Published in final edited form as:
Pediatr Infect Dis J. 2010 August ; 29(8): 721–727. doi:10.1097/INF.0b013e3181e74a2f.

Birth defects among children born to HIV-infected women: Pediatric AIDS Clinical Trials Protocols 219 and 219C

Susan B. Brogly, PhD[1], **Mark J. Abzug, MD**[2], **D. Heather Watts, MD**[3], **Coleen K. Cunningham, MD**[4], **Paige L. Williams, PhD**[1], **James Oleske, MD**[5], **Daniel Conway, MD**[6], **Rhoda S. Sperling, MD**[7], **Hans Spiegel, MD**[8], and **Russell B. Van Dyke, MD**[9]

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

[2]Department of Pediatrics (Infectious Diseases), University of Colorado Denver School of Medicine and the Children's Hospital

[3]Pediatric, Adolescent, and Maternal AIDS Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

[4]Department of Pediatrics, Division of Infectious Diseases, Duke University Medical Center

[5]Department of Pediatrics, University of Medicine & Dentistry of New Jersey

[6]Department of Pediatrics, Drexel University College of Medicine

[7]Department of Obstetrics, Gynecology, and Reproductive Science, Mount Sinai School of Medicine

[8]Adolescent AIDS Program, Montefiore Medical Center

[9]Department of Pediatrics, Tulane University Health Science Center

Abstract

Background—Some studies have detected associations between *in utero* antiretroviral therapy (ARV) exposure and birth defects but evidence is inconclusive.

Methods—2,202 HIV-exposed children enrolled in the Pediatric AIDS Clinical Trials Group 219 and 219C protocols before one year of age were included. Birth defects were classified using the Metropolitan Atlanta Congenital Defects Program (MACDP) coding. Logistic regression models were used to evaluate associations between first trimester *in utero* ARV exposure and birth defects.

Results—117 live-born children had birth defects for a prevalence of 5.3% (95% CI: 4.4, 6.3). Prevalence did not differ by HIV infection status or overall ARV exposure; rates were 4.8% (95% CI: 3.7, 6.1) and 5.8% (95% CI: 4.2, 7.8) in children without and with first trimester ARV exposure, respectively. The defect rate was higher among children with first trimester efavirenz exposure (5/32, 15.6%) versus children without first trimester efavirenz exposure [adjusted odds ratio (aOR)=4.31 (95% CI: 1.56, 11.86)]. Protective effects of first trimester zidovudine exposure on musculoskeletal defects were detected [aOR=0.24 (95% CI: 0.08, 0.69)], while a higher risk of heart defects was found [aOR=2.04 (95% CI: 1.03, 4.05)].

Conclusion—The prevalence of birth defects was higher in this cohort of HIV-exposed children than in other pediatric cohorts. There was no association with overall ARV exposure, but there were some associations with specific agents including efavirenz. Additional studies are needed to rule out confounding and to evaluate newer ARV agents.

Background

Since 1998 the US Public Health Service has recommended the use of combination antiretroviral therapy (ARV) to prevent mother-to-child HIV transmission (1). Because zidovudine and other nucleoside analogues can affect nuclear and mitochondrial DNA replication, the safety of *in utero* exposure to these drugs is of concern (2). In addition, there is inadequate fetal and neonatal safety data for non-nucleoside analogues and protease inhibitors. Efavirenz, a non-nucleoside analogue, is considered a potential teratogen on the basis of animal data and case reports (1,3-6).

While existing data on *in utero* ARV exposure and birth defects have been mostly reassuring (7-9), some studies have reported elevated risks with specific exposures (10,11); others have been limited by small sample size or possible confounding. The US Woman and Infants Transmission Study documented a birth defect rate of 3.56 per 100 live births in 2,527 infants born to HIV-infected women from 1990 through 2000 (12), which was not significantly different than the rate major of defects of 2.76 per 100 live births in the general pediatric population estimated by the Metropolitan Atlanta Congenital Defects Program (MACDP) (11). However, first trimester zidovudine exposure was significantly associated with an increased risk of hypospadias among male infants. The US Antiretroviral Pregnancy Registry (APR) estimated an overall prevalence of defects of 2.9% (95% CI: 2.4, 3.5) among greater than 4,300 first trimester ARV exposed children, which did not differ from the rate among children exposed in later trimesters (13). The Pediatric AIDS Clinical Trials Group (PACTG) protocols 219 and 219C provided an opportunity to further estimate the independent association between *in utero* ARV exposure, including newer agents, and birth defects.

Methods

Study Population

The source population was children enrolled in PACTG protocols 219 and 219C, a multisite US cohort of children born to HIV-infected women initiated to study the long-term effects of *in utero* ARV exposure and complications of pediatric HIV infection (14). Protocol 219 followed HIV-infected and HIV-uninfected perinatally exposed children at clinics across the US from May 1993 through August 2000. Children currently or previously enrolled in another PACTG protocol and children whose mothers were enrolled in a PACTG perinatal protocol during pregnancy were eligible. In September 2000 a revised protocol was initiated, PACTG 219C, and the eligibility criterion mandating enrollment in another PACTG protocol was removed. The present study was restricted to children enrolled in 219 or 219C before one year of age to improve the accuracy of birth defect information recorded on protocol case report forms. The study was approved by site institutional review boards, and parents or guardians provided informed consent.

Data Collection

Study visits, which included physical examinations, were scheduled every three months for HIV-infected children, and every six months until two years of age (protocol 219), or every three months through one year of age (protocol 219C) and annually thereafter for HIV-uninfected children. Protocol 219 did not include a direct question regarding the presence of defects, but birth defects were a primary outcome and were recorded on diagnosis case report forms. Protocol 219C included a direct question regarding birth defects. Detailed data on birth defects also were collected in PACTG perinatal protocols 076, 185, 249, 250, 316, 332, 353, 354, 358, and 386 and the International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) protocol P1025. Forty-two percent of mother-infant pairs in protocol 219 and

219C participated in one of these perinatal protocols during pregnancy-gestation; these data were used to supplement 219 and 219C data.

Exposure

Gestational age at birth was estimated from the date of last menstrual period, ultrasound measurement before 22 weeks gestation, or newborn examination. Trimesters were defined as first trimester, conception to <14 weeks gestation; second trimester, 14 weeks to <28 weeks gestation; and third trimester, 28 weeks to delivery. The primary determinant was first trimester *in utero* ARV exposure. We considered overall ARV exposure, ARV classes, and specific ARV agents to which at least one child with a birth defect was exposed in the first trimester. The reference group consisted of children unexposed to the particular ARV drug (or class) during the first trimester, and thus included ARV unexposed children, children exposed to ARV in labor only, children unexposed to the particular ARV drug but to other ARV, and children exposed to the particular ARV drug in the second and/or third trimester only (15). We also examined ARV exposure by trimester of first exposure (unexposed, first trimester, second or third trimester); however, since the first trimester estimates were substantially unchanged in this model from the former classification, results from the more parsimonious models were presented.

Outcome

The outcome was the presence of a birth defect documented within the first year of life. Clinicians blinded to ARV exposure reviewed and classified the reported defects according to the MACDP guidelines as major defects or conditional defects (16). To further prevent misclassification we followed a modified version of MACDP guidelines employed by the APR (13), in which children with two or more conditional defects in the absence of a major defect were considered a case. Therefore, a child with at least one major defect or at least two conditional defects in the absence of a major defect was considered a case. Children classified as having birth defects solely based on conditional MACDP defects were categorized separately from those with major defects.

Statistical Analysis

The prevalence and exact 95% confidence interval (CI) of birth defects per 100 live births was estimated overall, by cohort (219 versus 219C), and infant HIV-infection status. Differences in birth defect prevalence across these and other characteristics were assessed using the Chi-square test, Fisher's exact test, and Cochran-Armitage trend test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Logistic regression models were used to estimate associations between first trimester *in utero* ARV exposure of any drug and of specific drugs and the most common categories of birth defects (all birth defects, musculoskeletal defects, and heart defects) including both HIV-infected and uninfected children. Potential confounders with a p-value <0.25 in univariate analysis were initially included in adjusted models, but only those that produced at least a 10% change in the estimated odds ratio were retained in final models. Children with recognized chromosomal abnormalities or congenital infections such as toxoplasmosis were excluded from regression analyses.

Results

Of 5,931 children in protocols 219 and 219C, 2,202 enrolled by one year of age and constituted the study population. Following clinical review of birth defects according to MACDP guidelines, 117 children had at least one defect, 103 with at least one major defect, and 14 with two or more conditional defects but no major defect. Among these 117 children, 77 had one birth defect, 30 had two, six had three, and four had four. Overall defect prevalence was 5.3% (95% CI: 4.4, 6.3) including all 117 cases, and was 4.7% (95% CI: 3.8, 5.6) including 103

cases with major defects. Prevalence was 4.9% (95% CI: 2.6, 8.2) and 5.4% (95% CI: 4.4, 6.5) in HIV-infected and HIV-uninfected/indeterminate children (Table 1), respectively, and was 4.8% (95% CI: 3.7, 6.1) in first trimester unexposed children, and 5.8% (95% CI: 4.2, 7.8) in first trimester ARV exposed children (Table 2).

The majority of defects occurred in the heart and musculoskeletal system (Supplemental Digital Content 2, http://links.lww.com/INF/A514). Prevalence was significantly higher among children whose mother had participated in a PACTG study during pregnancy and increased with increasing maternal age (Table 1). Prevalence also was higher among males and children with first trimester folate antagonist exposure (i.e. trimethoprim/sulfamethoxazole), although these differences were not statistically significant and folate antagonist exposure was unavailable for over half of the children. There was no difference in defect prevalence by highest $\log_{10}$ median maternal HIV viral load [3.4 copies/mL (children with defects) versus 3.5 copies/mL (children without defects)], or lowest median maternal CD4 count [(360 cell/mL (children with defects) versus 372 cells/mL (children without defects)] during pregnancy. Defect prevalence significantly differed by protocol: rates were 6.8% (95 % CI: 5.2, 8.7) and 4.4 (95 % CI: 3.3, 5.6) for children enrolled in protocol 219 (whether or not in 219C) and in 219C alone. Supplemental Digital Content 1, http://links.lww.com/INF/A513 shows the prevalence of birth defects by year of birth; 1992 and 2006 were excluded because of the small number of children born in these years. No overall difference in prevalence by year of birth was identified.

The unadjusted and adjusted estimates between first trimester *in utero* ARV exposure and birth defects are shown in Table 2. In unadjusted analyses there was no significant association with overall first trimester ARV exposure or first trimester exposure to specific drug classes. Significantly more children with birth defects were exposed to efavirenz in the first trimester. The mothers of all five cases were taking efavirenz at the time of conception and three stopped efavirenz around the time pregnancy would have been identified; the other two mothers stopped efavirenz in the second trimester. All mothers of the five efavirenz-exposed children with defects also were receiving lamivudine plus other ARV. The defects of these efavirenz exposed children included laryngiomalacia (N=1), meningomyelocele with Arnold-Chiari Malformation Type II (N=1), hypospadias (N=1), varus feet and hypertonicity of extremities (N=1), and cleft palate (N=1).

The rate of birth defects also was higher in children exposed to lopinavir/ritonavir in the first trimester than in children unexposed to lopinavir/ritonavir in the first trimester. The defects of the six lopinavir/ritonavir exposed children included hydronephrosis (N=1), supernumerary nipple and umbilical hernia (N=1), atrial septal defect (N=1), pyloric stenosis (N=2), and ventricular septal defect and hemangioma (N=1). None of the children with defects were exposed to both efavirenz and lopinavir/ritonavir in the first trimester.

In models adjusted for first trimester folate antagonist exposure, year of birth, and perinatal study participation, the association with efavirenz persisted while the association with lopanivir/ritonavir was marginally significant (p=0.07). To further examine possible confounding we examined maternal and infant characteristics by perinatal protocol participation (data not shown). In models adjusted for year of birth, participation in a perinatal protocol was higher among infants with first trimester exposure to any ARV (OR=1.47, 95% CI: 1.21, 1.79) and to any nucleoside analogue (OR=1.48, 95% CI: 1.22, 1.80), and was lower among infants with first trimester exposure to any non-nucleoside analogue (OR=0.57, 95% CI:0.38, 0.85). However, other characteristics generally were in the direction of a higher possible risk of defects in those who did not participate in a perinatal protocol (e.g. more mothers < 20 and >30 years of age, more maternal cocaine use, lower infant birth weights,

more preterm births, and more HIV-infected infants) except for maternal alcohol use, which was higher among perinatal study participants.

We also examined associations between *in utero* ARV exposure and the most common categories of specific defects: musculoskeletal and heart (Supplemental Digital Content 2, http://links.lww.com/INF/A514). Because of the lower number of cases (N=36 and 34, respectively), these models were only adjusted for perinatal protocol participation and first trimester folate antagonist exposure. Protective effects of first trimester zidovudine exposure on musculoskeletal defects were detected in unadjusted (OR=0.30, 95% CI: 0.10, 0.84) and adjusted models (OR= 0.24, 95% CI: 0.08, 0.69). Protective effects on musculoskeletal defects also were found with overall first trimester ARV exposure and any first trimester nucleoside analogue exposure in adjusted models. These latter findings appeared to be driven by zidovudine exposure; the frequency of exposure was similar for any ARV, for any nucleoside analogue, and for zidovidine. In contrast, significantly more children with heart defects—MACDP category of heart, other, which excludes conotruncal and obstructive defects (Supplemental Digital Content 2, http://links.lww.com/INF/A514) — were exposed to zidovudine in the first trimester in unadjusted (OR= 2.11, 95% CI: 1.07, 4.16) and adjusted models (OR= 2.04, 95% CI: 1.03, 4.05). This association was marginally significant when conotruncal and obstructive defects were included (OR= 1.78, 95% CI: 0.93, 3.40, p=0.08).

To examine possible selection bias we assessed enrollment into 219 and 219C of children who participated in PACTG 076, 316 or IMPAACT P1025 by defect status and *in utero* ARV exposure. These latter three studies were examined because birth defect information was collected and reviewed in these studies by the 076, 316 and P1025 investigators; thus data on birth defects from these three perinatal studies were available. It should be noted that 74% of children in 219 and 219C who participated in a perinatal protocol were in one of these studies. Among children who participated in PACTG 076, 316 or IMPAACT P1025, more children with (31.2%) than without defects (24.8%) enrolled in protocols 219 and 219C (p=0.054). However, the only important differences in enrollment by defect status and *in utero* ARV exposure were among children without defects: enrollment was higher among children unexposed to abacavir (17.0% exposed vs. 25.2% unexposed enrolled, p=0.048), and exposed to saquinavir (44.4% exposed vs. 24.6% unexposed enrolled, p=0.018). This differential enrollment among children without defects would increase and decrease estimated associations with abacavir and saquinavir exposure, respectively. No other evidence of selection bias was identified.

Discussion

In HIV-uninfected and HIV-infected children enrolled in protocols 219 and 219C by one year of age we documented a birth defect prevalence of 5.3% including all 117 cases, and 4.7% including 103 major cases only. No differences were found according to infant HIV infection status. While we did not detect an association between overall *in utero* ARV exposure and defects, associations with particular ARV drugs were identified.

Our study is the first to provide evidence of an association between efavirenz and birth defects in a population-based investigation, although the small number of infants with first trimester efavirenz exposure must be considered. Of the 5 children in our study with birth defects and first trimester efavirenz exposure, only one had a neural tube defect and has previously been described (5) and retrospectively reported to the APR. In prospectively reported APR cases, defects were detected in 13 (3.2%) of 407 live births with first trimester efavirenz exposure, which was similar to the overall APR rate; no specific pattern of defects was observed (one case of meningomyelocele and one case of facial cleft with anophthalmia) (13). However, 3 (15%) of 20 infant cynomolgus monkeys with first trimester efavirenz exposure at levels

similar to human exposure had defects (anencephaly and unilateral anophthalmia, micro-ophthalmia, and cleft palate) (6). We also detected associations between first trimester lopinavir/ritonavir exposure and defects, but this did not remain significant after adjustment for other covariates, perhaps because of low power. Animal studies have not demonstrated teratogenic effects, but have shown delayed skeletal ossification and skeletal variation at maternally toxic doses (1).

The rate of birth defects in our cohort was higher than the 2.9% prevalence reported by the APR (13). Other US (12) and European (8) studies of children born to HIV-infected women have not reported an elevated defect prevalence of birth defects, excluding the PACTG 076 randomized trial in which a rate of major defects of 8% was detected, and all ARV exposure occurred after the first trimester (17). It is possible that differential ascertainment across studies could account for the differences. Six hundred thirty-six children in our study population had echocardiograms, most per study protocol, and more children with (41%) than without defects (28%) had echocardiograms. Early screening echocardiography can detect important subclinical malformations and produce rates of cardiac defects 5-10% higher than expected (18,19). Additionally, children whose mother had participated in a perinatal protocol were more likely to have a birth defect, possibly suggesting differential ascertainment.

To investigate potential selection bias we examined enrollment into 219 and 219C among children who had participated in perinatal protocols PACTG 076, 316 and IMPAACT P1025. Despite the higher enrollment of children with defects into our cohort, it was non-differential with respect to most *in utero* ARV exposures, and importantly, those with which we detected notable associations. Selection bias of our estimated associations between defects and ARV exposure is not of major concern. It should also be noted that IMPAACT P1025 is a cohort study and no ARV was given as part of the protocol (20); likewise, in PACTG 316, all women were on clinically-indicated ARV and the only randomized component was single-dose nevirapine at labor and delivery (21).

To control for possible confounding models were adjusted for perinatal protocol participation, exposure to folate antagonists, and year of birth. We examined other potential confounders of the association between *in utero* ARV exposure and birth defects, including maternal drug use, but had incomplete information. Some residual confounding may persist. Finally, because of the large number of ARVs available for use during pregnancy, it is impossible to adjust for all other ARVs when estimating effects of a particular ARV, and this should be considered in weighing the evidence from our study as well as other studies.

It is possible that some associations might have been attenuated if particular defects result from exposure to a particular ARV. We attempted to look at more refined categories of birth defects where power was sufficient. A lower risk of musculoskeletal defects and a higher risk of heart defects were found with first trimester zidovudine exposure. These findings were based on a small number of cases and require confirmation in other studies. An association between first trimester zidovudine exposure and septal heart defects was noted in PACTG protocol 185 and in a German study, although selection bias could not be ruled out (13).

A potential limitation of our study is that children, not pregnant women, enrolled in protocols 219 and 219C. Therefore, birth defects resulting in fetal loss were not included. Birth defects in stillbirths occurring after 20 weeks gestation were included in WITS (12) and the APR (13). If defects caused by a specific exposure resulted in an increase in stillbirths then our estimates would likely be attenuated.

In this US cohort of children born to HIV-infected women we identified a higher prevalence of birth defects than other studies. Overall first trimester *in utero* ARV exposure was not associated with an increased risk of defects. However, some associations with first trimester

in utero exposure to particular ARVs were identified. Further study is needed to rule out possible confounding, and to examine associations between ARV exposure and specific birth defects. Practitioners are urged to report all pregnant women receiving ARV during pregnancy to the APR (www.APRegistry.com) as early as possible and preferably before the pregnancy outcome is known.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) [U01 AI068632], the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) [AI068632]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This work was supported by the Statistical and Data Analysis Center at Harvard School of Public Health, under the NIAID cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group. Support of the sites was provided by the NIAID (NIAID) the NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network funded by NICHD (contract number N01-DK-9-001/HHSN267200800001C). The following institutions and individuals participated in PACTG Protocols 219 and/or 219C: Baylor Texas Children's Hospital: F Minglana, ME Paul, CD Jackson; University of Florida, Jacksonville: MH Rathore, A Khayat, K Champion, S Cusic; Chicago Children's Memorial Hospital: R. Yogev, E. Chadwick; University of Puerto Rico, University Children's Hospital AIDS Program: I. Febo-Rodriguez, S. Nieves; Bronx Lebanon Hospital Center; M Purswani, S Baksi, E Stuard, M Dummit; San Juan Hospital: M Acevedo, M Gonzalez, L Fabregas, ME Texidor; University of Miami: GB Scott, CD Mitchell, L Taybo, S Willumsen; University of Medicine & Dentistry of New Jersey: L Bettica, J Amour, B Dashefsky, J Oleske; Charity Hospital of New Orleans & Earl K. Long Early Intervention Clinic: M Silio, T Alchediak, C Boe, M Cowie; UCSD Mother, Child & Adolescent HIV Program: SA Spector, R Viani, M Caffery, L Proctor; Howard University: S Rana, D Darbari, JC Roa, PH Yu; Jacobi Medical Center: M Donovan, R Serrano, M Burey, R Auguste; St. Christopher's Hospital for Children, Philadelphia: J. Chen, J. Foster; Baystate Medical Center Children's Hospital: BW Stechenberg, DJ Fisher, AM Johnston, M Toye; Los Angeles County Medical Center/USC: J Homans, M Neely, LS Spencer, A Kovacs; Children's Hospital Boston:S Burchett, N Karthas; Children's Hospital of Michigan: E. Moore, C. Cromer; St. Jude Children's Research Hospital, Memphis: PM Flynn, N Patel, M Donohoe, S Jones; New York University School of Medicine/Bellevue Hospital: W Borkowsky, S Chandwani, N Deygoo, S Akleh; The Children's Hospital at Downstate: E Handelsman, HJ Moallem DM Swindell, JM Kaye; The Columbia Presbyterian Medical Center & Cornell University New York Presbyterian Hospital: A Higgins, M Foca, P LaRussa, A Gershon; The Children's Hospital of Philadelphia: RM Rutstein, CA Vincent, SD Douglas, GA Koutsoubis; Children's Hospital of Oakland: A Petru, T Courville; UCSF, Moffitt Hospital: D Wara, D Trevithick; Children's Hospital, University of Colorado, Denver: E. McFarland, C. Salbenblatt;Johns Hopkins University Pediatrics: N Hutton, B Griffith, M Joyner, C Kiefner; Children's Hospital and Regional Medical Center, Washington: M Acker, R Croteau, C McLellan, K Mohan; Metropolitan Hospital Center: M. Bamji, I. Pathak, S. Manwani, E. Patel; Children's National Medical Center: H. Spiegel, V. Amos; University of Massachusetts Medical School: K Luzuriaga; University of Alabama at Birmingham:R Pass, M Crain; University of Maryland Medical Center: J Farley, K Klipner; Schneider Children's Hospital: VR Bonagura, SJ Schuval, C Colter, L Campbell; Boston Medical Center: SI Pelton, AM Reagan; University of Illinois: KC Rich, K Hayani, M Bicchinella; SUNY Stony Brook: S Nachman,, D Ferraro, S Madjar; North Broward Hospital District: A. Puga; Duke University: F Wiley, K Whitfield, O Johnson, R Dizney; Harlem Hospital: S Champion, M Frere, M DiGrado, EJ Abrams; Cook County Hospital: J. Martinez; University of South Alabama: M Mancao; Connecticut Children's Medical Center: J. Salazar, G. Karas; University of North Carolina at Chapel Hill: T Belho, B Pitkin, J Eddleman; Ruiz Arnau University Hospital: W. Figueroa, E. Reyes; SUNY Upstate Medical University: LB Weiner, KA Contello, WA Holz, MJ Famiglietti; Children's Medical Center of Dallas; University of Florida at Gainesville: R Lawrence, J Lew, C Delany, C Duff; Children's Hospital at Albany Medical Center: AD Fernandez, PA Hughes, N Wade, ME Adams; Lincoln Medical & Mental Health Center; Phoenix Children's Hospital: JP Piatt, J Foti, L Clarke-Steffen; Public Health Unit of Palm Beach County: J. Sleasman, C. Delaney; Medical College of Georgia: CS Mani; Yale University School of Medicine: WA Andiman, S Romano, L Hurst, J de Jesus; Vanderbilt University Medical Center: G Wilson; University of Rochester Medical Center: GA Weinberg, F Gigliotti, B Murante, S Laverty; St. Josephs Hospital and Medical Center, New Jersey: N. Hutchcon, A. Townley; Emory University Hospital: S. Nesheim, R. Dennis; University of South Florida: P Emmanuel, J Lujan-Zilberman, C Graisberry, S Moore; Children's Hospital of the King's Daughters: RG Fisher, KM Cunnion, TT Rubio, D Sandifer; Medical University of South Carolina: GM Johnson; University of Mississippi Medical Center: H. Gay, S. Sadler; Harbor-UCLA Medical Center: M Keller, J Hayes, A Gagajena, C Mink; Mount Sinai Medical Center: D. Johnson; Children's Hospital of Los Angeles: J. Church, T. Dunaway, C. Salata; Long Beach Memorial: A. Deveikis, L. Melton; Robert Wood Johnson Medical School: S Gaur, P Whitley-Williams, A Malhotra, L Cerracchio; Sinai Children's Hospital: M Dolan, J D'Agostino, R Posada; The Medical Center, Pediatric Columbus, Georgia: C. Mani, S. Cobb; Medical

College of Virginia: SR Lavoie, TY Smith; Cooper Hospital - University Medical Center: A. Feingold, S. Burrows-Clark; University of Cincinnati: J. Mrus, R. Beiting; Columbus Children's Hospital: M Brady, J Hunkler, K Koranyi; Sacred Heart Children's CMS of Florida: W. Albritton; St. Luke's/Roosevelt Hospital Center: R Warford, S Arpadi; Incarnation Children's Center, New York: A. Gershon, P. Miller; Montefiore Medical – AECOM: A. Rubinstein, G. Krienik; Children's Hospital of Los Angeles: A. Kovacs and E. Operskalski; San Francisco General Hospital: D. Wara, A. Kamrin, S. Farrales; Cornell University New York Presbyterian: R. Johan-Liang, K. O'Keefe; St. Louis Children's Hospital: KA McGann, L Pickering, GA Storch; North Shore University Hospital: S. Pahwa, L. Rodriquez; Oregon Health and Science University: P. Lewis, R. Croteau.

References

1. Perinatal HIV Guidelines Working Group. Public Health Services Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. 2009. http://www.aidsinfo.nih.gov.ezp-prod1.hul.harvard.edu/guidelines
2. Venhoff N, Walker U. Mitochondrial disease in the offspring as a result of antiretroviral therapy. Expert Opinion on Drug Safety 2006;5(3):373–381. [PubMed: 16610967]
3. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS 2002;16(2):299–300. [PubMed: 11807320]
4. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. Archives of Internal Medicine 2002;162(3):355. [PubMed: 11822930]
5. Saitoh A, Hull A, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. Journal of Perinatology 2005;25(8):555–556. [PubMed: 16047034]
6. Nightingale S. From the food and drug administration. Journal of the American Medical Association 1998;280:1472. [PubMed: 9809716]
7. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. Journal of Acquired Immune Deficiency Syndrome 2003;32(4):380–387.
8. European Collaborative Study. Does highly active antiretroviral therapy increase the risk of congenital anomalies in HIV-infected women? Journal of Acquired Immune Deficiency Syndrome 2005;40(1): 116–118.
9. Townsend C, Willey B, Cortina-Borja M, et al. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. AIDS 2009;23(4):519–524. [PubMed: 19165088]
10. Jungmann E, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? Sexually Transmitted Infections 2001;77(6):441–443. [PubMed: 11714944]
11. Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. Morbidity and Mortality Weekly Report 2008;57(1):1–5. [PubMed: 18185492]
12. Watts D, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. Journal of Acquired Immune Deficiency Syndrome 2007;44(3):299–305.
13. Antiretroviral Pregnancy Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989 through 31 July 2008. Wilmington, NC: Registry Coordinating Center; 2008. Available from URL: www.APRegistry.com
14. Brogly S, Ylitalo N, Mofenson L, et al. In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. AIDS 2007;21(8):929–938. [PubMed: 17457086]
15. Louik C, Lin A, Werler M, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. New England Journal of Medicine 2007;356(26):2675–2683. [PubMed: 17596601]
16. Correa A, Cragan JD, Kucik ME, et al. Reporting birth defects surveillance data 1968-2003. Birth Defects Research Part A: Clinical and Molecular Teratology 2007;79(2):65–186.

17. Sperling R, Shapiro D, McSherry G, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 Study. AIDS 1998;12(14):1805–1813. [PubMed: 9792381]

18. Lai WW, Lipshultz SE, Easley KA, et al. Prevalence of congenital cardiovascular malformations in children of human immunodeficiency virus-infected women: the prospective P2C2 HIV Multicenter Study. P2C2 HIV Study Group, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Journal of the American Colleges of Cardiology 1998;32(6):1749–1755.

19. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American Colleges of Cardiology 2002;39(12):1890–1900.

20. Brogly S, Read JS, Shapiro D, et al. Participation of HIV-infected pregnant women in research in the United States. AIDS Research and Human Retroviruses 2007;23(1):51–53. [PubMed: 17263632]

21. Dorenbaum A, Cunningham C, Gelber R, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. Journal of the American Medical Association 2002;288(2):189–198. [PubMed: 12095383]

Table 1

Prevalence of at least one major or at least two conditional birth defects by infant characteristic of children in PACTG protocols 219 and 219C.

Characteristic	Birth defect (N=117)		No defect (N=2,085)		P-value*
	N	%	N	%	
HIV infection status					
Infected	13	4.9	254	95.1	0.58
Uninfected	104	5.4	1814	94.6	
Indeterminate	0	0	17	100	
Sex					
Female	50	4.5	1061	95.5	0.09
Male	67	6.1	1024	93.9	
Race/ethnicity					
Non-Hispanic white	17	7.5	209	92.5	0.30
Non-Hispanic black	58	4.6	1199	95.4	
Hispanic	38	5.7	633	94.3	
Other	1	4.0	24	96.0	
Unknown	3	13.0	20	87.0	
Year of birth					
1992 to 1996	26	5.4	454	94.6	0.24
1997 to 2001	54	6.2	820	93.8	
2002 to 2006	37	4.4	811	95.6	
Protocol					
219 ± 219C	58	6.8	794	93.2	0.013
219C only	59	4.4	1291	95.6	
Earliest year of enrollment in 219 or 219C					
1993 to 1996	23	5.5	394	94.5	0.037
1997 to 2000	40	7.3	507	92.7	
2001 to 2006	54	4.4	1184	95.6	
Enrolled in perinatal study during gestation					
Yes	76	8.3	838	91.7	<0.0001
No	41	3.2	1247	96.8	
Maternal age at birth (years)					

Characteristic	Birth defect (N=117)		No defect (N=2,085)		P-value*
	N	%	N	%	
<20	5	3.5	138	96.5	0.049
20 to <25	23	4.6	474	95.4	
25 to <30	32	5.7	534	94.4	
30 to <35	27	5.4	472	94.6	
≥35	21	7.1	274	92.9	
Unknown	9	4.5	193	95.5	
Gestational age at birth (weeks)					
<32	6	12.0	44	88.0	0.33
32 to <37	18	6.3	268	93.7	
≥37	65	6.8	892	93.2	
Unknown	28	3.1	881	96.9	
Birth weight (grams)					
<2,500	28	7.0	370	93.0	0.10
≥ 2,500	89	5.0	1706	95.0	
Unknown	0	0	9	100	
1st trimester in utero folate antagonist exposure					
Unexposed	68	8.0	785	92.0	0.08
Exposed	7	16.3	36	83.7	
Unknown	42	3.2	1264	96.8	
In utero alcohol exposure					
Unexposed	41	5.3	732	94.7	0.25
Exposed	16	7.4	201	92.6	
Unknown	60	5.0	1152	95.0	
In utero tobacco exposure					
Unexposed	35	5.3	621	94.7	0.44
Exposed	20	6.6	284	93.4	
Unknown	62	5.0	1180	95.0	
In utero marijuana exposure					
Unexposed	49	6.1	760	93.9	0.18
Exposed	5	3.3	145	96.7	
Unknown	63	5.1	1180	94.9	

Pediatr Infect Dis J. Author manuscript; available in PMC 2011 August 1.

Characteristic	Birth defect (N=117)		No defect (N=2,085)		P-value*
	N	%	N	%	
In utero cocaine exposure					
Unexposed	47	5.9	754	94.1	0.38
Exposed	8	4.2	181	95.8	
Unknown	62	5.1	1150	94.9	
In utero heroin exposure					
Unexposed	51	5.6	852	94.4	1.00
Exposed	3	5.0	57	95.0	
Unknown	63	5.1	1176	94.9	
In utero methadone exposure					
Unexposed	54	5.7	890	94.3	0.43
Exposed	4	8.5	43	91.5	
Unknown	59	4.9	1152	95.1	

*P-value from Chi-square test, Fisher's exact test (*in utero* heroin exposure) or Cohrane-Armitage trend test (maternal age); subjects with unknown data excluded.

Table 2

Prevalence and odds ratio of at least one major or at least two conditional birth defects according to first trimester *in utero* ARV exposure among children in protocols 219 and 219C*

First trimester *in utero* exposure	Birth defect (N=105)		No defect (N=1,928)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)**
	N	%	N	%		
Any antiretroviral						
Unexposed***	61	4.8	1209	95.2	Ref.	Ref.
Exposed	44	5.8	719	94.2	1.21 (0.81, 1.81)	1.10 (0.72, 1.67)
Nucleoside/nucleotide analogues						
Unexposed	61	4.8	1218	95.2	Ref.	Ref.
Exposed	44	5.8	710	94.2	1.24 (0.83, 1.84)	1.12 (0.73, 1.69)
Abacavir						
Unexposed	100	5.1	1854	94.9	Ref.	Ref.
Exposed	5	6.3	74	93.7	1.25 (0.50, 3.17)	1.50 (0.57, 3.96)
Didanosine						
Unexposed	104	5.2	1882	94.8	Ref.	Ref.
Exposed	1	2.1	46	97.9	0.39 (0.05, 2.88)	0.34 (0.05, 2.57)
Lamivudine						
Unexposed	69	4.7	1394	95.3	Ref.	Ref.
Exposed	36	6.3	534	93.7	1.36 (0.90, 2.06)	1.37 (0.87, 2.16)
Stavudine						
Unexposed	95	5	1814	95	Ref.	Ref.
Exposed	10	8.1	114	91.9	1.68 (0.85, 3.30)	1.53 (0.76, 3.09)
Tenofovir						
Unexposed	101	5.1	1887	94.9	Ref.	Ref.
Exposed	4	8.9	41	91.1	1.82 (0.64, 5.19)	1.39 (0.45, 4.34)
Zidovudine						
Unexposed	72	5	1356	95	Ref.	Ref.
Exposed	33	5.5	572	94.5	1.09 (0.71, 1.66)	0.98 (0.64, 1.52)
Non nucleoside analogues						
Unexposed	97	5.1	1794	94.9	Ref.	Ref.
Exposed	8	5.6	134	94.4	1.10 (0.53, 2.32)	1.46 (0.67, 3.16)

First trimester *in utero* exposure	Birth defect (N=105)		No defect (N=1,928)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)**
	N	%	N	%		
Efavirenz						
Unexposed	100	5	1901	95	Ref.	Ref.
Exposed	5	15.6	27	84.4	3.52 (1.33, 9.34)	4.31 (1.56, 11.86)
Nevirapine						
Unexposed	100	5.2	1815	94.8	Ref.	Ref.
Exposed	5	4.2	113	95.8	0.80 (0.32, 2.01)	1.05 (0.41, 2.70)
Protease inhibitors						
Unexposed	82	4.9	1598	95.1	Ref.	Ref.
Exposed	23	6.5	330	93.5	1.36 (0.84, 2.19)	1.36 (0.81, 2.28)
Indinavir						
Unexposed	101	5.1	1879	94.9	Ref.	Ref.
Exposed	4	7.5	49	92.5	1.52 (0.54, 4.29)	1.50 (0.51, 4.35)
Lopinavir/ritonavir						
Unexposed	99	5	1886	95	Ref.	Ref.
Exposed	6	12.5	42	87.5	2.72 (1.13, 6.55)	2.46 (0.93, 6.52)
Nelfinavir						
Unexposed	92	5.1	1719	94.9	Ref.	Ref.
Exposed	13	5.9	209	94.1	1.16 (0.64, 2.11)	1.23 (0.66, 2.30)
Saquinavir						
Unexposed	104	5.2	1899	94.8	Ref.	Ref.
Exposed	1	3.3	29	96.7	0.63 (0.09, 4.67)	0.46 (0.06, 3.49)

* Four children with trisomy 21 and one child with congenital toxoplasmosis excluded; seven and 157 children with and without birth defects excluded due to unknown timing of *in utero* antiretroviral exposure.

** Adjusted for participation in a PACTG perinatal study, 1st trimester folate antagonist exposure and year of birth.

*** Includes children unexposed to any ARV during gestation (14 children with defects and 272 children without defects) and children exposed to ARV in the 2nd and/or 3rd trimester only.