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Infant Growth Outcomes After Maternal Tenofovir Disoproxil Fumarate Use During Pregnancy

Carla E. RANSOM, MD[1], **Yanling HUO, MS**[2], **Kunjal PATEL, DSc, MPH**[2], **Gwendolyn B. SCOTT, MD**[3], **D. Heather WATTS, MD**[4], **Paige WILLIAMS, PhD**[2], **George K. SIBERRY, MD, MPH**[4], and **Elizabeth G. LIVINGSTON, MD**[5] **for the P1025 Team of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group**

[1]Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, TN

[2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

[3]Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL

[4]Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institutes of Child Health and Human Development National Institutes of Health Bethesda, MD

[5]Department of Obstetrics and Gynecology Duke University Medical School, Durham, NC

Abstract

OBJECTIVE—To determine whether maternal use of tenofovir disoproxil fumarate (TDF) for treatment of HIV in pregnancy predicts fetal and infant growth.

METHODS—The study population included HIV-uninfected liveborn singleton infants of mothers enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group protocol P1025 (born 2002-2011) in the United States and exposed in utero to a combined (triple or more) antiretroviral (ARV) regimen. Infant weight at birth and 6 months was compared between infants exposed and unexposed to tenofovir in utero using two-sample T- and Chi-square tests and multivariable linear and logistic regression models including demographic and maternal characteristics.

RESULTS—Among 2025 infants with measured birth weight, there was no difference between those exposed (N=630, 31%) versus unexposed to tenofovir in mean birth weight (2.75 vs. 2.77 kg, p=0.64), or mean gestational age- and sex-adjusted birth weight z-score (WASZ) (0.14 vs. 0.14, p=0.90). Among 1496 infants followed for 6 months, there was no difference in mean weight at 6 months between tenofovir-exposed (N=457, 31%) and tenofovir-unexposed infants (7.64 vs. 7.59 kg, p= 0.52), or in mean WASZ (0.29 vs. 0.26, p= 0.61). Tenofovir exposure during the 2nd/ 3rd trimester, relative to no exposure, significantly predicted under-weight (WASZ < 5%) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95], p=0.04). Duration of tenofovir exposure did not predict neonatal or infant growth.

Correspondence related to manuscript: Carla Ransom, MD, B-1100 Medical Center North, Nashville, TN 37232-2519, 615-322-0093 (office phone), 615-343-8403 (fax), carla.ransom@vanderbilt.edu.

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CONCLUSIONS—By most measures, in utero exposure to tenofovir did not significantly predict infant birth weight or growth through 6 months of age.

Keywords

tenofovir; mother-to-child transmission; infant growth; TDF; HIV; pregnancy

INTRODUCTION

Routine use of combination antiretroviral drug regimens in pregnancy has resulted in a decline in the rate of maternal to child transmission of HIV from over 20% to less than 1%[12]. Current U.S. guidelines recommend that HIV-infected pregnant women receive a three-drug regimen of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI)[3]. Current World Health Organization (WHO) guidelines are similar, recommending a three drug regimen of two NRTIs and an NNRTI[4]. The preferred NRTIs in pregnancy are zidovudine and lamivudine. Use of tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor and preferred drug in non-pregnant adults[5], has been increasing in pregnancy[6] despite its recommendation as an alternative drug in pregnancy due to concerns about potential adverse effects on the infant.

Human data on perinatal exposure to tenofovir include small case series, retrospective datasets, and prospective data from the Antiretroviral Pregnancy Registry and from the Pediatric HIV/AIDS Cohort Study (PHACS) network. In a small cohort study, Nurutdinova did not find any congenital malformations or growth abnormalities in 14 babies followed to 12 months who were exposed to tenofovir[15]. In a study by Eastwood, TDF exposed pregnancies were associated with efficacious viral suppression and lower risk for cesarean delivery for HIV viremia compared to those not exposed to TDF, with no increased risk for adverse neonatal outcome, including no difference in birth weight, preterm birth, or neonatal morbidity[16]. Among prospective cases reported to the Antiretroviral Pregnancy Registry, there was no overall increase in birth defects among infants exposed to tenofovir (n=1092) in the first trimester compared to later exposure (n=782), and compared to baseline population risk[17, 18]. Pharmacokinetics studies demonstrate about 60% placental transfer of tenofovir[19].

Long-term follow-up data on the effect of tenofovir on neonatal and infant growth are sparse and conflicting. Analysis from the Safety Monitoring for ART Toxicity (SMARTT) study of the Pediatric HIV/AIDS Cohort Study reported that children born to women who had received TDF as part of their HAART regimen during pregnancy were more likely to have lower length-for age and head-circumference-for-age z-scores at 1 year[6], despite no observed difference in growth measurements at birth. A single case report suggested fetal growth restriction with exposure[20]. This is in contrast to the Development of AntiRetroviral Therapy in Africa (DART) trial, which in a subgroup analysis showed no effect of intrauterine tenofovir exposure on growth outcomes at birth through infancy[21]. Overall, the literature is limited in scope on neonatal and infant growth outcomes after tenofovir exposure in utero. In short, the question on whether maternal use of TDF in pregnancy has adverse effects on infant growth remains unsolved. After initial reports from the SMARTT study suggested impaired infant growth (not confirmed in the final analysis)[6], we began our study on a similar population. We hypothesized that maternal use of TDF during pregnancy would predict impaired growth during infancy. Our primary objective was to evaluate the impact of in utero tenofovir exposures on growth during infancy by determining if tenofovir exposure during pregnancy is an independent predictor of birth weight and infant weight at 6 months of age, representing a delayed effect on infant growth. This is an important question

to examine: with the increasing use of TDF in pregnancy despite limited safety data in the literature, large studies like ours are desperately needed to either confirm the safety profile in pregnancy or illuminate safety concerns which may temper its use.

METHODS

Study population

The study population included women enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) protocol 1025, a prospective observational cohort study designed to assess the use and safety of antiretrovirals in HIV infected pregnant women and their infants. Approximately 37% of P1025 participants overall and 45% of TDF-exposed infants were also co-enrolled in the SMARTT study[6]. Beginning in October 2002, HIV-infected pregnant women were enrolled if they were at least 13 years old and between 14 weeks' gestation and 14 days postpartum. Since December 2007, enrollment was allowed as early as 8 weeks' gestation. Institutional review boards approved the protocol at all 56 clinical sites located in the US and Puerto Rico, and written informed consent was obtained from those enrolled. The population eligible for this study consisted of all liveborn singleton infants with an estimated date of confinement on or before September 15, 2011. Infants found to be HIV-infected were excluded. For this analysis, only the first eligible pregnancy with a livebirth > 23 weeks gestation was included for women enrolled for more than one pregnancy. This was done to avoid the need to account for correlation between multiple infants born to the same mother and simplify the analysis and interpretation of data. Only infants whose mothers used a combination ARV regimen (triple ARV regimen or greater) during pregnancy were included. Birth weight and infant weight at 6 months (+/− 1 month) were utilized for this analysis.

ARV classification and covariates

Sociodemographic characteristics, obstetrical history, substance use information, maternal antiretroviral use, and laboratory testing results were collected through medical chart abstraction or self-administered questionnaires. Potential covariates of interest included maternal viral load, CD4+ lymphocyte count, and CDC class at delivery, pre-gestational and gestational diabetes and hypertension, smoking during pregnancy, body mass index (BMI) closest to delivery, age, race, ethnicity, education, and year of delivery.

Outcomes of interest

Infant birth weight was defined in four different ways: absolute weight (continuous); gestational age- and sex-adjusted weight z-score (continuous); gestational age- and sex-adjusted weight z-score less than 5^{th} percentile (< −1.645), and small for gestational age (SGA: gestational age- and sex-adjusted weight z-score < 10^{th} percentile). The Olsen growth curves[22] were used to calculate the z-score for all the infants (preterm and term) per completed gestational age and sex. Due to the absence of growth curves at 42 weeks of gestation, the CDC standards for the full term infants were used for the infants born at 42 weeks.

Infant weight at 6 months of age was defined in three different ways: absolute weight (continuous); age- and sex-adjusted weight z-score (continuous); and age- and sex-adjusted weight z-score less than 5^{th} percentile (< −1.645), chosen because we felt this would be a clinically significant measure of weight at 6 months. The CDC growth charts were employed to calculate the z-score for term infants at their exact age at measurement (gestational age ≥ 37 weeks)[23]. For preterm infants (gestational age < 37 weeks), the exact age at the weight measurement was adjusted by subtracting the difference between 40 weeks and the gestational age at birth. The CDC growth standards were then applied to calculate

the z-score based on the adjusted age. For weight at both birth and 6-months of age, several outcome definitions were chosen in an attempt to detect any signal that maternal TDF use in pregnancy would have toxic effects on infant growth.

Exposure

Maternal TDF use during pregnancy was defined in three ways: any TDF use during pregnancy; duration of TDF use during pregnancy (no use vs. < 4 weeks vs. 4-12 weeks vs. > 12 weeks of use); and the earliest trimester in which TDF was used during pregnancy (no use vs. 1st trimester vs. 2nd trimester vs. 3rd trimester). The categories for TDF duration were chosen a priori based on clinical experience on what constituted short, medium, and prolonged exposure to TDF.

Statistical analysis

Multivariable regression models were built to evaluate whether maternal TDF use predicted infant weight measurements (general linear model for continuous weight outcomes and logistic regression model for binary weight outcomes), independent of potential covariates. The potential covariates were identified separately for each outcome from bivariable analyses with a p-value < 0.10. For each weight outcome, a separate regression model was fit including each of the three TDF exposures and the same set of potential covariates. Other covariates included in any of the multivariable regression models: Birth Weight: race, ethnicity, mode of delivery, parity, last CD4 count during pregnancy, last RNA during pregnancy, last CDC classification during pregnancy, maternal obesity, pre-gestational diabetes, gestational diabetes, chronic hypertension, use of antihypertensive medication during pregnancy, use of diabetes medication during pregnancy, preeclampsia, smoking during pregnancy; Weight at 6-months of age: race, ethnicity, education, mode of delivery, preeclampsia. SAS Version 9.2 (SAS Institute Inc, Cary, NC) was used to conduct all statistical analyses, and two-sided p-values <0.05 were considered statistically significant.

RESULTS

STUDY POPULATION

As of October 1, 2011, 2477 live-born infants with estimated date of confinement at or before September 15, 2011 enrolled in the P1025 study. After excluding infants who were HIV-infected (n=14), had HIV tests that were pending (n=10), were born at or before 23 weeks' gestation (n=1), or not from a singleton birth (n=44 sets of twins; n=2 sets of triplets), the remaining 2358 infants were further reduced to only include the infants from their mothers' first enrollments on study for a total of 2161 eligible infants in this analysis. Of the 2145 infants for whom maternal TDF use data were available, 2099 were exposed to a combined ARV regimen during pregnancy. The analyses were performed on the 2025 infants with birth weight available and 1496 infants with weight at 6 months of age available. (Figure 1).

DEMOGRAPHICS, GROWTH AND TDF EXPOSURE

Of 2025 infants with birth weight data available, 630 (31%) were exposed to tenofovir (Table 1). The median duration of TDF exposure among those exposed was 22.9 weeks. Compared to women unexposed to TDF, women exposed to TDF in pregnancy were more likely to be on a cARV regimen containing a PI (91% vs. 79%, p<0.001), more often had CDC classification C (18% vs. 8%, p<0.001), lower last CD4+ counts (CD4 < 200 copies/mm^3: 15% vs. 8%, p<0.001) and higher last RNA (RNA>400 copies/ml: 19% vs. 15%, p=0.03) prior to delivery, and were older (age at delivery ≥ 35 years: 21% vs. 15%, p<0.001), but were otherwise similar. For infants exposed to tenofovir, 66% were exposed in

the first trimester and 74% were exposed for at least 12 weeks duration (Table 2). Of the 98 and 225 infants with gestational age and sex adjusted birth weight z-scores <5th percentile and <10th percentile respectively, approximately 30% were exposed to TDF in utero (Table 2). Other characteristics of the study population are provided in Table 1.

The adjusted associations of maternal TDF use with birth weight are presented in Table 3 (weight in kg and z-scores) and in Table 4 (low birth weight). No significant associations were observed between TDF exposures (any TDF exposure, trimester of the 1st reported TDF use, and duration of TDF exposure) and the weight outcomes of interest. As expected, women who had a higher last CD4 count during pregnancy (CD4 < 200 vs. ≥ 350 cells/mm^3), women defined as obese (BMI>40) during pregnancy, those who had at least one previous birth with greater than 20 weeks gestation, and those who had a pre-gestational or gestational diabetes diagnosis, were more likely to deliver a heavier baby as measured by one or more of the weight outcomes of interest compared to women who did not have these characteristics. In contrast, black women, women who used antihypertensive medications during pregnancy, women who had a pre-eclampsia diagnosis and those who smoked cigarettes during pregnancy were more likely to deliver a baby with lower weight as measured by one or more of the weight outcomes of interest compared to women who did not have these characteristics.

Of 1496 infants with weight data available at 6 months of age, 457 (31%) were exposed to tenofovir (Table 2). The median duration of TDF exposure among those exposed was 21.3 weeks. For infants exposed to TDF in this group, 66% were exposed in the first trimester and 72% were exposed for >12 weeks duration. Of the 61 infants with age and sex adjusted 6 month weight z-scores <5th percentile, 38% were exposed to TDF in utero. The group of women with infants followed for 6 months was not different than the entire group with infant birth weight available with respect to measured demographic and clinical information.

The multivariable associations of TDF exposures with weight at 6 months are presented in Table 3 and Table 4. In comparison to mothers with no TDF exposure, maternal initiation of TDF during the 2nd/3rd trimester was predictive of low infant weight at 6-months of age based on age- and sex-adjusted weight z-score < 5th percentile. No other significant associations were observed between TDF exposures (any TDF exposure, trimester of the 1st reported TDF use, and duration of TDF exposure) and other weight measures (absolute weight, age- and sex-adjusted weight Z-score). Women who completed at least a high school education were more likely to have a heavier baby in terms of absolute weight and age- and sex-adjusted weight z-score at 6-months of age; babies whose mother had a pre-eclampsia diagnosis were more likely to have a lower mean absolute weight at 6-months of age than those whose mother didn't have a pre-eclampsia diagnosis. Hispanic women were less likely to have a baby with age- and sex-adjusted weight z-score below the 5th percentile at 6-months of age, compared to Non-Hispanic women.

PRETERM BIRTH

No significant associations were observed between the TDF exposures and the preterm birth outcome. Of the 2099 infants exposed in utero to a combined ARV regimen, there were no differences in preterm birth among infants whose mothers were exposed to a TDF regimen compared to those who weren't (117 (18%) versus 232 (16%), p=0.26). Non-obese women, women on anti-hypertensive therapy during pregnancy, women with preeclampsia, and women with a last reported CD4+ lymphocyte count <200 cells/mm^3 during pregnancy were more like to deliver a baby prematurely.

DISCUSSION

With the increasing use of TDF by HIV-infected pregnant women, studies examining the safety profile of this drug in exposed neonates are crucial. In this large cohort of infants born to HIV-infected women receiving combination ARV regimens during pregnancy, in utero exposure to tenofovir does not appear to be associated with either infant birth weight or infant growth through six months of age. While there was a marginal association with being underweight at 6 months of age in women who initiated TDF in the second or third trimester, there was no association between duration of maternal TDF use and 6-month weight outcomes. In addition, no association was found with absolute weight or overall age and sex adjusted z-score. As expected, women who were obese, diabetic, parous and without hypertensive diseases of pregnancy tended to have larger babies, both at birth and at 6 months of age.

While we feel it may not be clinically significant, the isolated finding of lower age and sex adjusted weight z-score of $<5^{th}$ % at 6 months of age in infants of women who initiated TDF in the second or third trimester should not be completely overlooked. There are several studies in humans that suggest a delay in effect from ARV exposure not occurring until several months to years after exposure. For instance, febrile seizures were significantly more common in ARV-exposed compared to ARV-unexposed HIV-exposed infants; this effect did not appear until 6-12 months of age[24]. In the Women and Infants Transmission Study (WITS), the significant difference in CD8+ cell counts by ARV exposure did not appear until 6-24 months[25]. In the Surveillance Monitoring for ART Toxicities (SMARTT) trial, data at 1 year but not at birth demonstrated lower mean length-for-age and head-circumference-for-age z-scores associated with maternal TDF use[6]. More encouraging are results from the Development of AntiRetroviral Therapy in Africa (DART) trial[21], which recently reported no evidence that TDF effects growth of infants up to 2 years of age, in a cohort of 226 live births. The clinical relevance and underlying biologic mechanisms of this finding in our study are uncertain. Long term studies are needed to determine whether this short term effect on growth has any long lasting impact in childhood or adult life.

Our study has several strengths. We had a large sample size, with large (31%) proportion of infants having tenofovir exposure. In addition, we were able to examine growth in several different ways (absolute weight, underweight, and small for gestational age). We were also able to examine tenofovir exposure by several different measures, to determine if exposure in the first trimester had an effect or if cumulative dose of tenofovir had an effect. Neither appears to have affected fetal or infant growth.

There are, however, some limitations to our study. Tenofovir is eliminated by the kidneys. Renal toxicity with Fanconi syndrome and nephrogenic diabetes insipidus has been reported in children[7] and adults [8, 9, 10, 11] exposed to TDF. There have also been reports of bone toxicity in infant rhesus macaques[12, 13]. Due to the rarity of these outcomes in infants and reporting bias, our study was unable to examine the effects of tenofovir exposure on either the kidneys or bones. It is reassuring that long-term safety data in rhesus macaques shows the renal toxicity to be dose related, with no increased risk of congenital anomalies and good long-term safety data for the offspring[14]. However, examining the renal effects of tenofovir exposure in utero is an unmet research need.

Like any cohort study, there is potential for selection bias in the non-random allocation of women to TDF as part of their multi-agent HAART. In addition, more women exposed to TDF were on a PI containing HAART regimen than those not exposed to TDF, which may lead to confounding in results. Approximately 26% of the infants with birth weight available do not have available 6 month weight values to study. In addition, we were not able to

examine growth beyond 6 months. Another limitation is that we only examined growth as a function of weight and not length or head circumference. We recognize this is an important limitation, especially in light of findings from the SMARTT study demonstrating adverse effects on length-for age and head-circumference-for-age z-scores at 1 year[6], despite no observed difference in growth measurements at birth. We also do not have data on maternal adherence to drug therapy, and thus true fetal exposure. Current guidelines from the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission assign TDF as an alternate agent (not first line) for the treatment of acute HIV infection in pregnant women while it is considered first line treatment in other groups. The need for long-term data on TDF is vital given the rising use in a pregnant population. Long-term growth and developmental outcomes are still needed in children exposed to tenofovir in future large cohorts. There are many challenges to obtaining long-term safety data on drugs used to treat HIV in pregnancy. This population has many socioeconomic and cultural barriers to seeking and maintaining care, there is difficulty in monitoring drug adherence, and this group is often exposed to multiple drug regimens. While we acknowledge that 45% of TDF-exposed infants were also co-enrolled in the SMARTT study[6], we feel our study still significantly contributes to the literature on this population given the sparse literature on the topic, the challenges to obtaining this information, and the growing use of TDF in clinical obstetric practice. The results of our study present an overall reassuring picture for both fetal growth as well as neonatal growth as reflected by weight in neonates exposed to TDF in pregnancy. Future studies should be designed to focus on rare neonatal outcomes (fracture, neutropenia, etc.) as well as long-term delayed effects on infant growth.

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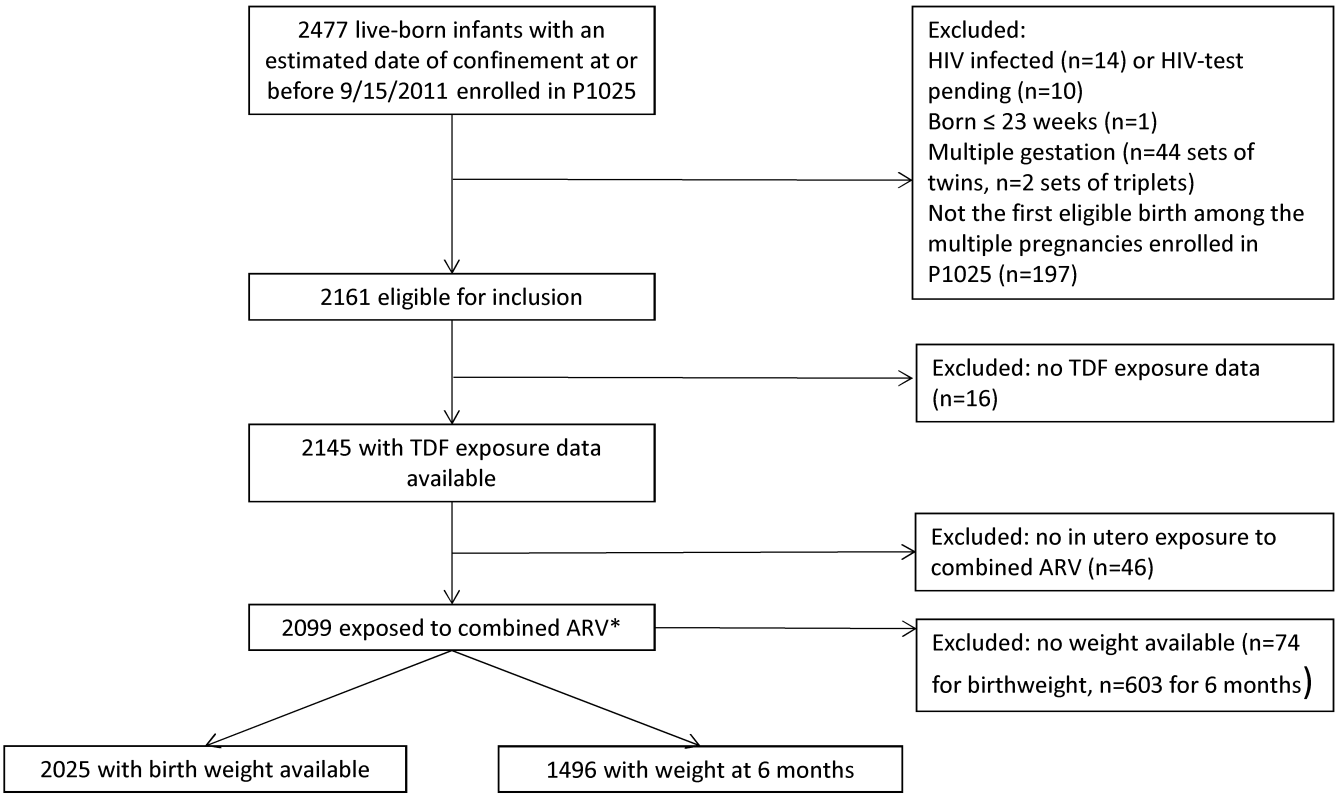

*Combination ARV defined as at least 3 drugs

Figure 1.
Flow diagram

Table 1

Distribution of Baseline Maternal Characteristics by TDF Exposure, Among Infants who Had Weight Measurement at Birth and Exposed to Combined ARV Regimen in Utero (N=2025) *

Characteristics	Total (N=2025)	TDF Exposure		P-value
		Unexposed (N=1395)	Exposed (N=630)	
Black race	1,224 (65%)	850 (65%)	374 (63%)	0.36
Hispanic	623 (31%)	446 (32%)	177 (28%)	0.08
Highest education level completed < High School	767 (38%)	531 (38%)	236 (38%)	0.80
Had at least one prior birth (>20 weeks)	1,406 (69°%)	975 (70%)	431 (69%)	0.54
Mode of delivery: Cesarean	1,065 (53%)	726 (52%)	339 (54%)	0.45
Maternal obesity (BMI > 40)	230 (15%)	166 (15%)	64 (13%)	0.23
ARV regimen				
Pl-containing	1,676 (83%)	1,102 (79%)	574 (91%)	< 0.001
NNRTI-containing (No PI)	145 (7%)	115 (8%)	30 (5%)	
NRTI only	204 (10%)	178 (13%)	26 (4%)	
Last maternal CDC classification during pregnancy:				
Category C	216 (11%)	104 (8%)	112 (18%)	<0.001
Last maternal CD4 (cells/mm^3) during pregnancy				<0.001
≥ 350	1,406 (71%)	1,019 (75%)	387 (62%)	
200 – 349	375 (19%)	236 (17%)	139 (22%)	
< 200	206 (10%)	112 (8%)	94 (15%)	
Last maternal RNA during pregnancy > 400 (copies/mL)	326 (16%)	208 (15%)	118 (19%)	0.03
Maternal age at delivery ≥ 35 years	334 (16%)	204 (15%)	130 (21%)	<0.001
Pre-Gestational diabetes	33 (2%)	25 (2%)	8 (1%)	0.39
Gestational diabetes	91 (4%)	58 (4%)	33 (5%)	0.28
Any diabetes medication use during pregnancy	49 (2%)	36 (3%)	13 (2%)	0.48
Chronic hypertension	130 (6%)	90 (6%)	40 (6%)	0.93
Gestational hypertension	46 (2%)	35 (3%)	11 (2%)	0.29
Any antihypertensive medication use during pregnancy	64 (3%)	46 (3%)	18 (3%)	0.60
Pre-eclampsia	94 (5%)	62 (4%)	32 (5%)	0.53
Ever smoked cigarettes during pregnancy	310 (22°%)	218 (23%)	92 (21%)	0.49

Subjects with missing data were excluded from the calculations: TDF Exposed: race (39), ethnicity (4), education (1), parity (1), mode of delivery (1), obesity (137), CDC classification (11), last CD4 during pregnancy (10), last RNA during pregnancy (8), smoked cigarettes during pregnancy (191); TDF Unexposed: race (96), ethnicity (8), education (2), mode of delivery (1), obesity (309), CDC classification (16), last CD4 during pregnancy (28), last RNA during pregnancy (24), smoked cigarettes during pregnancy (431).

*The distributions of the baseline maternal characteristics among the 1496 infants who had 6-month weight measurements were similar.

Table 2

Distribution of Maternal TDF Use in Pregnancy among the Infant Study Population by Weight at Birth (N=2025) and 6-months of Age (N=1496)

Characteristics	Birth weight			Weight at 6 months of age	
	Total (N=2025)	Age and sex adjusted z-score <5% (N=98)	Age and sex adjusted z-score <10% (N=225)	Total (N=1496)	Age and sex adjusted z-score <5% (N=61)
TDF use during pregnancy					
Unexposed	1,395 (69%)	69 (70%)	153 (68%)	1,039 (69%)	37 (61%)
Exposed	630 (31%)	29 (30%)	72 (32%)	457 (31%)	24 (39%)
Trimester of 1st reported TDF exposure					
1st Trimester	418 (21%)	20 (20%)	45 (20%)	302 (20%)	12 (20%)
2nd or 3rd Trimester	212 (10%)	9 (9%)	27 (12%)	155 (10%)	12 (20%)
Unexposed	1,395 (69%)	69 (70%)	153 (68%)	1,039 (69%)	37 (61%)
Duration of TDF exposure during pregnancy					
< 4 weeks	40 (2%)	2 (2%)	4 (2%)	28 (2%)	2 (3%)
4 - 12 weeks	124 (6%)	5 (5%)	11 (5%)	101 (7%)	6 (10%)
>12 weeks	466 (23%)	22 (22%)	57 (25%)	328 (22%)	16 (26%)
Unexposed	1,395 (69%)	69 (70%)	153 (68%)	1,039 (69%)	37 (61%)

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Table 3

Adjusted Mean Weight and Weight Z-score by Maternal TDF Use during Pregnancy, among Infants Exposed in Utero to a Combined ARV Regimen

	Birth Weight (n = 2025)				Weight at 6-months of Age (n = 1496)			
	Weight (kg)		Gestational age- and sex-adjusted Z-score		Weight (kg)		Age- and sex- adjusted Z-score	
TDF Exposure	**Mean (SE)**	**P-value***	**Mean (SE)**	**P-value***	**Mean (SE)**	**P-value***	**Mean (SE)**	**P-value***
Any TDF exposure								
Unexposed **	2.77 (0.06)	Ref	0.14 (0.11)	Ref	7.59 (0.08)	Ref	0.26 (0.05)	Ref
Exposed	2.75 (0.06)	0.64	0.14 (0.11)	0.90	7.64 (0.09)	0.52	0.29 (0.07)	0.61
Trimester of 1st reported exposure								
1st trimester	2.75 (0.06)	0.53	0.15 (0.12)	0.90	7.67 (0.10)	0.31	0.34 (0.08)	0.29
2nd/3rd trimester	2.77 (0.07)	0.97	0.11 (0.13)	0.66	7.57 (0.12)	0.80	0.19 (0.10)	0.55
Duration of exposure								
< 4 weeks	2.75 (0.11)	0.84	0.14 (0.19)	0.97	7.64 (0.24)	0.83	0.17 (0.23)	0.71
4 – 12 weeks	2.79 (0.08)	0.66	0.24 (0.14)	0.32	7.64 (0.14)	0.72	0.31 (0.13)	0.66
> 12 weeks	2.74 (0.06)	0.48	0.11 (0.12)	0.57	7.64 (0.09)	0.58	0.30 (0.08)	0.62

Other covariates included in any of the multivariate regression models: Birth Weight: race, ethnicity, mode of delivery, parity, last CD4 count during pregnancy, last RNA during pregnancy, last CDC classification during pregnancy, maternal obesity, pre-gestational diabetes, gestational diabetes, chronic hypertension use of antihypertensive medication during pregnancy, use of diabetes medication during pregnancy, preeclampsia, smoke during pregnancy; Weight at 6-months of Age: race, ethnicity, education, mode of delivery, preeclampsia.

*P-values from multivariate regression model comparing the adjusted means.

**Reference group for the comparisons of adjusted means between TDF exposures.

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Table 4

Adjusted Odds Ratio (OR) for Under-weight Outcomes by TDF Exposure during Pregnancy, among Infants Exposed in Utero to a Combined ARV Regimen

	Birth Weight (n = 2025)				6-month Weight (n = 1496)	
	Gestational age- and sex-adjusted Z-score < 5th percentile		Gestational age- and sex-adjusted Z-score < 10th percentile		Age- and sex- adjusted Z-score < 5th percentile	
TDF Exposure	**OR (95% CI)**	**P-value***	**OR (95% CI)**	**P-value***	**OR (95% CI)**	**P-value***
Any TDF exposure						
		0.65			1.40	
Exposed	0.89 (0.52, 1.48)	0.65	1.09 (0.77,1.52)	0.64	(0.81,2.36)	0.22
Trimester of 1st reported exposure						
		0.73		0.97		0.92
1st trimester	0.90 (0.49, 1.59)		1.01 (0.67,1.49)		1.04 (0.50,1.99)	
		0.71		0.38		0.04
2nd/3rd trimester	0.85 (0.34, 1.86)		1.26 (0.74,2.07)		2.06 (1.01,3.95)	
Duration of exposure						
		0.95		0.80		0.28
< 4 weeks	1.06 (0.16, 3.90)		1.15 (0.33,3.10)		2.27 (0.36,8.10)	
		0.99		0.53		0.51
4 – 12 weeks	1.00 (0.33, 2.44)		0.79 (0.34,1.59)		1.38 (0.47,3.30)	
		0.57		0.44		0.34
> 12 weeks	0.84 (0.46, 1.48)		1.16 (0.79,1.66)		1.34 (0.71,2.40)	

Other covariates included in any of the multivariate regression models: Birth Weight: race, ethnicity, parity, last CD4 count during pregnancy, maternal obesity, gestational diabetes, preeclampsia, smoke during pregnancy; Weight at 6-months of Age: ethnicity

*P-values from multivariate regression model for adjusted odds ratios. TDF-unexposed was the reference group for all comparisons.