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Prevalence of Congenital Anomalies in Infants with *in Utero* Exposure to Antiretrovirals

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Abstract

Background—While use of efficacious interventions, including antiretrovirals (ARVs), has reduced dramatically the rate of mother-to-child transmission (MTCT) of HIV, the safety of *in utero* ARV exposure remains of concern.

Methods—Data regarding 1112 infants enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPACT) protocol P1025 born between 2002 and 2007 were analyzed for this study. Congenital anomalies were classified based on the Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines. Associations between congenital anomalies and timing of first *in utero* exposure to ARVs were evaluated by logistic regression analysis.

Results—61 of the 1112 infants had congenital anomalies identified and confirmed, resulting in a prevalence of 5.49/100 live births (95%CI: 4.22–6.99). Among the 80 anomalies identified, the organ systems involved included: cardiovascular (n=33), musculoskeletal (n=15), renal (n=9), genitourinary (n=6), craniofacial (n=4), and central nervous system (n=2). First trimester exposure

to efavirenz was associated with a significantly increased risk of congenital anomalies (OR 2.84, 95% CI: 1.13–7.16). No significant associations were observed between exposure to other individual ARVs or classes of ARVs started at any time during pregnancy and infant congenital anomalies.

Conclusions—The observed rate of congenital anomalies in this cohort is higher than previously reported for the general population, but is consistent with rates observed in other recent studies of children born to HIV-infected women. Cardiovascular anomalies occurred most frequently. With the exception of a known teratogen (efavirenz), no statistically significant associations between *in utero* exposure to ARVs and congenital anomalies were identified.

Keywords

congenital anomalies; *in utero* exposure; HIV; antiretroviral

INTRODUCTION

Use of antiretrovirals (ARVs) for prevention of mother-to-child transmission (pMTCT) of HIV has been advocated since 1994 (1), when the results of the groundbreaking Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 (2) were made available. PACTG 076 demonstrated a reduction in mother-to-child transmission from 22.6% in the placebo group to 7.6% with use of a three-part regimen of zidovudine. (2, 3) Zidovudine and other nucleoside reverse transcriptase inhibitors (NRTIs) have putative fetal safety concerns based on the incorporation of these ARVs into human nuclear and mitochondrial DNA and the depletion of mitochondrial DNA in laboratory and animal studies. (4–8) With the subsequent availability of additional ARVs, use of combination ARV regimens during pregnancy, whether for treatment of the mother's own HIV infection or for pMTCT, has been associated with lower rates of MTCT. (9–11) It is now recommended that HIV-infected pregnant women receive combination ARV regimens with at least three agents, one of which should be a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). (12) Although zidovudine has been used for years for pMTCT, there is relatively little experience with the newer ARVs, and concerns exist regarding potential adverse effects of *in utero* ARV exposure. In particular, efavirenz, a frequently-used NNRTI, is not recommended for use by pregnant women (FDA Pregnancy Category D, positive evidence of fetal risk) based upon evidence from non-human primate data and case reports of neural tube defects. (12–16) As newer ARV classes and agents become available, and ARV regimens more complex, continued surveillance of congenital anomalies of infants exposed to ARVs is vital.

IMPACT protocol P1025 prospectively collected data on pregnant HIV-infected women and their infants. The objectives of this study were to estimate the prevalence of congenital anomalies in this population, and to assess the association between *in utero* exposure to ARVs and congenital anomalies.

METHODS

P1025 Protocol

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPACT) Group protocol P1025 is a prospective, observational study designed to assess use and outcomes of ARVs during pregnancy and interventions for pMTCT (including ARV prophylaxis). Enrollment into P1025 began in October 2002 and is ongoing. HIV-infected women ≥ 13 years of age were eligible for enrollment after the 8th week of pregnancy up to 14 days following delivery. Women diagnosed with HIV infection at the time of delivery or within

14 days following delivery were eligible to enroll up to 28 days after delivery. All infants born to enrolled mothers were eligible for enrollment. Infant protocol visits including physical examination were scheduled at birth, within the first seven days of life, and at two, six, 16, 24, 36, and 48 weeks of age. Potential congenital anomalies were identified by physical examination at the study sites and/or through review of prenatal and neonatal records. Case report forms completed at each visit asked whether any congenital anomalies had been identified.

Study Population

The study population consisted of children born to HIV-infected women enrolled in P1025. Data available as of October 26, 2007 were analyzed. Eligible infants were those with an estimated delivery date on or before September 10, 2007 and for whom the congenital anomaly case report form had been submitted. In order to ensure that infant outcomes reasonably could be considered independent of one another, only infants who were singleton births and whose mothers had not participated in the protocol during previous pregnancies were included.

Outcome

Data for infants identified through computerized screening as having congenital anomalies recorded on clinical case report forms were reviewed by a panel of clinicians who were blinded to the mother's ARV exposure during pregnancy. Definitive classification of a congenital anomaly was made by clinician consensus, using the Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines. (17)

ARV Exposure and Possible Confounders

Any ARV to which at least one infant with an identified congenital anomaly was exposed *in utero* was evaluated for this study. Due to known reports of adverse infant outcomes associated with *in utero* exposure to folate antagonists (18–21) and selective serotonin-reuptake inhibitor (SSRI) antidepressants (22–23), and maternal substance use (including alcohol, tobacco, marijuana, cocaine, heroin, and methadone) during pregnancy (24–25), we assessed the occurrence of anomalies in relation to *in utero* exposure to these drugs.

Statistical Analysis

Group comparisons were performed using the chi-square test or Fisher exact test (when expected cell frequencies were small) for nominal variables and the Cochran–Mantel–Haenszel chi-square test for ordinal variables. A two-sided p-value < 0.05 was defined as statistically significant. Logistic regression was used to estimate associations between the timing of initial *in utero* exposure to ARVs and the presence of an anomaly. For each ARV evaluated, exposure was categorized as either starting in the first trimester, starting in the second or third trimester, or unexposed. A priori, it was decided to consider all covariates with a univariate p-value less than or equal to 0.25 and folate antagonist use (regardless of p-value) for inclusion in the multivariate model for each ARV using a stepwise selection algorithm. This algorithm selected only those covariates with a p-value less than or equal to 0.15 when entered into a model that also included the ARV exposure variable (and other covariates selected at earlier steps). Analyses were conducted using SAS 9.1 (SAS Institute, Cary NC) and LogXact 8 (Cytel Inc, Cambridge MA) software.

RESULTS

Derivation of the Study Population and Congenital Anomalies in This Population

Of 1306 enrolled infants, 1112 met inclusion criteria for this analysis (see Figure, Supplemental Digital Content 1). Congenital anomalies were identified in 61 of the 1112 infants. The prevalence of congenital anomalies in this population was 5.49/100 live births (95% confidence interval: 4.22–6.99). There were 80 anomalies identified in these 61 infants, the most common of which were cardiovascular (33 of 80, 41.3%), followed by musculoskeletal anomalies (15 of 80, 18.8%) (see Table, Supplemental Digital Content 2)

Prevalence of Congenital Anomalies According to Maternal and Infant Characteristics

Table 1 shows the prevalence of congenital anomalies according to maternal and infant characteristics. There were no statistically significant differences in the presence or absence of congenital anomalies according to any maternal characteristic shown. The only infant characteristic associated with congenital anomalies was birth weight; those with low birth weight (<2500 grams) were statistically significantly more likely to have congenital anomalies.

Association between Antiretroviral Exposure and Presence or Absence of Congenital Anomalies

Table 2 shows the prevalence of congenital anomalies for ARV classes and individual drugs within each class by timing of first *in utero* exposure. Earliest ARV use during pregnancy was divided approximately evenly between first trimester and second/third trimester. There were only 12 children unexposed to ARVs *in utero*, and none of these was diagnosed with a congenital anomaly. Of those with first ARV exposure during the first trimester or second/third trimester, 6.4% and 4.8%, respectively, were reported to have congenital anomalies.

Table 2 also shows the results of the multivariate logistic regression analyses. Those covariates in Table 1 with a p-value less than or equal to 0.25 (i.e., maternal characteristics: age, alcohol use, selective serotonin-reuptake inhibitor (SSRI) use; infant characteristics: year of birth, birth weight and HIV infection status) and folate antagonist use were entered into the stepwise selection algorithm. The same four covariates (maternal age at enrollment, infant year of birth, birth weight and infant HIV infection status) were selected for the model for each ARV. In the multivariate logistic regression analyses, the only statistically significant association of an ARV with risk of congenital anomalies was for efavirenz exposure during the first trimester (adjusted OR 2.84, 95% confidence interval: 1.13–7.16). Six (12.8%) of the 47 infants with first trimester exposure to efavirenz had congenital anomalies, which were identified as patent foramen ovale (N = 1), gastroschisis (N = 1), postaxial polydactyly, Type A (N = 1), spina bifida cystica, Arnold-Chiari malformation (N = 1), talipes equinovarus (N = 1) and plagiocephaly (N = 1).

DISCUSSION

In this prospective study of outcomes in HIV-pregnant women and their infants, eighty congenital anomalies were identified in 61 of 1112 infants, yielding a congenital anomaly rate of 5.49/100 live births. First trimester efavirenz exposure was associated with a significantly increased risk of congenital anomalies (6 of 47, 12.8%).

Our findings support previous reports associating efavirenz exposure during the first trimester with congenital anomalies. (26–28) Since efavirenz was first approved by the Food and Drug Administration in 1998, the package labeling has carried a warning about use in pregnancy, based upon animal data indicating an increased risk of developmental anomalies.

(26) Three of 20 infant cynomolgus monkeys exposed to efavirenz throughout gestation at levels equivalent to those seen in humans had congenital anomalies (anencephaly and unilateral anophthalmia, microphthalmia, and cleft palate), compared with none of 20 monkeys in the control group. In 2005, Bristol-Myers Squibb changed the pregnancy category of efavirenz from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk), based upon four retrospective reports of neural tube defects (three cases of meningomyelocele and one case of Dandy Walker Syndrome) in infants exposed to efavirenz during the first trimester. (27) In a review of data from Pediatric AIDS Clinical Trials Group (PACTG) protocols 219 and 219C, investigators identified congenital anomalies in five of 32 infants (15.6%) exposed to efavirenz during the first trimester (adjusted OR 4.31, 95% CI: 1.56, 11.86), only one of which was a neural tube defect. (28) In the 219/219C study there was a congenital anomaly rate of 5.3/100 live births, very similar to the rate observed in our study. The data from 219/219C provide the first evidence of an association of efavirenz with congenital anomalies in a population-based study, although the number of infants with first trimester efavirenz exposure was small. It should be noted that some participants in PACTG 219C were also enrolled in P1025. However, only 15 cases overall were common to both studies, including two children exposed to efavirenz (a case of talipes equinovarus and a neural tube anomaly that had been previously reported). (15)

The prevalence of congenital anomalies in the P1025 study population (5.49/100 live births) is higher than that reported for the general population of the United States (approximately 3/100 live births). (29) Some studies of congenital anomalies among HIV-exposed infants with intrauterine exposure to ARVs have shown prevalences more similar to that of the general population. (Table 3). For example, the prevalence of congenital anomalies among infants with *in utero* exposure to ARVs was 2.9% for the Antiretroviral Pregnancy Registry, (30) 2.8–3.1.% for the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland, (31) and 3.56% for the Women and Infants Transmission Study. (32) Even lower prevalence of congenital anomalies has been reported from the European Collaborative Study (1.6%). (33) However, other studies of HIV-infected women and their infants have documented higher rates of congenital anomalies. (28, 34) Our observed prevalence is similar to the more recent reports from the 219/219C study (28) and from the National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) analysis of congenital anomalies among HIV-infected women in Argentina and Brazil. (34) In the NISDI cohort, the overall rate of congenital anomalies for infants born to HIV-infected women was 6.16/100 live births [95% confidence interval 4.6 to 7.7]. As in the current study, approximately 4% of the women in the NISDI cohort had first trimester exposure to efavirenz. In contrast to the P1025 and 219/219C data, there was no evidence of an association of efavirenz with congenital anomalies in the NISDI cohort. (34)

There are differences among the various studies of congenital anomalies in children exposed to antiretrovirals *in utero* that may account for the varying prevalence rates reported. Of the studies mentioned, ours demonstrated the highest percentage of infants (46.5%) with earliest *in utero* exposure to any ARV during the first trimester. Congenital anomalies may be under-reported in some of the studies. Differential ascertainment across the studies may explain differences in prevalence. In the 219/219C study, for which the cardiovascular system was the most common site for congenital anomalies, 29% of all infants had echocardiograms, most of which were required for clinical research. (28) Non-ARV drug exposure could account for differences in prevalence: for example, folate antagonist use was evaluated in the 219/219C study, (28) the NISDI study, (34) and in the current study, but was not specifically addressed in the other studies. The studies also differ in the number of infants evaluated.

As with the data from 219/219C, (28) the most common anomalies in our study were cardiovascular, followed by musculoskeletal. In 219/219C, first trimester exposure to zidovudine was associated with a higher risk of cardiovascular anomalies and a lower risk of musculoskeletal anomalies. Due to limited power, we were not able to assess for such associations in this review.

To address possible confounding factors, multivariate models were adjusted for year of birth, maternal age, gestational age at birth, birth weight, and infant HIV infection status. Maternal substance use (alcohol, tobacco, marijuana, cocaine, heroin and methadone) and *in utero* exposure to folate antagonists and selective serotonin-reuptake inhibitor (SSRI) antidepressants did not enter the multivariate models and were not significantly associated with presence of congenital anomalies in univariate analyses. Combination ARV regimens, whether for treatment or for pMTCT, are recommended during pregnancy. It is not possible to adjust for all other ARV agents when assessing the association of a given ARV with infant congenital anomalies.

The results of this study are consistent with the results of other recent cohort studies suggesting higher prevalences of congenital anomalies among infants born to HIV-infected women than have been reported for the general population. With the exception of a known teratogen (efavirenz), no statistically significant associations between *in utero* exposure to ARVs and congenital anomalies were identified. Our inability to identify other significant associations in this analysis may be due to lack of power; the limits of the 95% confidence intervals for the adjusted odds ratios indicate the magnitude of associations that are unlikely based on our results (i.e., those associations lying outside the confidence interval). Further research is indicated to evaluate for possible confounding factors. Information available from voluntary retrospective reporting of anomalies is limited by selection bias, in that adverse outcomes may be over-reported. The Antiretroviral Pregnancy Registry collects both prospective and retrospective data, and analyzes them separately. Clinicians caring for HIV-infected pregnant women are encouraged to report prospectively all women receiving ARVs during pregnancy to the Antiretroviral Pregnancy Registry (www.APRRegistry.com), whether or not anomalies are identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Prevalence of congenital anomalies according to maternal and infant characteristics

Characteristic		Congenital Anomaly		P-Value
		Yes (N=61)	No (N=1051)	
Maternal characteristics				
Age at enrollment (years)	≤ 24	25 (7%)	337 (93%)	0.11 ^(a)
	25–34	32 (5%)	554 (95%)	
	≥ 35	4 (2%)	160 (98%)	
Mode of delivery	Vaginal	33 (6%)	497 (94%)	0.31 ^(a)
	Cesarean section	28 (5%)	552 (95%)	
	Unknown	0 (0%)	2 (100%)	
Alcohol use during pregnancy	No	44 (6%)	659 (94%)	0.14 ^(a)
	Yes	12 (4%)	292 (96%)	
	Unknown	5 (5%)	100 (95%)	
Tobacco use during pregnancy	No	30 (5%)	601 (95%)	1.00 ^(a)
	Yes	9 (5%)	180 (95%)	
	Unknown	22 (8%)	270 (92%)	
Marijuana use during pregnancy	No	41 (5%)	722 (95%)	0.79 ^(a)
	Yes	5 (5%)	100 (95%)	
	Unknown	15 (6%)	229 (94%)	
Cocaine use during pregnancy	No	42 (5%)	744 (95%)	0.72 ^(b)
	Yes	1 (2%)	40 (98%)	
	Unknown	18 (6%)	267 (94%)	
Heroin use during pregnancy	No	40 (5%)	750 (95%)	1.00 ^(b)
	Yes	0 (0%)	14 (100%)	
	Unknown	21 (7%)	287 (93%)	
Methadone use during pregnancy	No	55 (6%)	933 (94%)	0.50 ^(b)
	Yes	1 (8%)	11 (92%)	
	Unknown	5 (4%)	107 (96%)	
CDC clinical stage at enrollment	A	47 (5%)	860 (95%)	0.52 ^(a)
	B	6 (8%)	67 (92%)	
	C	8 (6%)	124 (94%)	
Timing of initiation of prenatal care	1st trimester	41 (6%)	649 (94%)	0.73 ^(b)
	2nd trimester	15 (5%)	315 (95%)	
	3rd trimester	5 (7%)	71 (93%)	
	Labor & delivery	0 (0%)	6 (100%)	
	Unknown	0 (0%)	10 (100%)	
Timing of HIV diagnosis	Before pregnancy	45 (6%)	721 (94%)	0.40 ^(a)
	During pregnancy	16 (5%)	329 (95%)	
	Unknown	0 (0%)	1 (100%)	

Characteristic		Congenital Anomaly		P-Value
		Yes (N=61)	No (N=1051)	
Plasma HIV RNA concentration (copies/mL) near labor & delivery	< 400	50 (6%)	800 (94%)	0.32 ^(a)
	≥ 400	10 (5%)	185 (95%)	
	Not evaluated	0 (0%)	35 (100%)	
	Unknown	1 (3%)	31 (97%)	
Earliest ARV use during pregnancy	Unexposed	0 (0%)	12 (100%)	0.37 ^(a)
	1st trimester	33 (6%)	484 (94%)	
	2nd/3rd trimester	28 (5%)	554 (95%)	
	Unknown	0 (0%)	1 (100%)	
Earliest folate antagonist use during pregnancy	Unexposed	47 (5%)	840 (95%)	0.63 ^(a)
	1st trimester	8 (7%)	99 (93%)	
	2nd/3rd trimester	6 (5%)	112 (95%)	
Earliest selective serotonin-reuptake inhibitor (SSRI) use during pregnancy	Unexposed	58 (5%)	1,009 (95%)	0.11 ^(b)
	1st trimester	0 (0%)	25 (100%)	
	2nd/3rd trimester	3 (15%)	17 (85%)	
<i>Infant characteristics</i>				
Gender	Male	30 (6%)	513 (94%)	0.96 ^(a)
	Female	31 (5%)	538 (95%)	
Race	White Non-Hispanic	6 (6%)	90 (94%)	0.34 ^(a)
	Black Non-Hispanic	27 (4%)	589 (96%)	
	Hispanic	25 (7%)	331 (93%)	
	Other/Unknown	3 (7%)	41 (93%)	
Year of birth	2002	0 (0%)	5 (100%)	0.11 ^(c)
	2003	4 (3%)	148 (97%)	
	2004	14 (6%)	210 (94%)	
	2005	14 (5%)	265 (95%)	
	2006	18 (6%)	294 (94%)	
	2007	11 (8%)	129 (92%)	
Preterm birth (< 37 completed weeks of gestation)	Yes	13 (7%)	178 (93%)	0.38 ^(b)
	No	48 (5%)	873 (95%)	
Low birth weight (< 2500 grams)	Yes	15 (10%)	138 (90%)	0.01 ^(a)
	No	46 (5%)	903 (95%)	
	Unknown	0 (0%)	10 (100%)	
HIV infection status	Infected	2 (29%)	5 (71%)	0.06 ^(b)
	Uninfected	58 (6%)	992 (94%)	
	Unknown	1 (2%)	54 (98%)	

^(a) Chi-Square Test

^(b) Fisher's Exact Test

^(c) Cochran-Mantel-Haenszel Chi-Square

Table 2Association of trimester of first *in utero* ARV exposure and congenital anomalies

Timing of first <i>in utero</i> ARV exposure		Child has anomaly?		Adjusted odds ratio (95% CI)*
		Yes (N=61)	No (N=1051)	
Any NRTI	Unexposed	1 (7.1%)	13 (92.9%)	
	1st trimester	32 (6.3%)	480 (93.8%)	0.84 (0.11, 39.45)
	2nd/3rd trimester	28 (4.8%)	557 (95.2%)	0.62 (0.08, 29.05)
Lamivudine	Unexposed	5 (3.8%)	127 (96.2%)	
	1st trimester	25 (6.0%)	393 (94.0%)	1.68 (0.61, 4.58)
	2nd/3rd trimester	31 (5.5%)	530 (94.5%)	1.52 (0.56, 4.08)
Abacavir	Unexposed	40 (5.0%)	759 (95.0%)	
	1st trimester	9 (6.7%)	126 (93.3%)	1.45 (0.68, 3.10)
	2nd/3rd trimester	12 (6.8%)	165 (93.2%)	1.25 (0.62, 2.51)
Stavudine	Unexposed	57 (5.5%)	984 (94.5%)	
	1st trimester	2 (4.3%)	45 (95.7%)	1.02 (0.12, 4.24)
	2nd/3rd trimester	2 (8.7%)	21 (91.3%)	1.43 (0.15, 6.71)
Didanosine	Unexposed	57 (5.5%)	975 (94.5%)	
	1st trimester	4 (7.5%)	49 (92.5%)	1.61 (0.40, 4.73)
	2nd/3rd trimester	0 (0.0%)	26 100.0%	N/A (0, 3.60)
Emtricitabine	Unexposed	54 (5.5%)	936 (94.5%)	
	1st trimester	5 (7.9%)	58 (92.1%)	1.33 (0.49, 3.60)
	2nd/3rd trimester	2 (3.4%)	56 (96.6%)	0.56 (0.06, 2.31)
Tenofovir	Unexposed	45 (5.1%)	831 (94.9%)	
	1st trimester	11 (8.0%)	127 (92.0%)	1.69 (0.83, 3.44)
	2nd/3rd trimester	5 (5.2%)	92 (94.8%)	1.01 (0.38, 2.65)
Zidovudine	Unexposed	10 (5.3%)	177 (94.7%)	
	1st trimester	20 (5.6%)	336 (94.4%)	1.02 (0.45, 2.28)
	2nd/3rd trimester	31 (5.5%)	537 (94.5%)	1.02 (0.48, 2.17)
Any NNRTI	Unexposed	49 (5.4%)	857 (94.6%)	
	1st trimester	9 (7.1%)	118 (92.9%)	1.53 (0.72, 3.25)
	2nd/3rd trimester	3 (3.8%)	75 (96.2%)	0.77 (0.14, 2.69)
Efavirenz	Unexposed	55 (5.2%)	1000 (94.8%)	
	1st trimester	6 (12.8%)	41 (87.2%)	2.84 (1.13, 7.16)
	2nd/3rd trimester	0 (0.0%)	9 100.0%	N/A (0, 9.05)
Nevirapine	Unexposed	53 (5.6%)	901 (94.4%)	
	1st trimester	5 (5.8%)	81 (94.2%)	1.28 (0.49, 3.35)
	2nd/3rd trimester	3 (4.2%)	68 (95.8%)	0.86 (0.16, 2.98)
Any PI	Unexposed	14 (4.6%)	293 (95.4%)	
	1st trimester	22 (6.4%)	324 (93.6%)	1.32 (0.64, 2.71)
	2nd/3rd trimester	25 (5.5%)	433 (94.5%)	1.15 (0.58, 2.29)
Atazanavir	Unexposed	53 (5.3%)	954 (94.7%)	
	1st trimester	6 (9.2%)	59 (90.8%)	1.83 (0.73, 4.58)

		Child has anomaly?		
Timing of first <i>in utero</i> ARV exposure		Yes (N=61)	No (N=1051)	Adjusted odds ratio (95% CI)*
Fosamprenavir	2nd/3rd trimester	2 (5.1%)	37 (94.9%)	0.87 (0.10, 3.65)
	Unexposed	57 (5.3%)	1017 (94.7%)	
	1st trimester	1 (5.6%)	17 (94.4%)	1.18 (0.03, 8.28)
Lopinavir/Ritonavir	2nd/3rd trimester	3 (15.8%)	16 (84.2%)	3.19 (0.52, 13.05)
	Unexposed	43 (5.3%)	762 (94.7%)	
	1st trimester	11 (8.5%)	119 (91.5%)	1.66 (0.81, 3.38)
Nelfinavir	2nd/3rd trimester	7 (4.0%)	169 (96.0%)	0.80 (0.35, 1.82)
	Unexposed	39 (5.8%)	638 (94.2%)	
	1st trimester	5 (3.3%)	148 (96.7%)	0.44 (0.16, 1.27)
Ritonavir	2nd/3rd trimester	17 (6.0%)	264 (94.0%)	1.00 (0.55, 1.82)
	Unexposed	51 (5.2%)	929 (94.8%)	
	1st trimester	6 (8.5%)	65 (91.5%)	1.60 (0.64, 3.99)
Saquinavir	2nd/3rd trimester	4 (6.7%)	56 (93.3%)	1.18 (0.29, 3.54)
	Unexposed	59 (5.4%)	1031 (94.6%)	
	1st trimester	1 (8.3%)	11 (91.7%)	1.33 (0.03, 10.26)
	2nd/3rd trimester	1 (11.1%)	8 (88.9%)	1.64 (0.04, 13.41)

ARV = antiretroviral, NRTI = nucleoside/nucleotide reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

* The odds ratios were adjusted for infant HIV status, year of birth, birth weight, and maternal age at enrollment. When cell counts were small, exact logistic regression was used to obtain estimates. The odds ratio estimate could not be computed when there was a zero cell count.

Table 3

Comparison of Studies Evaluating ARV Exposure and Congenital Anomalies

	ECS (33)	NSHPC (31)	WTIS (32)	219/219C (28)	P1025	NISDI (34)
Number of infants evaluated	1,767	8,242	2,527	2,202	1,112	974
Congenital anomaly prevalence, (95% CI)	1.5%	2.8% (2.5–3.2%)	3.56% (2.89–4.38%)	5.3% (4.4–6.3%)	5.49% (4.22–6.99%)	6.16% (4.60–7.72%)
Study period included in analysis	1986–2003	1990–2007	1990–2004	1993–2000	2002–2007	2002–2007
Evaluations	Per clinical care	Investigators contacted infants' physicians for follow-up (no specified time period)	Scheduled study visits during infancy, follow-up visits every 6 months beginning at 12 months of age	Scheduled study visits every 6 months until 2 years of age then annually (protocol 219) or every 3 months until 12 months of age then annually (protocol 219C)	Scheduled study visits at birth, within the first 7 days of life, and at 2, 6, 16, 24, 36, and 48 weeks of age.	Scheduled study visits at birth, 6–12 weeks of age, and 6 months of age
Race/ethnicity/country of residence	White: 72% Black African: 21% Black(other): 4%	White: 15.7% Black African: 76.4%	White: 13.3% Black: 37.5% Hispanic: 25.6%	White: 10.3% Black: 57.1% Hispanic: 30.5%	White: 8.6% Black: 55.4% Hispanic: 32%	Argentina: 34.6% Brazil: 65.4%
1 st trimester ARV exposure	40%	22.4%	29.8%	34.7%	46.5%	25%
1 st trimester NNRTI exposure	30%	58.7%	13.4%	7%	11.4%	10.1%
1 st trimester EFV exposure	0.5%	2.5%	1.2%	1.5%	4.2%	4.3%
1 st trimester PI exposure	39.8%	38.4%	39.6%	17.4%	31.1%	9.4%

ARV = antiretroviral, NRTI = nucleoside/nucleotide reverse transcriptase inhibitor, EFV = efavirenz, PI = protease inhibitor, ECS = European Collaborative Study, NSHPC = National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland, WTIS = Women and Infants Transmission Study, 219/219C = Pediatric AIDS Clinical Trials Group (PACTG) protocols 219 and 219C, P1025 = (the current study) International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group protocol P1025, NISDI = National Institute of Child Health and Human Development (NICHD) International Site Development Initiative