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Congenital Anomalies and *in utero* Antiretroviral Exposure in HIV-exposed Uninfected Infants

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Abstract

Importance—Most studies examining the association of prenatal antiretroviral exposures with congenital anomalies (CAs) in children born to HIV-infected women have been reassuring, but some suggest increased risk with specific antiretrovirals.

Objectives—To evaluate associations of *in utero* antiretroviral exposures with CAs in HIV-exposed uninfected children.

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Contributions: PLW and DHW were the primary authors who conceived and designed the study. PLW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PLW was responsible for conducting statistical analyses, and led the writing of the manuscript. MC, CY, RH, RBV, KR, JSR, ES, MR, HM, and DHW provided input on the study design, interpretation of analyses, and revisions to manuscript. Tulane University receives financial support from Gilead Sciences for partial support of the PHACS project. Dr Van Dyke receives no salary support or other funds from this funding source. All other authors declare that they have no conflicts of interest related to this manuscript.

Design—prospective cohort study, the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring of ART Toxicities (SMARTT) study.

Setting—22 US medical centers

Participants—2580 HIV-exposed, uninfected children enrolled in SMARTT between 2007–2012.

Exposures—First trimester exposure to any antiretroviral and to specific antiretroviral medications.

Main Outcome—The primary endpoint was a CA, based on clinician review of infant physical examinations according to the Antiretroviral Pregnancy Registry modification of the Metropolitan Atlanta Congenital Defects Program. Rates of CAs were estimated overall and by birth year. Logistic regression models were used to evaluate associations of CAs with first trimester antiretroviral exposures, adjusting for demographic and maternal characteristics.

Results—CAs occurred in 175 of 2580 children, yielding a prevalence of 6.78% (95% CI: 5.85–7.82%); there were 242 confirmed major CAs (72 musculoskeletal, 55 cardiovascular). The prevalence of CAs increased significantly in successive birth cohorts (3.8% for children born <2002 up to 8.3% for 2008–2010). In adjusted models, there was no association of first trimester exposures to any antiretroviral, to combination antiretroviral regimens, or to any drug class with CAs. No individual antiretroviral in the reverse transcriptase inhibitor drug classes was associated with increased risk of CAs. Among protease inhibitors, higher odds of CAs were observed for atazanavir (adjusted odds ratio (aOR)=1.93, 95% confidence interval (CI):1.23,3.03) and for ritonavir used as a booster (aOR=1.52, 95%CI: 1.08,2.14). With first trimester atazanavir, risks were highest for skin and musculoskeletal CAs (aORs=5.24 and 2.55, respectively).

Conclusions and Relevance—Few individual antiretrovirals and no drug classes were associated with increased risk of CAs after adjustment for calendar year and maternal characteristics. While the overall risk remained low, there was a relative increase in successive years and with atazanavir exposure. Given the low absolute CA risk, the benefits of recommended ARV use during pregnancy still outweigh such risks, although further studies are warranted.

Introduction

The use of combination antiretroviral (ARV) regimens for prevention of mother-to-child transmission of HIV and for treatment of HIV-infected pregnant women has contributed to a substantial reduction in HIV-infected infants.[1] However, the safety of *in utero* exposure to such combination ARV regimens remains a concern, particularly as newer agents are approved and an increasing percentage of women enter pregnancy already on ARV therapy.[2]

Most prior studies examining the risk of congenital anomalies (CAs) according to *in utero* ARV exposure have been reassuring, but a few have suggested increased risk of CAs overall, or for certain CAs with specific ARVs.[3–13] In the international Antiretroviral Pregnancy Registry (APR), the estimated prevalence of CAs was 2.9% among over 6,900 children with first trimester ARV exposures, similar to the rate among children exposed in later trimesters.[5] The Women and Infants Transmission Study (WITS) found no increase in the overall rate of defects (3.56 per 100 live births) as compared to the general population

estimate of 2.76 from the Metropolitan Atlanta Congenital Defects Program (MACDP), but reported an increased risk of hypospadias after exposure to zidovudine (ZDV, or AZT) during the first trimester.[6] Two recent evaluations from US-based cohorts have shown an increased overall risk of CAs among infants with first trimester efavirenz exposure.[12,13] A single animal study and case reports have also reported CAs associated with efavirenz exposure,[14,15] leading to recommendations against use in pregnancy, although specific risks have not been confirmed.[2]

Previous studies predominantly included children born before 2007, preventing evaluation of newer ARVs and combinations with increasing use. In the US, prenatal use of tenofovir, emtricitabine, and lopinavir has increased dramatically since approval in 2000–2003 to 40–50% use by 2010, while nelfinavir use has declined substantially following safety warnings.[16–17] Atazanavir use has increased to ~20% by 2010. An Italian cohort showed similar trends through 2011.[18] In addition to changes in specific ARVs, the majority of infants in previously-studied cohorts were not exposed to ARVs in the first trimester, a critical window for teratogenicity. We used an ongoing US-based pregnancy cohort, the Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network, to examine the association of *in utero* ARV exposures and infant CAs over the last 15 years. Our objectives were (1) to evaluate changes in the rate of CAs over time as new ARVs and regimens were utilized; and (2) to evaluate the association of *in utero* ARV exposure with CAs.

Methods

We analyzed data from HIV-infected pregnant women and their children enrolled in the SMARTT study.[19] This study includes two cohorts: Static and Dynamic. Between 2007 and 2009, the Static Cohort enrolled mothers/caregivers and their children under 12 years of age who had detailed information on ARV use during pregnancy and pregnancy outcomes. The Dynamic Cohort began enrolling pregnant women and their infants between 22 weeks of gestation and one week after delivery into prospective surveillance in 2007. The protocol was approved by appropriate Institutional Review Boards, with written informed consent by mothers/guardians for study participation for themselves and their children.

Information on ARV use during pregnancy and medical conditions, including pregnancy outcomes, was collected by medical chart abstraction. CAs were identified at study-specified newborn and 1-year old physical examinations for those in the Dynamic Cohort, and from physical examinations performed in prior studies for those in the Static Cohort. Participants were considered evaluable for this analysis if they were enrolled and had a study visit by July 1, 2012.

Outcome Measure

The outcome of interest was the presence of a CA, defined as an abnormality in the structure of a body part that was documented within the first year of life. CAs were recorded on study-specific anomaly and diagnosis forms. Study authors blinded to ARV exposures reviewed the reported CAs and classified them according to the Antiretroviral Pregnancy Registry modification of the MACDP classification scheme[5], a well-documented system for

categorizing CAs. According to this system, an infant with at least one major anomaly, or at least two conditional anomalies in the absence of a major anomaly, is considered a CA case. Additional information was requested from sites if needed to classify potential anomalies. Each CA was reviewed by at least two team members, and discrepancies were discussed to obtain consensus.

Prenatal Antiretroviral (ARV) Exposures

The primary exposure of interest was reported maternal use of ARVs during the first trimester (<14 weeks gestation). Highly active antiretroviral therapy (HAART) regimens were defined as those containing three or more ARVs from two or more drug classes (nucleoside reverse transcriptase inhibitors, NRTIs; non-nucleoside reverse transcriptase inhibitors, NNRTIs; protease inhibitors, PIs; and integrase inhibitors). Children were classified according to first trimester exposure to any ARV, to individual ARVs, to ARV drug classes, and to HAART.[16] We also evaluated these exposures at any time during pregnancy and by timing of first ARV exposure.

Potential Confounders

Confounding was evaluated using prior knowledge (based on biological mechanisms and previous literature) and descriptive statistics from our cohort through the use of directed acyclic graphs.[20–21] Potential confounders evaluated included self-reported race, advanced maternal age at delivery (>35 years), pre-pregnancy body mass index (BMI), health conditions such as pre- gestational diabetes, maternal sexually transmitted infections (STIs, see Table 1) during pregnancy, plasma HIV RNA concentration (viral load) and CD4 counts (earliest available measures in pregnancy), self-reported substance use (alcohol, tobacco, and drug use), and first trimester use of other medications previously reported to be associated with CA risk [e.g., folate antagonists and antidepressants including selective serotonin reuptake inhibitors (SSRIs)].[22–26] Socioeconomic status also was considered, as reflected by household income and caregiver education levels. Low birth weight (<2500grams), preterm birth (<37 weeks gestation), and delivery by Cesarean section were described but not included as potential confounders since these measures could be on the causal pathway between ARV exposure and CA status,[20–21] and the latter procedure might be preferentially performed when a CA was suspected.

Statistical Methods

Rates of CAs and 95% confidence intervals (CIs) were estimated overall and by calendar year, and compared descriptively to the MACDP rates for the US population. The characteristics of children with and without CAs were compared using Chi-square tests, Fisher's exact test, and Wilcoxon ranksum tests as appropriate. Logistic regression analysis was used to evaluate associations between *in utero* ARV exposures described above and confirmed CAs. Adjusted models included birth cohort and other noted confounders with $p<0.10$ in multivariable models. Separate analyses were conducted for certain CA categories (e.g., cardiovascular, musculoskeletal, skin, male genital), although these had limited power.

To confirm the robustness of results, several sensitivity analyses were conducted. Analyses were repeated restricting to cases with at least one major CA (e.g., excluding children with

only conditional CAs) and excluding those with a chromosomal anomaly. We repeated all analyses restricting to the Dynamic Cohort, since its prospective follow-up from birth reduces the risk of recall bias and misclassification, and this restriction eliminates overlap with previous cohorts (P219C, P1025, WITS).[7,12,13] Last of all, sensitivity analyses including random effects were conducted to control for multiple children born to the same mother and to adjust for the clustering of children within research sites. Due to observed time trends, analyses were repeated stratifying by, rather than adjusting for, birth cohort but yielded similar results and are not presented. Analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC) and two-sided p-values ≤0.05 were considered statistically significant. Because SMARTT is a safety study, no correction for multiple comparisons was employed to minimize the probability of not detecting true associations (Type II error); however, the large number of tests increases the risk of spurious associations and thus findings warrant confirmation in future studies.

Results

Study Population and CA Status by Demographic and Maternal Characteristics

The demographic and maternal characteristics of the 2580 participants (N=1380 Dynamic born 2007–2012, N=1200 Static born 1995–2008) enrolled by July 1, 2012 are shown in Table 1. After team review, 175 infants met the modified MACDP criteria for a confirmed CA case, yielding a prevalence of 6.78% (95% CI: 5.85–7.82%). There were 162 unique children with at least one major CA (6.27%, 95% CI: 5.37, 7.29) and 13 children with two or more conditional but no major anomalies. These 162 children had a total of 242 confirmed major anomalies; musculoskeletal (N=72) and cardiovascular (N=55) anomalies were most common (**eTable1**). The prevalence of CAs was 3.8%, 5.2%, 8.0%, 8.3%, and 5.7% for children born <2002, 2002–2004, 2005–2007, 2008–2010, and >2010, with a significantly increasing trend (p=0.033) in successive years. However, there was no significant overall difference in prevalences between the Static and Dynamic Cohorts (6.4% vs 7.1%, p=0.53).

There was no significant difference in the distribution of CA cases by demographic or socioeconomic characteristics other than birth cohort (Table 1). Cases were more often delivered by Cesarean section and more often preterm than non-cases, but there was no association with higher maternal viral load (>1000 copies/mL), or with alcohol, tobacco, or other substance use. Use of SSRIs was rare during the first trimester (n=30, 1.2%), and only one of these infants had a CA. Use of folate antagonists (cotrimoxazole or pyrimethamine) was reported by 107 mothers, six (5.6%) of whom had CAs.

Multivariable logistic models for CA case status adjusted for low maternal CD4 count (<250 cells/mm^3) early in pregnancy and birth cohort. For musculoskeletal anomalies, adjusted models also included maternal alcohol use during the first trimester (aOR=2.09, 95%CI: 0.92,4.72). Of the 2580 children, 63 (6 cases, 57 non-cases) lacked detailed information regarding maternal ARV use needed to identify trimesters of exposure, yielding 2517 children for evaluation of ARV exposures.

Association of in utero ARV Exposures with CAs

There was a significantly higher prevalence of CAs for children exposed to HAART or to PIs in the first trimester (8.1% vs 5.8%, and 8.5% vs 5.8%, respectively), but these associations did not persist in adjusted models (see Table 2). No individual NRTIs were associated with an increased risk of CAs, but the combination of didanosine plus stavudine, while rare (<1% exposed), was associated with an 8-fold higher odds of CAs. For NNRTIs, neither efavirenz nor nevirapine was associated with CAs.

For PIs, there was a significantly higher prevalence of cases among children exposed to atazanavir (11.7% vs 6.2%), lopinavir (9.4% vs 6.3%), and ritonavir when used as a booster (>99% of use, 9.3% vs 5.8%). The associations persisted in adjusted models for atazanavir and ritonavir (Table 2). Atazanavir was usually used in combination with ritonavir (92%), and often with certain NRTIs. The combinations of atazanavir with ritonavir, tenofovir, or emtricitabine were each associated with increased risk of CAs, with similar adjusted ORs (2.01, 2.00, and 1.85, respectively), while combinations of atazanavir with either ZDV or lamivudine showed no significant association (aORs=0.89 and 1.48, respectively). Of the two primary regimens including ritonavir with another PI, atazanavir with ritonavir showed increased odds while ritonavir-boosted lopinavir did not (Table 2). Specific anomalies for children exposed to first trimester atazanavir are shown in **eTable2**

Associations for ARV exposures at any time during pregnancy indicated a significantly higher risk of CAs for those exposed to the combinations of either didanosine plus stavudine or to ZDV plus lamivudine. When the rate of CAs by timing of first exposure was examined (**eTable3)**, the results were generally consistent with the comparisons of first trimester exposure. For some ARVs, however, the highest prevalence of CAs occurred with first exposure during the second or third trimester (abacavir: 10.6%, stavudine: 17.1%).

Separate analyses conducted by type of anomaly indicated that first trimester atazanavir exposure was significantly associated with musculoskeletal and skin anomalies (Table 3). There was significantly higher odds of musculoskeletal anomalies among infants exposed to didanosine plus stavudine in the first trimester. Ritonavir as a booster was associated with increased risk of musculoskeletal CAs. We observed a significantly higher odds of male genital anomalies (eg., hypospadias and cryptorchidism) with first trimester ZDV exposure and lamivudine exposure (Table 3).

For some less commonly-used ARVs, including raltegravir (1.5% exposed), enfuvurtide (0.3%), maraviroc (0.1%), and etravirine (0.4%), there were no first trimester exposures. Raltegravir was the only one of these ARVs with any CAs, with a rate of 4.2% (3 of 71 exposed at any time during pregnancy) as compared to 6.8% for raltegravir-unexposed.

Sensitivity Analyses

When restricting cases to children with major anomalies and when excluding 11 children with chromosomal anomalies (eTable1), the significant associations with first trimester atazanavir, ritonavir (as a booster), and the combination of didanosine plus stavudine persisted, with very similar estimated effects. Similarly, sensitivity analyses accounting for

multiple children per mother and for clustering within research site provided results almost identical to those in Table 2.

In the Dynamic Cohort, a higher percentage of infants were exposed during the first trimester to HAART (47.2%) and to PIs (41.9%), but none were exposed to didanosine plus stavudine. In adjusted models, no significant associations for first trimester exposures were observed for the Dynamic Cohort, and the association for atazanavir was attenuated (aOR=1.55, 95%CI: 0.91,2.63). However, when ARV exposures at any time during pregnancy were evaluated, there was significantly higher odds of CAs among Dynamic infants exposed to lamivudine (aOR=2.13, 95%CI:1.26,3.60), ZDV (aOR=2.06, 95%CI: 1.23,3.44), ZDV plus lamivudine (aOR=2.43, 95%CI:1.45,4.06), and abacavir (aOR=1.58, 95%CI:1.00,2.49). In contrast, there was a protective association with darunavir exposure (aOR=0.21, 95%CI:0.05,0.84).

Examination of ARV exposures within the Dynamic Cohort by trimester of first exposure indicated that the increased risk for ZDV, lamivudine, and their combination was observed for both first and later trimesters as compared to those never exposed to these specific ARVs or combinations. The increased risk for abacavir in the Dynamic Cohort was only observed for those first exposed later in pregnancy as compared to abacavir-unexposed (aOR=2.20, 95%CI:1.31,3.71). For musculoskeletal anomalies, those exposed to first trimester atazanavir had significantly increased odds of CAs (aOR=2.49, 95%CI: 1.25, 4.95).

Discussion

We observed an overall prevalence of 6.78 CAs for every 100 live births, which is considerably higher than many prior studies of HIV-exposed infants in the U.S. and the U.K, with reported prevalences ranging from 2.8% to 5.5%[4–7, 12,13] and higher than the rate of 3.2% in a recent Italian cohort,[10] but is similar to the 6.2% rate reported by a Latin American study.[27] We observed an increasing trend in the rate of CAs from prior to 2002 through 2010, followed by a slight decline through 2012. The higher rates of CAs may reflect a real increase consistent with temporal trends demonstrated in various population studies,[28–29] increased ascertainment given the study-required evaluation for anomalies, and longer follow-up than some studies. It may also be partially attributable to the increasing percentage of mothers receiving ARVs early in pregnancy, which was less than 30% in earlier studies,[4,6,7,12,13] but is almost 50% of the current cohort.

The association of first trimester atazanavir exposure with CAs, particularly musculoskeletal and skin anomalies, has not previously been reported and warrants further investigation. Of note, the P1025 study also reported higher rates of CAs with first trimester atazanavir exposure (9.2% vs 5.3% for atazanavir-unexposed, aOR=1.83), although not attaining significance.[13] Most prior studies included births prior to 2007, and thus did not reflect increasing use of this particular ARV since its approval in 2003, up to 20% by 2010.[16] Furthermore, exposures to particular ARV combinations may be associated with higher risks. We observed higher odds of CAs for first trimester atazanavir exposure when combined with ritonavir, tenofovir, or emtricitabine, all with increased use over the last decade,[16–18] than with older ARVs (ZDV or lamivudine). In contrast, when ritonavir was

used to boost PIs other than atazanavir (primarily lopinavir), it was not associated with higher odds. Finally, while a variety of specific anomalies were reported for atazanavir-exposed children, the increased risk was highest for musculoskeletal and skin anomalies of generally milder severity.

In contrast to some prior studies, [12,13] we observed no association of CAs with first trimester efavirenz exposure. A recent meta-analysis also found no increased risk of overall CAs with efavirenz exposure.[30] We confirmed an increased risk for male genital anomalies with first trimester ZDV exposure;[6,31] this association remained marginally significant in the Dynamic Cohort and was thus not entirely attributable to overlap with prior studies.

Our study has several strengths, including its large size, relatively complete information on maternal health, substance use and pregnancy complications, and use of the well-validated MACDP classification system. We also considered other medications used during pregnancy, such as SSRIs and folate antagonists. However, a limitation of our study is the possibility of selection bias; mothers of Static Cohort infants with CAs may have been more willing to participate, which could have artificially increased the prevalence of CAs and may have accounted for the higher rate during 2005–2010 as compared to more recent years. Conversely, allowing enrollment up to one week after birth may exclude infants with severe CAs incompatible with life. In addition, the MACDP classification system, while providing specific objective criteria for identifying anomalies, may not allow discrimination by defect severity. Both misclassification and lack of specificity of CA outcomes as well as potential exposure misclassification could have resulted in attenuation of findings; thus, we evaluated specific CAs and both individual ARVs and combinations of ARVs in increasing use.

In conclusion, our study was reassuring in confirming a lack of increased risk of CAs among children exposed to ARVs during the first trimester of pregnancy. We observed a higher prevalence of CAs than have been reported in the general population, but after adjustment for calendar year and maternal characteristics, there was no relative increase in risk for those exposed versus unexposed to HAART or to PI-based regimens early in pregnancy. However, while the absolute risk of CAs was relatively low, some individual drugs, particularly atazanavir, showed relative increases in risk of overall CAs and specific anomalies, which warrant further study. As World Health Organization 2013 ARV guidelines are implemented globally, an increasing percentage of women with HIV will be expected to enter pregnancy already on ARVs.[32] Thus, risks associated with *in utero* ARV exposures must be considered in order to identify optimal regimens based on their safety profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Maternal Characteristics of 2580 SMARTT Infants Overall and by Congenital Anomaly Status

		Congenital Anomaly Status		
Characteristic	**Total (N=2580)**	**Not a case (N=2405)**	**Case (N=175)**	**P-Value**
Cohort				
Dynamic	1,380 (53%)	1,282 (53%)	98 (56%)	0.53
Static	1,200 (47%)	1,123 (47%)	77 (44%)	
Birth Cohort				
< 2002	391 (15%)	376 (16%)	15 (9%)	0.018
2002–2004	343 (13%)	325 (14%)	18 (10%)	
2005–2007	525 (20%)	483 (20%)	42 (24%)	
2008–2010	940 (36%)	862 (36%)	78 (45%)	
2011–2012	381 (15%)	359 (15%)	22 (13%)	
Female sex	1,254 (49%)	1,177 (49%)	77 (44%)	0.21
Race				
White	701 (27%)	651 (27%)	50 (29%)	0.87
Black/African American	1,703 (66%)	1,592 (66%)	111 (63%)	
Other	14 (1%)	13 (1%)	1 (1%)	
Latino/Hispanic	845 (33%)	781 (32%)	64 (37%)	0.28
Mother over 35 years old at birth of child	336 (13%)	307 (13%)	29 (17%)	0.20
Household Income<$20,000 per year	1,683 (65%)	1,570 (65%)	113 (65%)	0.72
Caregiver not High School Graduate	894 (35%)	831 (35%)	63 (36%)	0.68
Birth Characteristics				
Cesarean-section delivery	1,402 (54%)	1,293 (54%)	109 (62%)	0.026
Low birth weight (<2.5 kg)	483 (19%)	440 (18%)	43 (25%)	0.045
Preterm birth (Gestational age<37 wks)	527 (20%)	477 (20%)	50 (29%)	0.008
Pregnancy Complications				
Toxemia or pre-eclampsia	145 (6%)	129 (5%)	16 (9%)	0.040
Diabetes – gestational	116 (4%)	108 (4%)	8 (5%)	0.85
Diabetes – pre-gestational	51 (2%)	45 (2%)	6 (3%)	0.15
Diabetes – either of above	161 (6%)	148 (6%)	13 (7%)	0.51
Maternal Immunologic and Virologic Status				
HIV RNA > 1000 copies/mL at delivery	390 (15%)	368 (15%)	22 (13%)	0.38
Early HIV RNA > 1000 copies/mL	1,316 (51%)	1,227 (51%)	89 (51%)	1.00
CD4<250 cells/mm^3 at delivery	368 (14%)	350 (15%)	18 (10%)	0.17
Early CD4<250 cells/mm^3	470 (18%)	447 (19%)	23 (13%)	0.099
Maternal Substance Use During Pregnancy				
Hard drug use[1]	68 (3%)	63 (3%)	5 (3%)	0.81
Illicit drug use including hard drugs[1]	206 (8%)	191 (8%)	15 (9%)	0.77
Alcohol use	196 (8%)	180 (7%)	16 (9%)	0.46
Tobacco use	446 (17%)	414 (17%)	32 (18%)	0.76

Characteristic	Total (N=2580)	Congenital Anomaly Status		P-Value
		Not a case (N=2405)	Case (N=175)	
Maternal Medication Use During Pregnancy				
Methadone treatment	22 (1%)	22 (1%)	0 (0%)	0.40
Pain medication	99 (4%)	91 (4%)	8 (5%)	0.55
1st trimester SSRI	30 (1%)	29 (1%)	1 (1%)	0.72
1st trimester folate antogonist	107 (4%)	101 (4%)	6 (3%)	0.84
Maternal Sexually Transmitted Infection (STI) During Pregnancy				
Gonorrhea	72 (3%)	64 (3%)	8 (5%)	0.15
Chlamydia	215 (9%)	199 (9%)	16 (10%)	0.67
Trichomonas	282 (13%)	268 (13%)	14 (9%)	0.17
Syphilis	76 (3%)	72 (3%)	4 (2%)	0.82
Any of above STIs	511 (19%)	478 (20%)	33 (19%)	0.84

SSRI selective serotonin reverse inhibitor

[1]Hard drugs include cocaine, heroin, and opium. Illicit drugs include these hard drugs as well as marijuana, ecstasy, methamphetamines, and hallucinogens.

P-value calculated by Chi-Square test for birth cohort, and Fisher's exact test for all other characteristics. The above characteristics were unavailable for some participants, including race (n=162) ethnicity (n=3), maternal age (n=53), household income (n=185), caregiver education (n=25), delivery mode (n=52), preterm birth (n=45), low birth weight (n=23), diabetes (n=91, maternal VL (n=194), maternal CD4 (n=159), substance use during pregnancy (n=196), and maternal STIs (n=146 gonorrhea, 147 chlamydia, 149 syphilis, 355 trichomonas).

Table 2

Association of First Trimester Antiretroviral (ARV) Exposures with Congenital Anomalies

		Defect Rate		Unadjusted Model	Adjusted Model
	Percent Exposed	**Exposed**	**Unexposed**	**OR (95% CI)**	**OR (95% CI)**
By ARV Drug Class					
Any ARV	48.4	93/1219 (7.6%)	76/1298 (5.9%)	1.33 (0.97, 1.82)	1.20 (0.87, 1.67)
HAART	40.7	83/1025 (8.1%)	86/1492 (5.8%)	**1.44 (1.05, 1.97)**	1.35 (0.98, 1.87)
NNRTIs	8.5	13/214 (6.1%)	156/2303 (6.8%)	0.89 (0.50, 1.60)	0.97 (0.54, 1.74)
NRTIs	48.1	92/1211 (7.6%)	77/1306 (5.9%)	1.31 (0.96, 1.80)	1.19 (0.86, 1.65)
PIs	35.2	75/887 (8.5%)	94/1630 (5.8%)	**1.51 (1.10, 2.07)**	1.39 (1.00, 1.92)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir (ABC)	8.8	15/222 (6.8%)	154/2295 (6.7%)	1.01 (0.58, 1.74)	0.94 (0.53, 1.65)
Didanosine (ddI)	2.1	5/52 (9.6%)	164/2465 (6.7%)	1.49 (0.59, 3.80)	1.51 (0.59, 3.86)
Emtricitabine (FTC)	14.9	28/374 (7.5%)	141/2143 (6.6%)	1.15 (0.75, 1.75)	1.14 (0.74, 1.74)
Lamivudine (3TC)	31.7	63/797 (7.9%)	106/1720 (6.2%)	1.31 (0.95, 1.81)	1.14 (0.81, 1.60)
Stavudine (d4T)	2.7	4/68 (5.9%)	165/2449 (6.7%)	0.87 (0.31, 2.41)	1.11 (0.40, 3.12)
Tenofovir (TDF)	17.1	32/431 (7.4%)	137/2086 (6.6%)	1.14 (0.77, 1.70)	1.14 (0.76, 1.71)
Zidovudine (ZDV)	28.8	57/726 (7.9%)	112/1791 (6.3%)	1.28 (0.92, 1.78)	1.10 (0.78, 1.56)
ddI + d4T	0.3	2/7 (28.6%)	167/2510 (6.7%)	**5.62 (1.08, 29.2)**	**8.19 (1.53, 43.4)**
ZDV + 3TC	27.2	57/684 (8.3%)	112/1833 (6.1%)	**1.40 (1.00, 1.95)**	1.19 (0.84, 1.69)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Efavirenz (EFV)	3.7	7/94 (7.4%)	162/2423 (6.7%)	1.12 (0.51, 2.47)	1.13 (0.51, 2.50)
Nevirapine (NVP)	4.6	7/115 (6.1%)	162/2402 (6.7%)	0.90 (0.41, 1.96)	1.03 (0.47, 2.26)
Protease Inhibitors (PIs)					
Atazanavir (ATV)	8.8	26/222 (11.7%)	143/2295 (6.2%)	**2.00 (1.28, 3.11)**	**1.95 (1.24, 3.05)**
Darunavir (DRV)	2.1	1/54 (1.9%)	168/2463 (6.8%)	0.26 (0.04, 1.88)	0.30 (0.04, 2.21)
Fosamprenavir (FPV)	1.7	4/42 (9.5%)	165/2475 (6.7%)	1.47 (0.52, 4.18)	1.35 (0.47, 3.86)
Lopinavir (LPV/r)	13.5	32/341 (9.4%)	137/2176 (6.3%)	**1.54 (1.03, 2.31)**	1.37 (0.90, 2.09)
Nelfinavir (NFV)	8.7	15/220 (6.8%)	154/2297 (6.7%)	1.02 (0.59, 1.76)	0.91 (0.51, 1.65)
Ritonavir (as booster)	25.2	59/635 (9.3%)	110/1882 (5.8%)	**1.65 (1.19, 2.30)**	**1.56 (1.11, 2.20)**
Saquinavir (SQV)	1.3	2/33 (6.1%)	167/2484 (6.7%)	0.90 (0.21, 3.77)	0.98 (0.23, 4.15)

OR=odds ratio, CI=confidence interval, HAART=highly active antiretroviral treatment.

* Each row reflects a separate logistic regression model, both unadjusted and adjusted for low maternal CD4 count (< 250 cells/mm^3) early in pregnancy and birth cohort.

Table 3

Associations of First Trimester Exposure to Specific Antiretrovirals with Specific Anomalies

	Defect Rate		Unadjusted Models	Adjusted Models*
ARV Exposure/Type of Anomaly	**Exposed**	**Unexposed**	**OR (95% CI)**	**OR (95% CI)**
Atazanavir (ATV)				
Cardiac	7/222 (3.2%)	33/2295 (1.4%)	2.23 (0.98, 5.11)	2.02 (0.88, 4.64)
Musculoskeletal	11/222 (5.0%)	46/2295 (2.0%)	**2.55 (1.30, 5.00)**	**2.57 (1.30, 5.08)**
Skin	3/222 (1.4%)	6/2296 (0.3%)	**5.23 (1.30, 21.0)**	**6.01 (1.43, 25.3)**
Ritonavir (RTV, as booster)				
Cardiac	16/635 (2.5%)	24/1882 (1.3%)	**2.00 (1.06, 3.79)**	1.83 (0.96, 3.49)
Musculoskeletal	22/635 (3.5%)	35/1882 (1.9%)	**1.89 (1.10, 3.25)**	**1.79 (1.02, 3.14)**
Lopinavir/RTV (LPV/RTV)				
Cardiac	6/341 (1.8%)	34/2176 (1.6%)	1.13 (0.47, 2.71)	0.79 (0.40, 2.34)
Musculoskeletal	11/341 (3.2%)	46/2176 (2.1%)	1.54 (0.79, 3.01)	1.40 (0.70, 2.83)
Zidovudine (ZDV)				
Male Genital	8/726 (1.1%)	6/1791 (0.3%)	**3.31 (1.15, 9.59)**	**3.18 (1.10, 9.22)**
Lamivudine (3TC)				
Male Genital	8/797 (1.0%)	6/1720 (0.3%)	**2.90 (1.00, 8.38)**	**2.77 (0.96, 8.03)**
Didanosine and Stavudine (ddI+d4T)				
Cardiac	0/7 (0%)	40/2510 (1.6%)	N/A	N/A
Musculoskeletal	1/7 (14.3%)	56/2510 (2.2%)	7.30 (0.86, 61.7)	8.29 (0.96, 71.8)

ARV=antiretroviral, OR=odds ratio, CI=confidence interval

*Models adjusted for: **any anomaly** low maternal CD4 count (< 250 cells/mm^3) early in pregnancy and birth cohort; **cardiac anomaly** birth cohort; **musculoskeletal anomaly** low maternal CD4 count early in pregnancy and first trimester maternal alcohol consumption; **skin anomaly** low maternal CD4 count early in pregnancy; **male genital anomaly** maternal age >35 years at delivery.