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

Abstract #863LB

Paige L. Williams[1], Cenk Yildirim[1], Marilyn Crain[2], Rohan Hazra[3], Russell B. Van Dyke[4], Kenneth Rich[5], Jennifer S. Read[6], Emma Stuard[7], Mobeen Rathore[8], Hermann A. Mendez[9], and D. Heather Watts[10], for the Pediatric HIV/AIDS Cohort Study

[1]Harvard School of Public Health, Boston, MA ; [2]University of Alabama at Birmingham, Birmingham AL; [3]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD; [4]Tulane University School of Medicine, New Orleans LA; [5]University of Illinois at Chicago, Chicago, IL; [6]The George Washington University, School of Medicine Washington DC; [7]Bronx-Lebanon Hospital, Bronx, NY; [8]University of Florida Center for HIV/AIDS Research, Education and Service, Jacksonville, FL; [9]SUNY Downstate Medical Center, Brooklyn, NY; [10]Office of the US Global AIDS Coordinator, Washington, DC

Paige Williams, PhD
Departments of Biostatistics and Epidemiology
Harvard School of Public Health
Tel: 617-432-3872
Fax: 617-432-2832
Email: paige@hsph.harvard.edu

ABSTRACT

Background: Most studies examining the association of maternal antiretroviral (ARV) use during pregnancy with congenital anomalies (CAs) in their children have been reassuring, but some suggest increased risk with specific ARVs.

Methodology: We evaluated HIV-exposed uninfected children enrolled in the PHACS Surveillance Monitoring of ART Toxicities (SMARTT) study, an ongoing cohort study initiated in 2007 at 22 US sites. Clinicians blinded to ARV exposures reviewed reported anomalies according to the Metropolitan Atlanta Congenital Defects Program (MACDP). Rates of CAs were estimated overall and by birth cohort. Logistic regression models were used to evaluate associations between CAs and 1st trimester exposure to any ARV, including regimens, specific ARVs, and drug classes. Models were adjusted for demographic and maternal characteristics (including CD4, viral load, substance use, other medications, and pregnancy complications).

Results: Among 2580 children born by July 2012 (49% female, 66% black, 33% Hispanic), 175 (6.78%, 95% CI: 5.85-7.82%) had a total of 242 confirmed major CAs (most common were musculoskeletal (n=72) and cardiovascular (n=56)). The prevalence of CAs by birth cohort was 3.8%, 5.2%, 8.0%, 8.3%, and 5.7% for children born <2002, 2002-2004, 2005-2007, 2008-2010, and >2010, respectively. In unadjusted models, 1st trimester exposures to combination ARV regimens or to protease inhibitors (PIs) were associated with increased risks of CAs [odds ratio (OR)=1.44, p=0.022 and OR=1.51, p=0.010, respectively], but these associations did not persist after adjustment. No individual NNRTI (including efavirenz) or NRTI was associated with an increased risk of CAs, but the combination of ddI+d4T (<1% exposed) was associated with 8-fold higher odds [adjusted OR (aOR)=8.41, p=0.015]. Among individual PIs, atazanavir (ATV) was associated with significantly higher odds of CAs in both unadjusted models and adjusted models (aOR=1.93, p=0.004). With 1st trimester atazanavir, risks were highest for skin CAs (aOR=5.24, p=0.020) and musculoskeletal CAs (aOR=2.51, p=0.009).

Conclusions: Few individual ARVs or drug classes were associated with increased risk of CAs after adjustment for child and maternal characteristics, with the exception of the combination of ddI+d4T, now rarely used, and atazanavir, which is increasing in use. As newer ARVs and combination regimens become more widely used, continued monitoring is essential.

BACKGROUND

- Most prior studies examining the risk of congenital anomalise according to in utero ARV use exposures have been reassuring, but a few have suggested increased risk of congenital anomalies with specific ARV agents or for specific anomalies
- Most prior studies included children born prior to 2007, preventing evaluation of newer ARVs and ARV combinations in increasing use. In addition, the majority of these earlier cohorts of children were not exposed to any ARV in the 1st trimester, a well-known critical window for many teratogenic effects.

OBJECTIVES

- To estimate the rate of congenital anomalies (CAs) in children in the PHACS SMARTT study and the change in rates over time as new ARV drugs and combination regimens were utilized
- To evaluate the association of *in utero* ARV exposures with CAs, including 1st trimester exposure to any ARV and to specific ARV drugs.

METHODS

Study Population

- HIV-exposed uninfected (HEU) children from the PHACS SMARTT study, including both a retrospectively evaluated cohort (Static, n=1200) and a prospective cohort (Dynamic, n=1380) enrolled between gestation week 22 and 1 week after birth.
- Data on pregnancy and infant outcomes were obtained at a study-related newborn examination for those in the Dynamic cohort, and from prior studies for those in the Static cohort.
- Children were included if they were enrolled and had a visit by 7/1/2012, and had information on *in utero* ARV exposures

Outcomes and Exposures

- *Congenital Anomalies*: The outcome of interest is the presence of a congenital anomaly (CA) defined as an abnormality in the structure of a body part, and documented within the first year of life.
- Authors blinded to ARV exposures reviewed CAs and classified them according to a modified MACDP classification scheme[1]; infants with ≥1 major anomaly or ≥2 conditional anomalies were considered a case
- *In utero ARV exposures:* primary interest was 1st trimester exposure to any ARV, specific ARVs, ARV regimens, and ARV classes.

Statistical Methods

- Rates of CAs (number per 100 live-births) and 95% confidence intervals (CIs) were estimated overall and by calendar period, and compared to the MACDP rates as a measure of the US population
- Logistic regression analysis was used to evaluate associations between confirmed CAs and 1st trimester exposures to any ARV, ARV regimens, ARV drug classes, and to specific ARV agents.
- Models were fit both unadjusted and adjusted for potential confounders, including:
  - Socio-demographic characteristics (race, ethnicity, maternal age pre-pregnancy BMI, household income, caregiver education)
  - Birth characteristics (low birth weight, preterm birth, C-section)
  - Maternal conditions (STIs, pregnancy complications)
  - Maternal health (CD4, CD4%, viral load)
  - Maternal substance use (alcohol, tobacco, illicit and hard drugs)
  - Other medications (antidepressants, folate antagonists)
- Sensitivity analyses were conducted:
  - Using random effect models to account for multiple children per mother and clustering within research site,
  - To exclude chromosomal anomalies, evaluate the Dynamic cohort separately, and evaluate specific types of anomalies separately.

RESULTS

Table 1: Types of Major Congenital Anomalies in 2580 SMARTT Children

	All Major Anomalies (may include multiple anomalies per infant)		Major Anomalies (unique infants within each category)	
Anomaly Category	N	(%)	N	(%)
Musculoskeletal	72	(29.8%)	59	(29.4%)
Cardiovascular	55	(22.7%)	41	(20.4%)
Facial	20	(8.3%)	17	(8.5%)
Central Nervous System	19	(7.9%)	14	(7.0%)
Male Genital	16	(6.6%)	15	(7.5%)
Renal	16	(6.6%)	12	(6.0%)
Chromosomal	11	(4.6%)	11	(5.5%)
Skin	10	(4.1%)	10	(5.0%)
Mouth/Upper Gastrointestinal	7	(2.9%)	7	(3.5%)
Cleft Disorders	4	(1.6%)	3	(1.5%)
Lower Gastrointestinal	3	(1.2%)	3	(1.5%)
Respiratory	3	(1.2%)	3	(1.5%)
Other*	6	(2.5%)	6	(3.0%)
TOTAL	**242**		**201**	

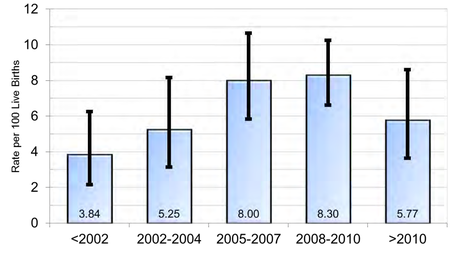
Other anomalies include: congenital adrenal hyperplasia (2), fetal alcohol syndrome, hemihypertrophy, and Wolfe-Parkinson-White syncrome.

Table 2: Association of Maternal ARV Use in 1st trimester with Congenital Anomalies

	%	Rate of Anomaly		Adjusted Models*	
Maternal ARV Use	exposed	Exposed	Unexposed	OR (95% CI)	P-value
By ARV Regimen and Drug Class					
Any 1st trimester ARV	48.4	7.6%	5.9%	1.17 (0.84, 1.62)	0.36
1st trimester HAART	40.7	8.1%	5.8%	1.31 (0.95, 1.82)	0.10
1st trimester NNRTIs	8.5	6.1%	6.8%	0.92 (0.51, 1.66)	0.79
1st trimester NRTIs	48.1	7.6%	5.9%	1.15 (0.83, 1.60)	0.39
1st trimester PIs	35.2	8.5%	5.8%	1.34 (0.96, 1.86)	0.082
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir (ABC)	8.8	6.8%	6.7%	0.94 (0.53, 1.67)	0.84
Didanosine (ddI)	2.1	9.6%	6.7%	1.45 (0.56, 3.72)	0.45
Emtricitabine (FTC)	14.9	7.5%	6.6%	1.09 (0.71, 1.68)	0.69
Lamivudine (3TC)	31.7	7.9%	6.2%	1.13 (0.80, 1.59)	0.48
Stavudine (d4T)	2.7	5.9%	6.7%	1.10 (0.39, 3.09)	0.86
Tenofovir (TDF)	17.1	7.4%	6.6%	1.10 (0.73, 1.66)	0.64
Zidovudine (ZDV)	28.8	7.9%	6.3%	1.09 (0.77, 1.55)	0.63
ddI + d4T	0.3	28.6%	6.7%	**8.41 (1.51, 46.8)**	**0.015**
ZDV + 3TC	27.2	8.3%	6.1%	1.18 (0.83, 1.67)	0.37
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Efavirenz (EFV)	3.7	7.4%	6.7%	1.05 (0.48, 2.33)	0.90
Nevirapine (NVP)	4.6	6.1%	6.7%	1.02 (0.46, 2.24)	0.97
Protease Inhibitors (PIs)					
Atazanavir (ATV)	8.8	11.7%	6.2%	**1.93 (1.23, 3.03)**	**0.004**
Darunavir (DRV)	2.1	1.9%	6.8%	0.29 (0.04, 2.12)	0.22
Fosamprenavir (FPV)	1.7	9.5%	6.7%	1.32 (0.46, 3.77)	0.61
Lopinavir (LPV/r)	13.5	9.4%	6.3%	1.35 (0.89, 2.06)	0.16
Nelfinavir (NFV)	8.7	6.8%	6.7%	0.89 (0.49, 1.61)	0.70
Ritonavir (as booster)	25.2	9.3%	5.8%	**1.52 (1.08, 2.14)**	**0.016**
Saquinavir (SQV)	1.3	6.1%	6.7%	0.81 (0.19, 3.49)	0.78

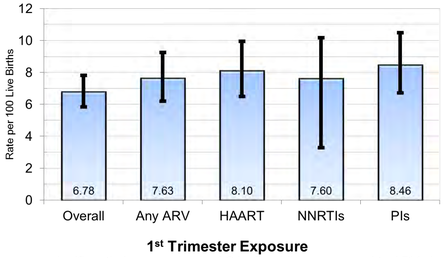
* Logistic regression models adjusted for preterm birth, low early CD4 (<250 cells/mm^3), and birth cohort.

Figure 1: Rates of Congenital Anomalies over Birth Cohorts



There was a significant increase over birth cohorts in the rate of CAs (p-value for trend =0.033), although the rate dropped in the most recent cohort (births >2010)

Figure 2: Rates of Congenital Anomalies for 1st Trimester ARVs and ARV Classes



There was no significantly increased risk of CAs for children exposed to ARVs in the 1st trimester, either overall or by drug class, after adjusting for covariates.

Table 3: Association of Specific ARVs in 1st Trimester with Specific Anomalies

	Adjusted Models*	
Type of Anomaly	OR (95% CI)	P-value
Atazanavir		
Musculoskeletal	2.51 (1.26, 4.98)	0.009
Cardiac	1.99 (0.86, 4.59)	0.108
Skin	5.24 (1.29, 21.2)	0.020
Ritonavir (as a booster)		
Musculoskeletal	1.77 (1.01, 3.10)	0.048
Cardiac	1.75 (0.92, 3.34)	0.089
ddI + d4T		
Musculoskeletal	8.99 (0.98, 82.5)	0.052
Cardiac	N/A (no cardiac CAs)	---

Logistic regression models adjusted for: **cardiac anomaly**–preterm birth and birth cohort; **musculoskeletal anomaly**–preterm birth, low early CD4, female sex, and maternal alcohol consumption; **skin anomaly**–female sex.

SUMMARY OF RESULTS

- We observed an overall prevalence of 6.78 CAs per 100 live births; this rate is considerably higher than in the general population and also higher than for other studies of children born to HIV-infected mothers (2.9% for APR[1], 2.8% for NSHPC[2], 3.56% in WITS[3], 5.3% in 219C[4], 5.49% in P1025[5], 3.2% in a recent Italian cohort[6] and 6.16% in the NISDI study[7] in Latin America).
- We observed no increased rate of anomalies for infants with 1st trimester exposure to any ARV, and no association with 1st trimester exposure to any individual NRTI or NNRTI (including efavirenz).
- Among PIs, 1st trimester exposure to atazanavir (aOR=1.93, p=0.004) and to ritonavir (as booster, aOR=1.52, p=0.016) were associated with higher odds of anomalies in both adjusted and unadjusted models.
- With 1st trimester atazanavir, risks were highest for skin (aOR=5.24, p=0.020) and musculoskeletal CAs (aOR=2.55, p=0.007).
- Certain ARV combinations were also associated with higher odds of anomalies, including ddI+d4T (used by <1% of mothers, aOR=8.41, p=0.015), and both ATV+TDF (aOR=2.00, 95% CI: 1.22, 3.28) and ATV+FTC (aOR=1.85, 95% CI: 1.10, 3.14).
- Similar findings were observed when restricted to the Dynamic cohort.

CONCLUSIONS

- In one of the largest and most recent cohorts, we observed a high rate of congenital anomalies but few associations with maternal ARV use during pregnancy.
- These findings support continued use of ARVs by HIV-infected women during pregnancy. Findings of increased risk for infants whose mothers used atazanavir during pregnancy warrant further study.

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