Published in final edited form as:
AIDS. 2012 June 1; 26(9): 1151–1159. doi:10.1097/QAD.0b013e328352d135.

Safety of Tenofovir Use During Pregnancy: Early Growth Outcomes in HIV-Exposed Uninfected Infants

George K. SIBERRY, MD, MPH[1], **Paige L. WILLIAMS, PhD**[2], **Hermann MENDEZ, MD**[3], **George R. SEAGE III, DSc, MPH**[4], **Denise L. JACOBSON, PhD, MPH**[5], **Rohan HAZRA, MD**[1], **Kenneth C. RICH, MD**[6], **Raymond GRINER, MPH**[5], **Katherine TASSIOPOULOS, DSc, MPH**[4], **Deborah KACANEK, ScD**[5], **Lynne M. MOFENSON, MD**[1], **Tracie MILLER, MD**[6], **Linda A. DiMEGLIO, MD, MPH**[7], and **D. Heather WATTS, MD**[1] **for the Pediatric HIV/AIDS Cohort Study (PHACS)**

[1]Pediatric Adolescent Maternal AIDS Branch, *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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

[3]Department of Pediatrics, State University of New York Downstate, Brooklyn, NY

[4]Department of Epidemiology, Harvard School of Public Health, Boston, MA

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

[6]Division of Pediatric Clinical Research, Department of Pediatrics, Miller School of Medicine at the University of Miami, Miami, FL

[7]Section of Pediatric Endocrinology and Diabetology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

Abstract

Objective—To evaluate the association of tenofovir disoproxil fumarate (TDF) use during pregnancy with early growth parameters in HIV-exposed, uninfected (HEU) infants.

Design—US-based prospective cohort study of HEU children to examine potential adverse effects of prenatal TDF exposure.

Methods—We evaluated the association of maternal TDF use during pregnancy with small for gestational age (SGA); low birth weight (LBW, <2.5kg); weight-for-age z-scores (WAZ), length-forage z-scores (LAZ) and head circumference-for-age (HCAZ) z-scores at newborn visit; and LAZ, HCAZ, and WAZ at age one year. Logistic regression models for LBW and SGA were fit, adjusting for maternal and sociodemographic factors. Adjusted linear regression models were used to evaluate LAZ, WAZ and HCAZ by TDF exposure.

Results—Of 2029 enrolled children with maternal antiretroviral information, TDF was used by 449 (21%) HIV-infected mothers, increasing from 14% in 2003 to 43% in 2010. There was no

Author contributions: GKS and PW are the primary authors who conceived and designed the study. All authors are directly involved in the design and conduct of the PHACS protocol. PW was primarily responsible for conducting analyses of the data. GKS and PW led the writing of the manuscript. All authors collectively contributed to interpreting results and drafting and editing of the article.

All authors declare no conflict of interest.

These data were presented at the XVIII International AIDS Conference, Vienna, 2010.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institutes of Health or the Department of Health and Human Services.

difference between those exposed to combination regimens with versus without TDF for SGA, LBW, and newborn LAZ and HCAZ. However, at age one year, infants exposed to combination regimens with TDF had significantly lower adjusted mean LAZ and HCAZ than those without TDF (LAZ: −0.17 vs. −0.03, p=0.04; HCAZ: 0.17 vs. 0.42, p=0.02).

Conclusions—TDF use during pregnancy was not associated with increased risk for LBW or SGA. The slightly lower mean LAZ and HCAZ observed at age one year in TDF-exposed infants are of uncertain significance but underscore the need for additional studies of growth outcomes after TDF use during pregnancy.

Keywords

Tenofovir disoproxil fumarate; perinatal HIV exposure; infant growth; antiretroviral drugs; pregnancy

INTRODUCTION

Tenofovir disoproxil fumarate (TDF), in combination with other antiretroviral (ARV) drugs, is recommended as first-line therapy for HIV-infected adults because of its proven safety and efficacy[1]. The recommendation for TDF use in pregnant women for treatment of maternal HIV infections and for prevention of maternal-infant HIV transmission, however, has been limited by concerns about potential detrimental effects of maternal TDF use on fetal growth and bone mineralization[2].

In studies of pregnant Rhesus macaques, administration of tenofovir at high doses beginning in the first trimester resulted in lower crown-rump length, lower body weight and smaller adrenal glands but no difference in head, arm, or chest circumferences or extremity bone lengths, compared to tenofovir-unexposed control monkeys[3]. Tenofovir-exposed macaque fetuses also exhibited lower circulating insulin-like growth factor-1 (IGF-1) levels and did not demonstrate the normal rise in IGF-1 that occurs during the 2^{nd} and 3^{rd} trimesters[3]. Similarly, high dose tenofovir administration to infant macaques was associated with infant growth restriction[4]. With administration of lower tenofovir doses to macaques during pregnancy or after birth, however, growth restriction was not observed, suggesting that effects may be dose-dependent[4,5].

Human fetal TDF exposure data are generally limited to TDF initiated around the onset of labor[6]. Efficient transplacental transfer of tenofovir to human fetuses has been demonstrated [7]. In a chart review study, only one of 14 liveborn infants whose mothers used TDF during pregnancy was small for gestational age (SGA)[8]. There are no other published studies of infant growth outcomes after prolonged TDF use during pregnancy.

The purpose of this investigation was to evaluate the association of TDF exposure *in utero* with infant size at birth and infant growth at age one year.

METHODS

Study Population and Procedures

We conducted an analysis of *in utero* TDF exposure in combination with other ARVs based on data collected in the Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network. The SMARTT study enrolled two cohorts: the Static Cohort enrolled children aged 1–12 years who were previously enrolled in other prospective cohort studies or who otherwise had detailed information available on maternal ARV exposure by trimester; the Dynamic Cohort enrolled newborns and their mothers between 22 weeks gestation and 1 week after birth. The

SMARTT protocol was approved by Human Subject Research review boards at each of the participating sites and by the Harvard School of Public Health. Written informed consent was obtained from the parent or legal guardian.

Birth weight and gestational age (GA) were collected retrospectively in the Static Cohort; weight, length and head circumference (HC) were obtained at age one year only in Static Cohort subjects who enrolled in SMARTT by age one year. Birth weight, GA, current weight, length, and HC were obtained at the newborn exam (within 2 weeks after birth) and at each annual visit for Dynamic Cohort infants. Weight, length, and HC measurements followed standardized protocols, with each measurement performed three times at each visit. Maternal ARV drug use, maternal health status (HIV viral load, CD4 count and CD4%) early during pregnancy and prior to delivery, maternal genital infections and complications during pregnancy were obtained by chart abstraction, and alcohol, marijuana, and other illicit drugs use by self-report [9], both overall and by trimester. All subjects with reported birth weight and maternal ARV exposure information as of January 1, 2011 were included in the current analysis.

Statistical Methods

The Centers for Disease Control and Prevention (CDC) 2000 growth standards were used to calculate age- and sex-adjusted z-scores for birth weight and for weight (WAZ), length (LAZ), and HC (HCAZ) for full-term infants at the newborn visit and at age one year[10]. For premature infants, standards developed by Fenton and Suave [11] were used to correct for completed weeks of GAin calculation of z-scores. For infants born <37 weeks GA, Z-scores at age one year were corrected by subtracting weeks of prematurity (40 – birth GA) from the exact age at the 1-year visit. Infants with birth weight below the 10^{th} percentile for GA were considered SGA [12].

Associations of *in utero* TDF exposure with binary outcomes including low birth weight (LBW, <2.5kg) and SGA at birth were evaluated using logistic regression models to obtain unadjusted odds ratios (OR) and OR adjusted for potential confounders (aOR). We used multiple linear regression models to evaluate associations of *in utero* TDF exposure with birth WAZ and with WAZ, LAZ and HCAZ at the newborn visit and at the one-year study visit (including measurements from children aged 9–18 months) as continuous measures, adjusted for potential confounders. (While the one-year study visit window was 9–18 months of age, calculation of z-scores was based on the actual age at the time of that visit.) We also evaluated low birth length and HC based on z-scores <-1.50 ($< 6.7^{th}$ percentile) and based on newborn visit WAZ, LAZ and HCAZ <-1.88 ($< 3^{rd}$ percentile). Similarly, we considered binary outcomes of impaired infant growth at the age 1-year study visit based on WAZ, LAZ and HCAZ < -1.5 and < -1.88. We included small size outcomes defined as z-score < -1.5 in addition to the more standard definition of small size as z-score < -1.88 in order to have sufficient participants in the “small” category to be able to assess potential associations of several factors with small size outcomes.

We considered TDF exposure at any time during pregnancy and by TDF duration in months during pregnancy. To reduce potential for selection bias, we restricted our primary models to consider only those exposed *in utero* to combination ARV regimens (cARV) (>3 drugs from >2 drug classes) and compared those exposed to cARV including TDF to those exposed to cARV without TDF. Initial models did not include GA due to the possibility of this covariate being on the causal pathway between exposure and birth or growth outcomes. However, sensitivity analyses were conducted to adjust for GA, based on the well-established association of GA with these birth and growth outcomes.

Potential confounders we considered included sociodemographic factors (sex, race and ethnicity of infant; household income; caregiver education level; marital status), maternal health status during pregnancy (viral load and CD4 measurements and maternal genital infection), and maternal substance use (including smoking) during pregnancy. Univariate models for each potential confounder were first fit for each outcome. Multivariate models were then fit including TDF exposure and all covariates with $p<0.20$ in univariate models and then reduced to a core model for each outcome including the TDF variable and only those covariates with $p <0.10$ or which changed effect estimates for TDF by at least 10%.

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

Characteristics of study population

Of 2279 subjects enrolled in SMARTT (1240 in the Static Cohort and 1039 in the Dynamic Cohort), 2029 (89%) had detailed maternal ARV exposure information available, including exposure by trimester. Among these, 2006 had birth weight reported and 1980 had both birth weight and GA data allowing identification of SGA. For the Dynamic cohort, 812 had information on length and 800 on HC at birth or within 1 month after birth. Growth outcomes at age one year, limited to those who reached age one year by data freeze date, were available on 677 subjects with maternal ARV information. TDF exposure increased from 14% in 2003 to 43% in 2010; TDF was used by 449 (21%) of 2029 HIV-infected mothers overall, including 263 (13%) who used TDF during the 1st trimester. The median duration of TDF exposure was 4.8 months (interquartile range: 2.2, 8.0). Maternal and demographic characteristics are summarized in Table 1 within each subgroup forming the basis for analysis of LBW and SGA other birth measurements, and growth measurements at age 1 year.

Birth weight and SGA

LBW was observed in 382 (19%) and very LBW (<1.5kg) in 51 (2.6%) of the 2006 infants with birth weight data; 162 of 1980 infants (8.6%) were SGA. Among those exposed to maternal cARV (N=1582, 79%), there was no difference in prevalence of LBW by TDF exposure (19.5% for TDF-exposed vs 19.1% for TDF-unexposed, p=0.87)(Table 2). After adjusting for high maternal viral load prior to delivery, maternal tobacco use during pregnancy, female sex of infant, low annual household income, and birth cohort, there remained no association of LBW with TDF exposure (aOR = 0.87, p = 0.40). More advanced GA was strongly associated with a decreased odds of LBW (aOR=0.40 per week of gestation, $p<0.001$). However, adjusting for GA had little effect on the association of LBW with TDF exposure (aOR = 0.73, p=0.14). We also observed no association of LBW with duration of TDF exposure (aOR per month TDF exposure=1.00, p=0.88). Birth WAZ among those exposed *in utero* to cARV also showed no association with TDF exposure, with a mean WAZ of −0.58 (SE=0.04) for TDF-exposed vs −0.59 (SE=0.03) for TDF-unexposed, after adjustment for potential confounders (Table 3).

The results for SGA were similar to those for LBW (Table 2). There was no difference in prevalence of SGA by TDF exposure (8.3% for TDF-exposed vs 8.6% for TDF-unexposed, p=0.85); the lack of association persisted after adjustment for non-white race, maternal tobacco use during pregnancy, maternal gonorrhea infection, and low income level (aOR=1.04, p=0.88), and after additional adjustment for GA (aOR=0.96, p=0.85). There was also no association of duration of TDF exposure with SGA (aOR per month=1.04, p=0.31), adjusted for the above covariates. Sensitivity analyses fit separately to the Static and

Dynamic cohorts yielded results consistent with the overall study population, indicating no association of TDF exposure with LBW or SGA either with or without adjustment for potential confounders (data not shown).

Birth measurements among infants in the Dynamic study

Infants in the Dynamic cohort overall tended to be small at the newborn visit, with mean (SD) WAZ, LAZ and HCAZ (adjusted for prematurity, as necessary) of −0.61 (0.89), −0.19 (1.01) and −0.65 (0.86), respectively. Similar mean z-scores were observed within the subset of Dynamic infants exposed *in utero* to cARV (Table 3). All of the above mean z-scores were significantly lower than the standard reference population mean of 0. The percent with z-scores < −1.5 (< 6.7 percentile) and < −1.88 (< 3rd percentile), respectively, were 8.7% and 4.7% for LAZ and 15% and 6.1% for HCAZ.

In the Dynamic cohort, 35% of all HIV-infected mothers and 40% of those receiving cARV used TDF during pregnancy. Among those exposed to cARV (85%), there was no difference in mean newborn LAZ by TDF exposure (−0.25 vs −0.18 for TDF-exposed vs unexposed); nor was there any difference in mean newborn HCAZ (−0.66 vs −0.68 for TDF-exposed vs unexposed) (Table 3). There remained no difference after adjustment for potential confounders (Table 3). Additional analyses based on models using binary outcomes for LAZ and HCAZ < −1.5 (Table 2) and < −1.88 (data not shown) yielded similar results.

Age one year: Weight, length and head circumference

By one year of age, the infants were closer to US growth standards, with mean (SD) WAZ of −0.06 (1.15), mean LAZ of −0.03 (1.06), and mean HCAZ of 0.34 (1.20) for the overall cohort and similar means for the subset of infants with *in utero* cARV exposure (Table 4). There was a slight but statistically significantly lower mean LAZ and HCAZ in infants exposed to cARV with versus without TDF (Table 4). These differences in adjusted mean z-scores correspond approximately to an average 0.41 cm shorter one-year length and an average 0.32 cm smaller one-year HC in the TDF-exposed group. The adjusted mean LAZ was slightly below the standard population mean for the TDF group (−0.17) but near 0 for the non-TDF group (−0.03). In contrast, the mean HCAZ was above 0 for TDF-exposed and TDF-unexposed. At one year of age, there was no significant difference between those receiving cARV with versus without TDF for low growth measures defined as WAZ, LAZ or HCAZ <−1.5 (Table 5) or < − 1.88 (data not shown) in either crude or adjusted models. The findings at one year and at birth for all measures were similar when TDF exposure was further divided into early (first trimester) and later (second and third trimester) exposure versus no exposure (data not shown).

Other predictors of growth outcomes in the adjusted models

Increased odds of LBW was observed for female infants (aOR=1.29, 95% CI: 0.98, 1.70, p=0.07), those whose mothers had viral load >1000 copies/mL prior to delivery (aOR=1.57, 95% CI: 1.11, 2.21, p=0.01) or used tobacco during pregnancy (aOR=1.43, 95% CI: 1.02, 2.01, p=0.04), and children from families with annual household income <$20,000 (aOR=1.31, 95% CI: 0.96, 1.79, p=0.09). Odds of LBW were lower for infants born before 2002 versus those born 2008–2010 (aOR=0.54, 95% CI: 0.33, 0.89, p=0.06). Higher odds of SGA was associated with low income (aOR=1.95, 95% CI: 1.17, 3.25, p=0.01) and with maternal gonorrhea (aOR=2.78, p=0.02) or tobacco use (aOR=1.55, p=0.08) during pregnancy. Non-white infants had a marginally decreased odds of SGA (aOR=0.68, 95% CI: 0.44, 1.04, p=0.08).

Several socioeconomic and maternal health measures also showed significant associations with z-scores at birth and age one year: female infants had significantly lower newborn visit

WAZ and LAZ, lower caregiver education was associated with significantly lower newborn visit WAZ and HCAZ at age one year, and low household income was associated with significantly lower z-scores for WAZ and HCAZ at newborn visit and HCAZ at age one year. Maternal gonorrhea infection was associated with lower z-scores for all newborn visit measures (WAZ, LAZ, and HCAZ), while high maternal viral load prior to delivery was paradoxically associated with significantly higher WAZ and LAZ at age one year. While illicit drug use was relatively uncommon in our cohort (approximately 8%), its use was associated with significantly lower HCAZ at age one year, and maternal tobacco use was associated with significantly lower LAZ at age one year.

DISCUSSION

The increasing use of TDF by HIV-infected pregnant women warrants careful evaluation of the safety of this agent. Over 40% of pregnant mothers in our study used TDF during pregnancy in 2010, more than doubling TDF use in the last 5 years. TDF exposure was associated with significantly lower mean LAZ and lower HCAZ at age one year but not at birth, an unexpected finding of uncertain significance. The magnitudes of these differences were quite small - corresponding to an average difference of < 0.5cm for mean length and mean HC - and the biologic mechanisms underlying a delayed effect on infant growth outcomes after *in utero* TDF exposure are not readily explained. Later growth differences, especially for length where mean z-scores were less than 0 in the TDF group, should be evaluated in other cohorts. The overall findings of this extensive analysis, however, are highly reassuring. The proportion of children at age one year with low LAZ and low HCAZ ($z < -1.5$ and $z < -1.88$) did not differ by TDF exposure. Furthermore, there was no association of TDF exposure with lower weight, shorter length, or smaller HC in the newborn period, whether these outcomes were defined based on mean z-scores or on z-scores below thresholds of −1.5 and −1.88. Analyses of longer-term growth and neurodevelopmental outcomes are underway in the SMARTT protocol.

The association of maternal TDF use with lower length and HC at one year but not in the newborn period was not predicted by animal studies. This observation suggests that maternal TDF use does not affect fetal growth but could lead to a delayed effect on infant growth in the first year, after ongoing exposure to maternal TDF has ceased. Adjustment for maternal HIV disease, demographic factors, and substance use suggests that the impaired infant growth is not related to confounding of maternal TDF use by these well-known influences on infant outcomes. In addition, more than 99% of all infants received zidovudine prophylaxis, of whom 10% were given additional ARV drugs for prophylaxis (data not shown), making it unlikely that infant growth differences were related to different neonatal ARV drug exposures. While newborn length and gestational age at birth are important and often interrelated predictors of length at one year, the association of maternal TDF with lower infant length at one year persisted despite adjusting for these factors. Women in this U.S.-based study would have been counseled to not breastfeed their infants, eliminating the potential for ongoing infant TDF exposure through breast milk or nutritional differences due to feeding type (breastfeeding vs formula feeding) in first year of life. Thus, the association of maternal TDF use and lower mean infant length at one year does not appear attributable to these cofactors.

Several studies of ARV-exposed infants born to HIV-infected mothers demonstrate the potential for late adverse effects that may be attributable to perinatal ARV exposure. In the Women and Infants Transmission Study (WITS), the significant difference in CD8+ cell counts by ARV exposure status did not appear until 6–24 months of age, even after adjustment for potential confounders [13]. In a cohort of children with apparent mitochondrial dysfunction after perinatal exposure to zidovudine +/− lamivudine, neurologic

and developmental problems did not develop until age 4–14 months [14]. Similarly, febrile seizures were significantly more common in ARV-exposed infants than HIV-exposed, ARV-unexposed infants; however, this difference did not appear until age 6–12 months of age [15]. Among ARV-exposed French infants, the overall rate of cancer in long-term follow-up was no different from population-based rates, but there was a higher risk of central nervous system cancer at 1–8 years of age[16]. These examples emphasize the importance of evaluating outcomes both at birth and at later time points when assessing the safety of *in utero* exposure to ARV drugs.

Suggested mechanisms by which fetal/neonatal ARV exposure could result in persistent or delayed abnormalities have focused on NRTI toxicity to nuclear DNA of hematopoietic stem cells and NRTI damage to mitochondrial DNA [17,18]. TDF does not appear to have as much potential to cause mitochondrial dysfunction as zidovudine and other NRTIs in *in vitro* studies [19,20], but adverse effects on host DNA are plausible based on its nucleotide structure and mechanism of action. After oral administration, TDF is converted in the systemic circulation to tenofovir (TFV), which crosses the placenta. TFV undergoes phosphorylation intracellularly to its active form, tenofovir diphosphate (TDP), which competitively inhibits HIV reverse transcriptase and causes DNA chain termination. The long intracellular half-life of TDP contributes to convenient dosing of TDF and its potent anti-HIV effect. Circulating TFV is renally cleared through glomerular filtration and tubular secretion, but renal elimination in the fetus would be expected to be much slower than in adults. As a result, the fetus may accumulate substantially more intracellular TDP, resulting in high, potentially more toxic levels as well as much longer persistence of intracellular TDP, exerting effects beyond the end of exposure to maternal TDF at birth. If these effects include reduced bone mass accrual, as suggested by some studies of TDF in adults and children [21–24], the end result may be attainment of smaller HC and length. However, there is currently no direct evidence from animal or human studies that can confirm the potential for maternal TDF exposure to cause a delayed effect on infant growth.

The strengths of our investigation include large sample size, the prospective data collection of ARV medications during pregnancy within the Dynamic cohort, and the evaluation of growth outcomes at both birth and age one year. The size of the study provides 80% power to detect differences in mean z-scores ranging from 0.18 (newborn) to 0.29 (at age one year). The study is also well-powered to detect increased odds of LBW or SGA, with 80% power to detect ORs of 1.5 to 1.8. The use of a comparison group exposed to combination regimens without TDF reduces the chance results could be compromised by selection bias and controls for association of maternal combination regimens with LBW observed in some, though not all, studies [25–28].

Like all cohort studies, a limitation of this study is the non-random assignment of TDF to women during pregnancy which may result in unmeasured confounding, despite the adjustment for covariates expected to be important. None of the comparisons presented would be significant if adjusted for the 3 to 4 comparisons made per outcome (eg., LBW, WAZ at birth, WAZ at age 1); however, because this was a safety study with a limited number of comparisons addressing a single ARV drug, our concern for maintaining low type I error rates was balanced with equally high concern for minimizing type II error rates (i.e., minimizing the chance of not detecting true associations with TDF).

On the whole, these data provide reassurance about the lack of major detrimental effects on fetal and infant growth when TDF is used in combination ARV regimens in pregnancy. The unexpected observation of lower mean length and HC at one year of age warrants further studies monitoring longer-term growth outcomes of TDF-exposed infants in SMARTT and other large HEU cohorts.

Acknowledgments

FUNDING: The Pediatric HIV/AIDS Cohort Study (PHACS) was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute of Allergy and Infectious Diseases, the National Institute on Drug Abuse, the National Institute of Mental Health, the National Institute of Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (U01 HD052102-04) and the Tulane University School of Medicine (U01 HD052104-01).

We thank the children and families for their participation in the PHACS protocol "Surveillance Monitoring for ART Toxicities" (SMARTT), and the individuals and institutions involved in the conduct of PHACS SMARTT. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute of Allergy and Infectious Diseases, the National Institute on Drug Abuse, the National Institute of Mental Health, National Institute of Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, National Institute of Neurological Disorders and Stroke, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard University School of Public Health (U01 HD052102-04) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (U01 HD052104-01) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Mercy Swatson).

The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2009, in alphabetical order: **Baylor College of Medicine**: William Shearer, Norma Cooper, Lynette Harris; **Bronx Lebanon Hospital Center:** Murli Purswani, Emma Stuard, Anna Cintron; **Children's Diagnostic & Treatment Center**: Ana Puga, Dia Cooley, Doyle Patton; **Children's Hospital of Philadelphia**: Richard Rutstein, Carol Vincent, Nancy Silverman; **Children's Memorial Hospital**: Ram Yogev, Kathleen Malee, Scott Hunter, Eric Cagwin; **Jacobi Medical Center**: Andrew Wiznia, Marlene Burey, Molly Nozyce; **New York University School of Medicine**: William Borkowsky, Sandra Deygoo, Helen Rozelman; **St. Jude Children's Research Hospital**: Katherine Knapp, Kim Allison, Patricia Garvie; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; **SUNY Downstate Medical Center**: Hermann Mendez, Ava Dennie, Susan Bewley; **SUNY Stony Brook**: Sharon Nachman, Margaret Oliver, Helen Rozelman; **Tulane University Health Sciences Center**: Russell Van Dyke, Karen Craig, Patricia Sirois; **University of Alabama, Birmingham**: Marilyn Crain, Newana Beatty, Dan Marullo; **University of California, San Diego**: Stephen Spector, Jean Manning, Sharon Nichols; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Emily Barr, Robin McEvoy; **University of Florida/Jacksonville:** Mobeen Rathore, Kathleen Thoma, Ann Usitalo; **University of Illinois, Chicago:** Kenneth Rich, Delmyra Turpin, Renee Smith; **University of Maryland, Baltimore:** Douglas Watson, LaToya Stubbs, Rose Belanger; **University of Medicine and Dentistry of New Jersey:** Arry Dieudonne, Linda Bettica, Susan Adubato; **University of Miami:** Gwendolyn Scott, Erika Lopez, Elizabeth Willen; **University of Southern California:** Toinette Frederick, Mariam Davtyan, Maribel Mejia; **University of Puerto Rico Medical Center**: Zoe Rodriguez, Ibet Heyer, Nydia Scalley Trifilio.

References

1. [Accessed November 2, 2011.] Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents – October 14, 2011. http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7&ClassID=1
2. [Accessed November 2, 2011.] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States - September 14, 2011. http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9&ClassID=2
3. Tarantal A, Castillo A, Ekert J, Bischofberger N, Martin R. Fetal and Maternal Outcome After Administration of Tenofovir to Gravid Rhesus Monkeys (Macaca mulatta). J Acquir Immune Defic Syndr. 2002; 29(3):207. [PubMed: 11873070]
4. Van Rompay KK, Brignolo LL, Meyer DJ, Jerome C, Tarara R, Spinner A, et al. Biological effects of short-term or prolonged administration of 9-[2-(phosphonomethoxy) propyl]adenine (tenofovir) to newborn and infant rhesus macaques. Antimicrob Agents Chemother. 2004 May; 48(5):1469–87. [PubMed: 15105094]
5. Van Rompay K, Durand-Gasselin L, Brignolo L, Ray A, Abel K, Cihlar T, et al. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy:

summary of pharmacokinetics, biological and virological effects. Antimicrob Agents Chemother. 2008; 52(9):3144–60. [PubMed: 18573931]

6. Foster C, Lyall H, Olmscheid B, Pearce G, Zhang S, Gibb DM. Tenofovir disproxil fumarate in pregnancy and prevention of mother-to-child transmission of HIV-1: is it time to move on from zidovudine? HIV Medicine. 2009; 10:397–406. [PubMed: 19459986]
7. Hirt D, Urien S, Ekouévi DK, Rey E, Arrivé E, Blanche S, et al. ANRS 12109. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). Clin Pharmacol Ther. 2009; 85(2):182–9. [PubMed: 18987623]
8. Nurutdinova D, Onen NF, Hayes E, Mondy K, Overton ET. Adverse effects of tenofovir use in HIV-infected pregnant women and their infants. Ann Pharmacother. 2008; 42(11):1581–5. [PubMed: 18957630]
9. Tassiopoulos K, Read JS, Brogly S, Rich K, Lester B, Spector SA, et al. Substance use in HIV-Infected women during pregnancy: self-report versus meconium analysis. AIDS Behav. 2010; 14(6):1269–78. [PubMed: 20532607]
10. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Adv Data. 2000; 314:1–27. [PubMed: 11183293]
11. Fenton TF, Sauve RS. Using the LMS method to calculate z-scores for the Fenton preterm infant growth chart. Eur J Clin Nutr. 2007; 61:1380–85. [PubMed: 17299469]
12. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr. 2003; 3:13. [PubMed: 14678563]
13. Pacheco SE, McIntosh K, Lu M, Mofenson LM, Diaz C, Foca M, et al. Women and Infants Transmission Study. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. J Infect Dis. 2006; 194(8):1089–97. [PubMed: 16991083]
14. Blanche S, Tardieu M, Rustin P, Slama A, Barret B, Firtion G, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet. 1999; 354:1084–9. [PubMed: 10509500]
15. Landreau-Mascaro A, Barret B, Mayaux MJ, Tardieu M, Blanche S. Risk of early febrile seizures with perinatal exposure to nucleoside analogues. Lancet. 2002; 359:583–4. [PubMed: 11867117]
16. Benhammou V, Warszawski J, Bellec S, Doz F, André N, Lacour B, et al. ANRS-Enquête Périnatale Française. Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. AIDS. 2008; 22(16):2165–77. [PubMed: 18832880]
17. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S. Enquête Périnatale Française Study Group. Perinatal antiretroviral treatment and hematopoiesis in HIV –uninfected infants. AIDS. 2003; 17 (14):2053–61. [PubMed: 14502008]
18. Poirier MC, Olivero OA, Walker DM, Walker VE. Perinatal genotoxicity and carcinogenicity of anti-retroviral nucleoside analog drugs. Toxicol Appl Pharmacol. 2004; 199:151–61. [PubMed: 15313587]
19. Maagaard A, Kvale D. Mitochondrial toxicity in HIV-infected patients both off and on antiretroviral treatment: a continuum or distinct underlying mechanisms? J Antimicrob Chemother. 2009; 64(5):901–9. [PubMed: 19740910]
20. Biesecker G, Karimi S, Desjardins J, Meyer D, Abbott B, Bendele R, et al. Evaluation of mitcohndrial DNA content and enzyme levels in tenofovir DF-treated rats, rhesus monkeys, and woodchucks. Antiviral Res. 2003; 58:217–25. [PubMed: 12767469]
21. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, et al. ASSERT Study Group. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis. 2010; 51(8):963–72. [PubMed: 20828304]
22. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Gorup A5224s, a substudy of ACTG A5202. J Infect Dis. 2011; 203(12):1791–801. [PubMed: 21606537]

23. Hazra R, Gafni RI, Maldarelli F, Balis FM, Tullio AN, DeCarlo E, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. Pediatrics. 2005; 116(6):e846–54. [PubMed: 16291735]

24. Gafni RI, Hazra R, Reynolds JC, Maldarelli F, Tullio AN, DeCarlo E, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. Pediatrics. 2006; 118(3):e711–8. [PubMed: 16923923]

25. Powis KM, Smeaton L, Ogwu A, Lockman S, Dryden-Peterson S, van Widenfelt E, et al. Effects of in utero antiretroviral exposure on longitudinal growth of HIV-exposed uninfected infants in Botswana. J Acquir Immune Defic Syndr. 2011; 56(2):131–8. [PubMed: 21124227]

26. Briand N, Mandelbrot L, Le Chenadec J, Tubiana R, Teglas JP, Faye A, et al. ANRS French Perinatal Cohort. No relation between in-utero exposure to HAART and intrauterine growth retardation. AIDS. 2009; 23(10):1235–43. [PubMed: 19424054]

27. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002; 346(24):1863–70. [PubMed: 12063370]

28. Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG. Pediatric Spectrum of HIV Disease Consortium. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989–2004. Pediatrics. 2007; 119(4):e900–6. [PubMed: 17353299]

Table 1

Demographic and Maternal Characteristics for the SMARTT Participants within Subpopulations of Interest

Characteristic		Among those with birth weight information (N=2006)	Among those with birth length or head circumference (N=869)	Among those with weight, length or head circumference at 1 year of age (N=677)
Infant Characteristics[1]				
Cohort	Dynamic	855 (43%)	869 (100%)	480 (71%)
	Static	1151 (57%)	0 (0%)	197 (29%)
Birth Cohort	< 2002	374 (19%)	0 (0%)	0 (0%)
	2002–2004	327 (16%)	0 (0%)	0 (0%)
	2005–2007	513 (26%)	110 (13%)	233 (34%)
	2008–2010	792 (39%)	759 (87%)	444 (66%)
Female		974 (49%)	422 (49%)	342 (51%)
Black/African-American		1325 (66%)	597 (69%)	440 (65%)
Latino/Hispanic		669 (33%)	264 (30%)	223 (33%)
Caesarean Delivery		1078 (54%)	609 (61%)	397 (59%)
Gestational age	<32 weeks	52 (3%)	23 (3%)	24 (4%)
	32–<37 weeks	351 (17%)	152 (17%)	131 (19%)
	≥37 weeks	1516 (76%)	668 (77%)	516 (76%)
Maternal ARV Regimens During Pregnancy				
Maternal ARV Regimen	Combination with PI & NNRTI	132 (7%)	55 (6%)	44 (6%)
	Combination with PI	1277 (64%)	644 (74%)	515 (76%)
	Combination with NNRTI	173 (9%)	41 (5%)	26 (4%)
	Not on combination ARV	424 (21%)	129 (15%)	92 (14%)
TDF & combination ARV exposure	Combination with TDF	426 (21%)	293 (34%)	217 (32%)
	Combination without TDF	1156 (58%)	447 (51%)	368 (54%)
Maternal/Caregiver Demographic and Socioeconomic Characteristics[2]				
Maternal Age<25 years at birth of child		687 (34%)	268 (34%)	206 (30%)
Marital Status	Married	523 (26%)	192 (21%)	162 (24%)
	Separated/divorced/widowed	225 (11%)	64 (7%)	46 (7%)
	Single, never married	1261 (63%)	607 (71%)	456 (67%)
	Not Reported	8 (<1%)	6 (<1%)	1 (<1%)
Annual Household Income<$20,000		1271 (63%)	556 (64%)	424 (63%)
Caregiver < High School Education		691 (34%)	301 (35%)	229 (34%)
Maternal Health and Substance Use During Pregnancy[3]				
Maternal RNA > 1000 copies/mL early in pregnancy			457 (53%)	364 (54%)
Maternal RNA > 1000 copies/mL at delivery		1052 (52%)	125 (14%)	92 (14%)
Maternal CD4 < 250 cells/mm^3 early in pregnancy		331 (17%)	170 (20%)	137 (20%)
Maternal CD4 < 250 cells/mm^3 at delivery		363 (18%)	146 (17%)	125 (18%)

Characteristic	Among those with birth weight information (N=2006)	Among those with birth length or head circumference (N=869)	Among those with weight, length or head circumference at 1 year of age (N=677)
Illicit Drug Use (marijuana, cocaine, heroin or opiates)	304 (15%)	75 (9%)	46 (7%)
Hard Drug Use (cocaine, heroin, opiates)	156 (8%)	23 (3%)	19 (3%)
Alcohol Use	51 (3%)	83 (10%)	62 (9%)
Tobacco Use	337 (17%)	151 (17%)	118 (17%)
Maternal Genital Infection[4]	392 (20%)	160 (20%)	130 (19%)
Hepatitis B surface antigen-positive	50 (2%)	17 (2%)	15 (2%)

Information was missing or caregiver chose not to report data for:

[1] race (N=132, 7%), ethnicity (N=3,<1%), delivery mode (N=24,1%), and exact gestational age (N=87, 4% [although prematurity status was known for 70 of the 87]);

[2] maternal age at birth of child (N=27, 1%), marital status (N=8,<1%), household income (N=142,7%), and caregiver education (N=8,<1%);

[3] maternal viral load (N=155, 8%), maternal CD4 (N=120, 6%), substance use including alcohol and tobacco during pregnancy (N=163, 8%), genital infection (N=159, 8%), and hepatitis B status (N=268, 13%). Numbers missing are among the 2006 with birth weight information, but percentages missing are similar within the two other subgroups. Percentages in table do not exclude those missing information.

[4] Maternal genital infections among those with birth weight information included: gonorrhea, 3.0%; chlamydia 9.2%; trichomonas 11.9%; and syphilis, 3.2%.

SMARTT = Surveillance Monitoring for Antiretroviral Therapy Toxicities study. TDF = tenofovir disoproxil fumarate.

Table 2

Effects of Tenofovir disoproxil fumarate (TDF) exposure versus no TDF exposure on **newborn** outcomes among those on combination ARV regimens during pregnancy, SMARTT Study, 2007–2010, USA

Outcome[1]	Percent with Outcome		Unadjusted Models			Adjusted Models[2]			Fully Adjusted Models including gestational age		
	TDF Exposed	No TDF	N	OR (95% CI)	P-value	N	aOR (95% CI)	P-value	N	aOR (95% CI)	P-value
LBW	19.5%	19.1%	1582	1.02 (0.77, 1.36)	0.87	1338	0.87 (0.63, 1.20)	0.40	1302	0.73 (0.48, 1.11)	0.14
SGA	8.3%	8.6%	1569	0.96 (0.64, 1.44)	0.85	1189	1.04 (0.65, 1.64)	0.88	1148	0.96 (0.60, 1.52)	0.85
Length Z<−1.5[3]	8.7%	9.0%	701	0.96 (0.56, 1.65)	0.89	614	1.28 (0.73, 2.25)	0.40	609	1.18 (0.66, 2.10)	0.58
HC Z<−1.5[3]	13.9%	16.8%	690	0.80 (0.52, 1.22)	0.30	676	0.81 (0.52, 1.25)	0.34	672	0.82 (0.53, 1.28)	0.39

TDF=tenofovir disoproxil fumarate, LBW=Low birth weight, SGA= Small for Gestational Age, OR=Odds Ratio, aOR=adjusted Odds Ratio, CI=Confidence Interval.

[1] Low birth weight (LBW) defined as <2.5kg, Small for gestational age (SGA) defined as birth weight less than the 10th percentile for gestational age, according to Fenton (Fenton 2003).

[2] The estimates presented above are from separate models for each outcome adjusted for covariates with p<0.10 in multivariate models, including: *For LBW*: female infant sex, annual household income < $20,000, maternal viral load >1000 copies/mL prior to labor and delivery, maternal tobacco use during pregnancy, and birth cohort (2002–2004, 2005–2007, and 2008–2010 vs <2002); *For SGA*: annual household income < $20,000, non-white race, maternal tobacco use during pregnancy, and maternal gonorrhea during pregnancy; *For short birth length*: female sex and maternal gonorrhea infection; *For small head circumference at birth*: female sex, CD4<250 cells/mm^3 early during pregnancy, low caregiver education, and maternal age<25 years at delivery.

[3] Available only for Dynamic Cohort subjects, based on measurements at newborn study visit.

AIDS. Author manuscript; available in PMC 2013 June 01.

Table 3

Mean z-scores for birth weight and for weight, length, and head circumference (HC) at newborn visit, by exposure to combination ARV regimen with TDF vs. combination ARV regimen without TDF during pregnancy, unadjusted and adjusted for other covariates.

Gestation or Age-adjusted Z-score	Among combination ARV-exposed infants N, Mean (SD)	Exposed to combination regimens with TDF		Exposed to combination regimens without TDF		TDF vs non-TDF P-value[2]
		Unadjusted N, Mean (SD)	Adjusted[1] Mean (SE)	Unadjusted N, Mean (SD)	Adjusted[1] Mean (SE)	
Z-scores among all Participants at Birth: Dynamic (N=855) and Static (N=1151) Cohorts						
Weight	1567, −0.59 (0.85)	421, −0.59 (0.81)	−0.58 (0.04)	1146, −0.60 (0.86)	−0.59 (0.03)	0.77
Z-scores from Growth Measurements at the Newborn Exam (within 2 weeks of birth): Dynamic Cohort Only (N=815)						
Weight	702, −0.65 (0.82)	278, −0.62 (0.82)	−0.63 (0.05)	424, −0.66 (0.82)	−0.66 (0.04)	0.58
Length	701, −0.21 (1.00)	277, −0.25 (1.00)	−0.25 (0.07)	424, −0.18 (1.01)	−0.16 (0.05)	0.29
HC	690, −0.67 (0.85)	274, −0.66 (0.84)	−0.66 (0.06)	416, −0.68 (0.85)	−0.65 (0.05)	0.83

TDF=tenofovir disoproxil fumarate, HC=head circumference, SD=standard deviation, SE=standard error

[1]The estimates presented above are from separate models for each outcome adjusted for covariates with p<0.10 in multivariate models, including: Birth weight z-score (all subjects): gestational age, female sex, low income level, maternal use of illicit drugs during pregnancy, and low CD4 early in pregnancy; Birth weight z-score (from newborn exam): female sex, non-white race, low caregiver education, and maternal gonorrhea infection; Birth length z-score: gestational age, female sex and maternal gonorrhea; Birth HC z-score: gestational age, low household income level, and gonorrhea infection.

[2]P-value from linear regression model comparing adjusted means for TDF-exposed vs unexposed.

AIDS. Author manuscript; available in PMC 2013 June 01.

Table 4

Mean z-scores for weight, length, and head circumference (HC) **at age one year**, by exposure to combination ARV regimen with TDF vs. combination ARV regimen without TDF during pregnancy, unadjusted and adjusted for other covariates.

		Exposed to combination regimens with TDF		Exposed to combination regimens without TDF		
Gestation or Age-adjusted Z-score	**Among combination ARV-exposed infants N, Mean (SD)**	**Unadjusted N, Mean (SD)**	**Adjusted[1] Mean (SE)**	**Unadjusted N, Mean (SD)**	**Adjusted[1] Mean (SE)**	**TDF vs non-TDF P-value[2]**
Weight	585, −0.07 (1.16)	217, −0.11 (1.20)	−0.09 (0.08)	368, −0.05 (1.14)	−0.04 (0.06)	0.62
Length	582, −0.05 (1.09)	215, −0.17 (1.00)	−0.17 (0.07)	367, 0.02 (1.14)	−0.03 (0.06)	0.04
HC	570, 0.34 (1.20)	209, 0.23 (1.10)	0.17 (0.08)	361, 0.41 (1.25)	0.42 (0.06)	0.02

TDF=tenofovir disoproxil fumarate, HC=head circumference, SD=standard deviation, SE=standard error

[1]The estimates presented above are from separate models for each outcome adjusted for covariates with p<0.10 in multivariate models, including: Weight z-score at 1 year: gestational age and high maternal viral load prior to delivery; Length z-score at 1 year: Latino ethnicity, high maternal viral load prior to delivery, and maternal use of tobacco during pregnancy; HC z-score at 1 year: low income level, low caregiver education level, and maternal use of illicit drugs during pregnancy.

[2]P-value from linear regression model comparing adjusted means for TDF-exposed vs unexposed.

AIDS. Author manuscript; available in PMC 2013 June 01.

Table 5

Effects of exposure to combination ARV regimen with Tenofovir (TDF) vs. combination ARV regimen without TDF during pregnancy on infant growth outcomes at age one year, SMARTT Study, 2007–2010, USA

Gestation- or age-adjusted z-score< −1.5	Percent with Outcome		Unadjusted Models			Adjusted Models[1]			Fully Adjusted Models including gestational age		
	TDF Exposed	No TDF	N	OR (95% CI)	P-value	N	aOR (95% CI)	P-value	N	aOR (95% CI)	P-value
Weight	11.5%	9.5%	585	1.24 (0.72, 2.13)	0.44	582	1.25 (0.72, 2.15)	0.42	578	1.25 (0.73, 2.17)	0.42
Length	7.9%	8.2%	582	0.97 (0.52, 1.79)	0.91	561	0.94 (0.50, 1.78)	0.86	558	0.95 (0.50, 1.79)	0.87
HC	6.2%	5.8%	570	1.07 (0.53, 2.19)	0.84	545	1.15 (0.56, 2.39)	0.70	541	1.17 (0.57, 2.42)	0.67

ARV=antiretroviral regimens, TDF=tenofovir disoproxil fumarate, HC= head circumference, OR=odds ratio, aOR=adjusted odds ratio, CI=confidence interval

For low weight at 1 year: maternal age <25 years at delivery, high maternal viral load early in pregnancy, genital infection during pregnancy, and maternal use of hard drugs during pregnancy; *For short length at 1 year*: female sex; *For small head circumference at 1 year*: maternal use of hard drugs during pregnancy.

AIDS. Author manuscript; available in PMC 2013 June 01.