized measurement guidance. The measurement instruments were calibrated regularly per manufacturer's instructions. Shoes and outer layers of clothing were removed before weight measurements were taken. The data collectors were trained and experienced in weight and height measurement and followed standardized measurement guidelines. Infant feeding practices were assessed through interviews with the mothers using a structured questionnaire at every visit. The tool captured information which included whether they were still breastfeeding, the date of breastfeeding cessation if they had stopped, and the date of introduction of complementary feeds if these had been introduced.

Infant BMC Assessment

BMC was measured at the LS by dual-energy X-ray absorptiometry (DXA). The entry measurement was scheduled between days 6 and 21 of life and repeated at postnatal Week 26 ($\pm$6 weeks). Standardized procedures for obtaining the scan were followed to minimize differences between the substudy sites. All scanners were Hologic models cross-calibrated with a phantom, and each technician underwent webinar training and quality review of their first scan. DXA scans were centrally analyzed at the University of California San Francisco Department of Radiology and Biomedical Imaging. Sites uploaded actual DXA scan data onto a secure cloud drive, administered by the central readers. The central readers accessed the scan data from the cloud drive and analyzed them using a standard 4 vertebrae region of interest analysis method. Advanced analysis techniques were applied to regional data from standard LS regions. Interscan vertebral fusion replaced data for 1 or more invalid vertebrae with valid data from scans within the same visit.[24] DXA readers were blinded to study treatment assignment.

Infant Renal Health Assessment

Infant serum creatinine, serum calcium, and serum phosphate were measured at entry and postnatal Weeks 10, 26, and 74. Serum creatinine values below the lower limit of quantification (LLQ) were set to missing. The outcome measure for renal health was infant CrCl calculated using the revised Schwartz equation.[25]

Statistical Analysis

The accrual target of 400 mother–infant pairs was based on 80% power to detect 5%–7% between-group differences in LS-BMC.[26] Student *t* tests assuming unequal variances compared mean LS-BMC at Week 26 and calculated CrCl, calcium, and phosphate at Weeks 10, 26, and 74 as well as mean change from entry between arms. All differences are presented as mART minus iNVP. Two-sided *P* values are presented for the primary analyses (LS-BMC at Week 26 and calculated CrCl at Week 26), and there were no adjustments for multiple testing. All analyses were performed using SAS software version 9.4 (Copyright © 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC).

Further supplementary analyses for the primary outcome measures used adjusted linear regression models to increase precision of the estimates. Covariates included entry measurement, sex, gestational age (GA) at birth (<37 weeks or ≥37 weeks), and maternal antepartum ARV exposure at PP entry. Multiple imputation was used as sensitivity analyses for the primary outcome measures. Missing and values below the LLQ were imputed 1000 times for infants who survived through the Week 26 visit using a fully conditional specified model with 30 burn-in iterations that included randomization arm, maternal antepartum ARV exposure at PP entry, country, sex, GA at birth (continuous), entry calculated CrCl, and entry LS-BMC. These models assumed missing at random, and parameter estimates were combined using the Rubin rules.[27] The data cannot be made publicly available because of the ethical restrictions in the study's informed consent documents and in the IMPAACT Network's approved human subjects protection plan; public availability may compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Centre's data access committee by e-mail to sdac.data@fstrf.org or sdac.data@sdac.harvard.edu.

RESULTS

Overall, 400 mother–infant pairs enrolled in the PP Component of the P1084s substudy between August 2011 and October 2012. Two infants born to women in the mART arm were excluded from analyses because their mothers did not immediately initiate a TDF-based ARV regimen. All enrolled infants were singletons (Fig. 1). Approximately half of all infants were male (200/398), and the median (25th, 75th percentile) GA at birth was 39 weeks (38–40) (Table 1). A large majority of infants weighed 2500 g or more at birth (89%), and the median WHO weight-for-age *z*-score was −0.7 (−1.4–0.0). The median infant age at PP randomization was 10 days with a range of 7–12 days. The median entry calculated CrCl was slightly higher in the mART arm (62.0 mL/min/1.73 m^2 [49.8–77.8]) compared with the iNVP arm (57.8 mL/min/1.73 m^2 [48.6–68.8]). At entry, the median LS-BMC was 1.65 g (1.45–1.90) in the mART arm and 1.69 g (1.44–1.89) in the iNVP arm.

Most infants (92%) completed the substudy protocol; 4 infants died, 2 in each arm. The deaths were unrelated to study participation or to HIV infection. Median PROMISE study follow-up duration was similar across arms. The overall median follow-up time was 105 weeks (104–107), and only 5 infants were not on study at the start of the Week 26 window (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C66). Seven infants had a positive HIV test (defined as infected by at least 2 positive HIV-1 nucleic acid tests or probably infected based on an independent committee determination), 3 infants in the mART arm, and 4 in the iNVP arm. The median infant age at the first positive HIV test was 9 months (2–17). Treatment for HIV-infected infants was provided from their respective national programs and they continued in follow-up through scheduled exit.

Breastfeeding practices were similar between the 2 arms. The median time to breastfeeding cessation was 59.9 weeks in the iNVP arm and 60.6 in the mART arm. At the Week 26 visit, 98% and 99% of women had not ceased breastfeeding in the iNVP and mART arms, respectively. By the Week 26 visit, 96% of women in the mART arm were still on a TDF-containing regimen and 1% of women in the iNVP arm were on a TDF-containing regimen.

Bone Mineral Content

Summary statistics of LS-BMC at entry and Week 26 and percent and absolute change in LS BMC from entry to Week 26 are shown in Table 2. At Week 26, the mean (SD) LS-BMC of 2.64 g (0.48) in the mART arm, compared with the mean (SD) LS-BMC of 2.77 g (0.44) in the iNVP arm, was significantly lower: −0.13 g (−0.22 to −0.04), $P = 0.007$. Mean absolute (95% confidence interval [CI]) [−0.14 g (−0.23 to −0.06)] and percent (95% CI) [−10.88% (−18.53 to −3.23)] increase in LS-BMC from entry was smaller for mART than iNVP. Figure 2 shows the distribution of LS-BMC across study visits. Treatment effect estimates did not change substantially after adjusting for baseline covariates (≤8% change from unadjusted treatment effect estimate) and imputing missing values.

Renal Function

At Week 26, the mean (SD) calculated CrCl was 130.0 mL/min/1.73 m^2 (34.9) for the mART arm and 126.1 mL/min/1.73 m^2 (30.0) for the iNVP arm; the mean difference (95% CI) of 3.8 mL/min/1.73 m^2 (−3.0 to 10.7) was not significant ($P = 0.27$). Figure 3 shows the distribution of calculated CrCl. Overall conclusions did not change after adjusting for baseline covariates and imputing missing or values below the LLQ.

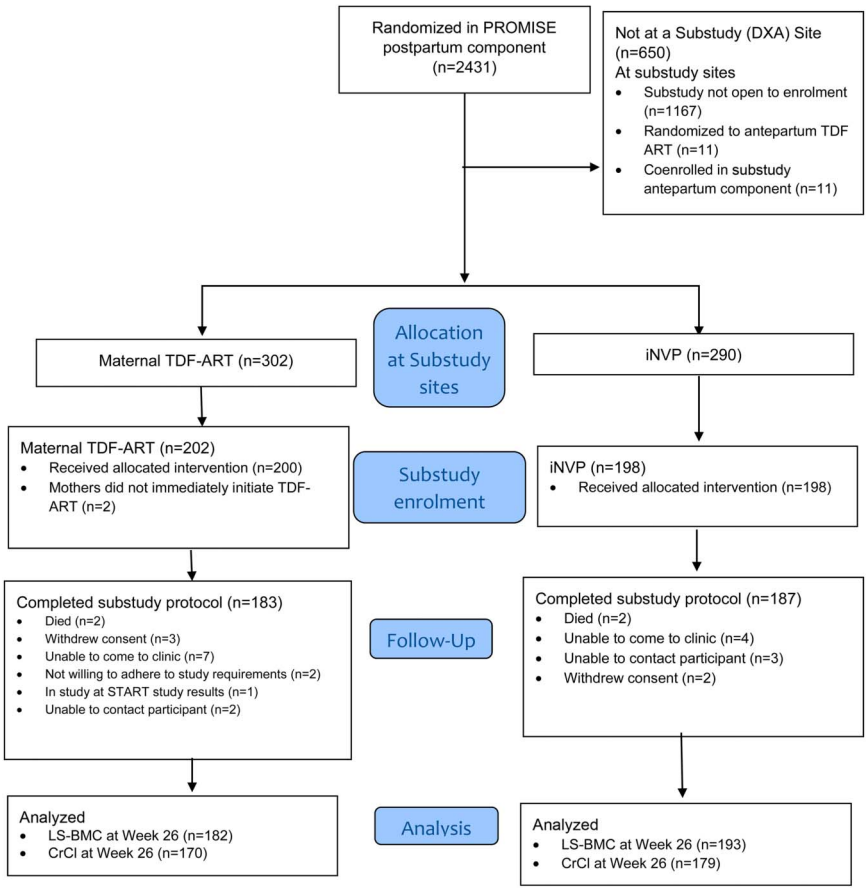

FIGURE 1. CONSORT flow diagram. full color online

TABLE 1. Infant Characteristics at Birth and Entry

Characteristic	Statistic	mART (N = 200)	iNVP (N = 198)	Total (N = 398)
Sex	Male	100 (50)	100 (51)	200 (50)
	Female	100 (50)	98 (49)	198 (50)
Gestational age at birth (wk)	Median (25th–75th)	39.0 (38.0–40.0)	39.0 (38.0–40.0)	39.0 (38.0–40.0)
	<34 wk	1 (1)	1 (1)	2 (1)
	34 to <37 wk	17 (9)	12 (6)	29 (7)
	≥37 wk	182 (91)	185 (93)	367 (92)
Weight at birth (g)	Median (25th–75th)	2900.0 (2600.0–3275.0)	3000.0 (2700.0–3300.0)	2965.0 (2660.0, 3300.0)
	2000 to <2500	23 (11.5)	22 (11)	45 (11)
	≥2500	177 (88.5)	176 (89)	353 (89)
WHO weight-for-age *z*-score (0–10 yrs)	Median (25th–75th)	−0.7 (−1.4 to −0.1)	−0.6 (−1.4 to 0.2)	−0.7 (−1.4 to 0.0)
Length at birth (cm)	Median (25th–75th)	49.0 (47.0–50.0)	48.5 (47.0–50.0)	48.5 (47.0–50.0)
Head circumference at birth (cm)	Median (25th–75th)	34.5 (34.0–35.0)	34.5 (34.0–35.3)	34.5 (34.0–35.0)
Age at entry (d)	Median (25th–75th)	10.0 (9.0–11.0)	10.0 (9.0–11.0)	10.0 (9.0–11.0)
LS-BMC at entry (g)	N	184	180	364
	Median (25th–75th)	1.65 (1.45–1.90)	1.69 (1.44–1.89)	1.67 (1.45–1.90)
Calculated CrCl at entry (mL/min/1.73 m^2)	N	178	179	357
	Median (25th–75th)	62.0 (49.8–77.8)	57.8 (48.6–68.8)	59.0 (49.6–72.7)
Calcium at entry (mg/dL)	N	184	183	367
	Median (25th–75th)	10.20 (9.76–10.68)	10.20 (9.60–10.68)	10.20 (9.70–10.68)
Phosphate at entry (mg/dL)	N	190	187	377
	Median (25th–75th)	6.20 (5.60–6.80)	6.30 (5.60–6.90)	6.20 (5.60–6.87)

25th, 25th percentile; 75th, 75th percentile.
Categorical variables are presented as n (%). Continuous variables are presented as median (25th, 75th percentile).

TABLE 2. Infant LS-BMC at Week 26

Outcome Measure	Statistic	mART (N = 200)	iNVP (N = 198)	Mean Difference (95% CI)
LS-BMC (g)	N	182	193	
	Mean (SD)	2.64 (0.48)	2.77 (0.44)	−0.13 (−0.22 to −0.04)
	P value*			0.007
Absolute change in LS-BMC (g)	N	170	175	
	Mean (SD)	0.96 (0.43)	1.10 (0.41)	−0.14 (−0.23 to −0.06)
Percent change in LS-BMC (%)	N	170	175	
	Mean (SD)	60.76 (34.33)	71.64 (37.87)	−10.88 (−18.53 to −3.23)

*P value based on t test assuming unequal variances.

Summary statistics for the change in calculated CrCl from entry to Week 10, 26, and 74 and the between-arm differences in the mean change in calculated CrCl are presented (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C67). On average, calculated CrCl increased from entry across all visits in both arms.

The mean (SD) calcium level at entry was 10.17 mg/dL (0.85) for the mART arm and 10.11 mg/dL (0.88) for the iNVP arm. At Week 26, the mean (SD) calcium level was 10.27 mg/dL (0.58) for the mART arm and 10.30 mg/dL (0.69) for the iNVP arm. Differences in the mean calcium level and the mean change in calcium were close to zero with narrow CIs that exclude a clinically relevant difference across all study visits. On average, calcium decreased from entry to Week 74 in both arms.

The mean (SD) phosphate level at entry was 6.20 mg/dL (1.65) for the mART arm and 6.21 mg/dL (1.00) for the iNVP arm. At Week 26, the mean (SD) phosphate was 5.89 mg/dL (0.58) in the mART arm, which was higher than in the iNVP arm, 5.73 mg/dL (0.67), with a mean difference (95% CI) of 0.16 mg/dL (0.03, 0.28); the difference (95% CI) in the mean change in phosphate from entry to Week 26 was 0.18 mg/dL (−0.13, 0.48). On average, phosphate decreased from entry to Week 74 in both arms.

DISCUSSION

At Week 26, the mean LS-BMC and the change in LS-BMC from entry were significantly lower among breastfeeding infants randomized to mART compared with infants randomized to receive iNVP. The mean calculated CrCl did not differ between the prevention arms at Week 26 or any time point. In secondary comparisons, the mean change in calculated CrCl from entry to Week 6, Week 26, and Week 74 was similar in both arms. Although mean calcium levels at Week 26 were similar in both arms, phosphate was higher in the m-ART arm compared with the iNVP arm, with a mean difference of 0.16 mg/dL (95% CI: 0.03 to 0.28).

Because there are no established definitions of normal LS-BMC values for infants, this study relied on comparison of LS-BMC by ARV regimen arm to assess potential effect of ARV exposure on infant bone mineralization. This study was powered to detect a 5%–7% difference and/or a difference of 0.5 SD; therefore. a difference in LS-BMC of 0.5–0.75 SD would be of enough concern to potentially influence decision-making about therapy.[26] At Week 26, the overall LS-BMC SD was 0.46. Although the point estimate of the difference in LS-BMC (0.13) is less than 50% of the SD, the upper limit of the CI (0.22) is approximately equal to 50% of the SD. These findings suggest that maternal TDF-containing ART may result in lower infant bone mineralization but the magnitude of that effect is unlikely to be clinically important.

In a review of studies that administered TDF containing ART to pregnant or breastfeeding women, the data consistently demonstrated low total exposure of TDF to the breastfed infant thus supporting the use of TDF containing regimens during breastfeeding.[28] Total exposure to TDF is higher in utero, and hence, there are reports of lower BMC in neonates exposed to TDF in utero compared with placebo[29,30]; however, when TDF is taken late in pregnancy, the effect on BMC may not be present.[31]

As reported previously, the mean calculated infant CrCl, calcium, and phosphate at birth did not differ across the 3 PROMISE antepartum randomization arms.[32] Here, we

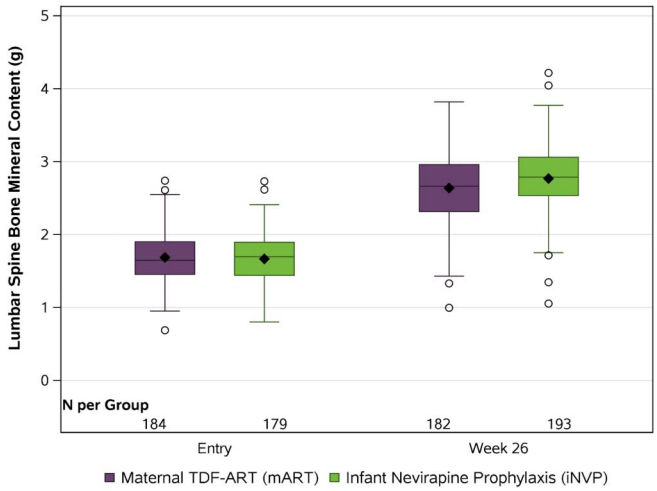

FIGURE 2. Infant entry and week 26 LS-BMC by study arm. Purple boxes represent the mART arm. Green boxes represent the iNVP arm. Box plots represent medians (bar), 25th percentile (lower limit of box), and 75th percentile (upper limit of box). The mean of the arms are shown by a small black diamond. Whiskers are drawn to the maximum (minimum) observation below (above) the upper (lower) fence, which is 1.5× interquartile range (IQR) above (below) the 75th (25th) percentiles. Values outside of the whiskers are represented by circles.

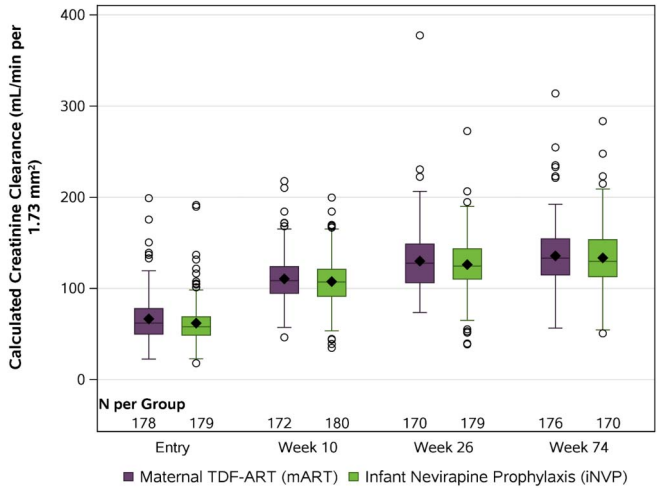

FIGURE 3. Infant entry, week 10, week 26, and week 74 calculated CrCl by study arm. Purple boxes represent the mART arm. Green boxes represent the iNVP arm. Box plots represent medians (bar), 25th percentile (lower limit of box), and 75th percentile (upper limit of box). The mean of the arms are shown by a small black diamond. Whiskers are drawn to the maximum (minimum) observation below (above) the upper (lower) fence, which is 1.5× interquartile range (IQR) above (below) the 75th (25th) percentiles. Values outside of the whiskers are represented by circles.

showed that the mean calculated CrCl and calcium at Week 26 in infants also did not differ between PP randomization arms among infants without in utero TDF exposure. Other studies have similarly reported no renal dysfunction or abnormal bone findings in infants exposed to TDF through breastmilk. In a substudy of a randomized controlled trial of TDF for prevention of vertical transmission of hepatitis B virus, no significant difference was noted in LS-BMC 1 year after birth between infants exposed to maternal TDF during pregnancy and through breastfeeding for 2 months after birth when compared with the placebo arm.[33,34]

Studies have also demonstrated no differences in CrCl between infants with variable exposures to maternal creatinine through breastfeeding and in utero when compared with those who are not exposed.[17,33,35,36]

From this study, there is no evidence that mART or iNVP had higher risk of abnormal (low or high) phosphate; however, mART seemed to lead to a small increase in infant serum phosphate, on average. This could be a spurious finding or may be related to mild demineralization in infant bone[37] leading to slight increases in serum phosphate, and it could also be as a result of alterations in phosphate content of breastmilk.[18]

This report presents data collected from a large sample of infants under clinical trial conditions. Progress in the field of bone densitometry of infants and very young children has been hampered, in part, by technical challenges in measuring small bones of low density and the need for infants to remain completely still during the scan. These shortcomings were overcome by using the expertise of the centralized DXA readers to provide robust estimates of infant BMC,[24] although follow-up was restricted to postnatal Week 26 only. Lack of DXA BMC norms for infants is another major impediment in the field of bone densitometry of infants. Our renal findings are limited in that 5 infants had recorded serum creatinine values of 0 mg/dL due to serum creatinine values below the LLQ. Because the LLQ was unknown, we considered all serum creatinine values below the LLQ to be missing for the primary, secondary, and supplementary analyses in a post hoc decision. Overall, conclusions did not change after imputing multiple values below the LLQ.

The randomized design of IMPAACT PROMISE permitted this analysis to compare the renal and bone toxicity at 26 weeks of life between infants exposed during breastfeeding to a maternal TDF-containing triple ARV regimen vs. unexposed infants. Because TDF-containing regimens are preferred regimens recommended for HIV treatment and prevention in pregnant and breastfeeding mothers, our findings contribute to the pool of data on the safety of breastmilk exposure to this widely used antiretroviral drug.

CONCLUSIONS

TDF-containing regimens continue to be prescribed to women of childbearing age. We observed no renal safety concerns in study infants exposed to TDF through breastmilk. Although the mean LS-BMC at Week 26 was lower in breastfeeding infants with mART compared with iNVP, the difference was less than 1 half of the SD (~0.23 g). Although a difference of this magnitude is unlikely to be clinically relevant, it could reflect an effect of maternal TDF use on infant bone, warranting further evaluation to assess the effect and clinical implication.

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