# Birth Defects Among Children Born to Human Immunodeficiency Virus-Infected Women

## *Pediatric AIDS Clinical Trials Protocols 219 and 219C*

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

**Methods:** A total of 2202 human immunodeficiency virus (HIV)-exposed children enrolled in the Pediatric AIDS Clinical Trials Group 219 and 219 C protocols before 1 year of age were included. Birth defects were classified using the Metropolitan Atlanta Congenital Defects Program coding. Logistic regression models were used to evaluate associations between first trimester in utero ARV exposure and birth defects.

**Results:** A total of 117 live-born children had birth defects for a prevalence of 5.3% (95% confidence interval [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]).

**Conclusions:** 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.

**Key Words:** in utero exposure, antiretroviral therapy, congenital abnormalities/anomalies, HIV

(*Pediatr Infect Dis J* 2010;29: 721–727)

Since 1998, the US Public Health Service has recommended the use of combination antiretroviral therapy (ARV) to prevent mother-to-child human immunodeficiency virus (HIV) transmission.[1] Because zidovudine and other nucleoside analogues can affect nuclear and mitochondrial deoxyribonucleic acid 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 2527 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% confidence interval [CI]: 2.4, 3.5) among greater than 4300 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

Accepted for publication February 8, 2010.

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Supported 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) (to the International Maternal Pediatric Adolescent AIDS Clinical Trials Group [IMPAACT]). 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 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).

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).



ISSN: 0891-3668/10/2908-0721
DOI: 10.1097/INF.0b013e3181e74a2f

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 United States 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 1 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 3 months for HIV-infected children, and every 6 months until 2 years of age (protocol 219), or every 3 months through 1 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 1 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 2 or more conditional defects in the absence of a major defect were considered a case. Therefore, a child with at least 1 major defect or at least 2 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% CI of birth defects per 100 live births was estimated overall, by cohort (219 vs. 219C), and infant HIV-infection status. Differences in birth defect prevalence across these and other characteristics were assessed using the $\chi^2$ test, Fisher 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 $P < 0.25$ 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 5931 children in protocols 219 and 219C, 2202 enrolled by 1 year of age and constituted the study population. Following clinical review of birth defects according to MACDP guidelines, 117 children had at least 1 defect, 103 with at least 1 major defect, and 14 with 2 or more conditional defects but no major defect. Among these 117 children, 77 had 1 birth defect, 30 had 2 birth defects, 6 had 3 birth defects, and 4 had 4 birth defects. 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 (Table, Supplemental Digital Content 1, 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 (ie, 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] vs. 3.5 copies/mL [children without defects]), or lowest median maternal CD4 count (360 cell/mL [children with defects] vs. 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. Figure, Supplemental Digital Content 2, 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. However, significantly more children with birth defects were exposed to efavirenz in the first trimester. The

**TABLE 1.** Prevalence of at Least One Major or at Least 2 Conditional Birth Defects by Infant Characteristic of Children in PACTG Protocols 219 and 219C

| Characteristic | Birth Defect (N = 117) | | No Defect (N = 2085) | | P* |
|---|---|---|---|---|---|
| | 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 | | | | | |
| 1992–1996 | 26 | 5.4 | 454 | 94.6 | 0.24 |
| 1997–2001 | 54 | 6.2 | 820 | 93.8 | |
| 2002–2006 | 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 | | | | | |
| 1993–1996 | 23 | 5.5 | 394 | 94.5 | 0.037 |
| 1997–2000 | 40 | 7.3 | 507 | 92.7 | |
| 2001–2006 | 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 (yr) | | | | | |
| <20 | 5 | 3.5 | 138 | 96.5 | 0.049 |
| 20–<25 | 23 | 4.6 | 474 | 95.4 | |
| 25–<30 | 32 | 5.7 | 534 | 94.4 | |
| 30–<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 (wk) | | | | | |
| <32 | 6 | 12.0 | 44 | 88.0 | 0.33 |
| 32–<37 | 18 | 6.3 | 268 | 93.7 | |
| ≥37 | 65 | 6.8 | 892 | 93.2 | |
| Unknown | 28 | 3.1 | 881 | 96.9 | |
| Birth weight (g) | | | | | |
| <2500 | 28 | 7.0 | 370 | 93.0 | 0.10 |
| ≥2500 | 89 | 5.0 | 1706 | 95.0 | |
| Unknown | 0 | 0 | 9 | 100 | |
| First 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 | |
| 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 $\chi^2$ test, Fisher exact test (in utero heroin exposure), or Cohrane-Armitage trend test (maternal age); subjects with unknown data excluded.

PACTG indicates Pediatric AIDS Clinical Trials Group.

mothers of all 5 cases were taking efavirenz at the time of conception and 3 stopped efavirenz around the time pregnancy would have been identified; the other 2 mothers stopped efavirenz in the second trimester. All mothers of the 5 efavirenz-exposed children with defects also were receiving lamivudine plus other ARV. The defects of these efavirenz exposed children included laryngomalacia (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 6 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 lopinavir/ritonavir was marginally significant ($P = 0.07$). To further explore 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 (Odd ratio [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 (eg, 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 (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A514). Because of the lower number of cases (N = 36 and 34, respectively),[2] 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

**TABLE 2.** Prevalence and Odds Ratio of at Least 1 Major or at Least 2 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 = 1928) | | 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) |
| 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 1 child with congenital toxoplasmosis excluded; 7 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, first 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 second and/or third trimester only.

ARV indicates antiretroviral therapy; OR, Odds Ratio; 95% CI, 95% confidence interval; PACTG, Pediatric AIDS Clinical Trials Group.

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 zidovudine. In contrast, significantly more children with heart defects—MACDP category of heart, other, which excludes conotruncal and obstructive defects (Table, Supplemental Digital Content 1, 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 3 studies were examined because birth defect information was collected and reviewed in these studies by the 076, 316, and P1025 investigators. 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 defects (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 1 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 1 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 (1 case of meningomyelocele and 1 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. A total of 636 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 of 5% to 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 nondifferential 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 the Women and Infants Transmission Study[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.

## ACKNOWLEDGMENTS

*The following institutions and individuals participated in PACTG Protocols 219 and/or 219C: Baylor Texas Children's Hospital: F. Minglana, M. E. Paul, C. D. Jackson; University of Florida, Jacksonville: M. H. 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, M. E. Texidor; University of Miami: G. B. Scott, C. D. 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 and Earl K. Long Early Intervention Clinic: M. Silio, T. Alchediak, C. Boe, M. Cowie; UCSD Mother, Child & Adolescent HIV Program: S. A. Spector, R. Viani, M.*

*Caffery, L. Proctor; Howard University: S. Rana, D. Darbari, J. C. Roa, P. H. 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: B. W. Stechenberg, D. J. Fisher, A. M. Johnston, M. Toye; Los Angeles County Medical Center/USC: J. Homans, M. Neely, L. S. 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: P. M. 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, H. J. Moallem, D. M. Swindell, J. M. Kaye; The Columbia Presbyterian Medical Center and Cornell University New York Presbyterian Hospital: A. Higgins, M. Foca, P. LaRussa, A. Gershon; The Children's Hospital of Philadelphia: R. M. Rutstein, C. A. Vincent, S. D. Douglas, G. A. 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: V. R. Bonagura, S. J. Schuval, C. Colter, L. Campbell; Boston Medical Center: S. I. Pelton, A. M. Reagan; University of Illinois: K. C. 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, E. J. 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: L. B. Weiner, K. A. Contello, W. A. Holz, M. J. 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: A. D. Fernandez, P. A. Hughes, N. Wade, M. E. Adams; Lincoln Medical & Mental Health Center; Phoenix Children's Hospital: J. P. Piatt, J. Foti, L. Clarke-Steffen; Public Health Unit of Palm Beach County: J. Sleasman, C. Delaney; Medical College of Georgia: C. S. Mani; Yale University School of Medicine: W. A. Andiman, S. Romano, L. Hurst, J. de Jesus; Vanderbilt University Medical Center: G. Wilson; University of Rochester Medical Center: G. A. 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: R. G. Fisher, K. M. Cunnion, T. T. Rubio, D. Sandifer; Medical University of South Carolina: G. M. 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: S. R. Lavoie, T. Y. 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: K. A. McGann, L. Pickering, G. A. Storch; North Shore University Hospital: S. Pahwa, L. Rodriquez; Oregon Health and Science University: P. Lewis, R. Croteau.*

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# Current Abstracts

*Edited by: Robert J. Leggiadro, MD*

## Multistate Outbreaks of Human *Salmonella typhimurium* Infections Associated With Pet Turtle Exposure—United States, 2008

Centers for Disease Control and Prevention. *MMWR*. 2010;59:191–196.

In September 2008, the Philadelphia Department of Public Health and the Pennsylvania Department of Health notified Centers for Disease Control and Prevention of an outbreak of possible turtle-associated human *Salmonella typhimurium* infections detected by identifying strains with similar pulsed-field gel electrophoresis patterns in PulseNet, a national molecular subtyping network for foodborne disease surveillance. The results of that investigation are summarized in this report.

A total of 135 cases in 25 states and the District of Columbia were identified in the national PulseNet database. Among 124 patients for whom demographic information was available, median age was 7 years (range: <1–94 years), and 54 (45%) patients were aged 5 years or younger; 63 (51%) were female. Seventy-eight percent of illnesses occurred during June to September.

Of 83 patients interviewed using a more extensive questionnaire, 35 (42%) had bloody diarrhea and 29 (35%) were hospitalized. No deaths were reported. Twenty (24%) of the 83 patients attended day care. Of 70 patients with primary cases, 26 (37%) reported exposure to turtles and 21 reported exposure to small turtles.

Among the 69% of patients who knew the source of the turtle, the majority of turtles were purchased from street vendors, flea markets, and nonpet stores (eg, souvenir or gift shops). Seven (10%) of the 70 primary patients reported other reptile exposures (eg, snakes or iguanas).

The Federal government prohibited sales of turtles with shell lengths <4 inches in 1975, after investigations demonstrated that small turtles were a major source of human *Salmonella* infections, particularly in children. Implementation of the prohibition resulted in a substantial decline in turtle-associated human salmonellosis, preventing an estimated 100,000 *Salmonella* infections annually in US children. Turtle-associated human salmonellosis cases continue to occur because the prohibition is not fully enforced and contains exceptions (eg, sales for bona fide scientific, educational, or exhibition purposes). Street vendors and flea markets are a common source of illegal sales.

This *S. typhimurium* outbreak is the third multistate, turtle-associated *Salmonella* outbreak in the United States since 2006. Before 2006, no large multistate turtle-associated *Salmonella* outbreaks were identified. One reason for this apparent increase might be PulseNet, which has improved the ability to detect multistate outbreaks. Increased pet turtle ownerships in the United States also might contribute to recent outbreaks.

Despite recommendations from Centers for Disease Control and Prevention to prevent turtle-associated salmonellosis in humans, recent outbreaks suggest that public education efforts have not been successful. Although many reptiles carry *Salmonella*, small turtles pose a greater risk to young children because they are perceived as safe pets, are small enough to be placed in the mouth, or otherwise can be handled inappropriately.

Direct or indirect reptile contact is associated with an estimated 6% of *Salmonella* infections in the United States and 11% of infections among persons younger than 21 years. Increasing enforcement of existing local, state, and federal regulations against the sale of small turtles, increasing penalties for illegal sales, and enacting more state and local laws regulating the sale of small turtles (eg, requiring *Salmonella* awareness education at the point of sale) could augment federal prevention efforts and facilitate a more rapid public health response.