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Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication

D. Heather Watts^{1,*}, Sharon Huang², Mary Culnane³, Kathleen A. Kaiser⁴, Angela Scheuerle⁵, Lynne Mofenson¹, Kenneth Stanley², Marie-Louise Newell⁶, Laurent Mandelbrot⁷, Jean-Francois Delfraissy⁸, and Coleen K. Cunningham⁹

¹Eunice Kennedy Shriver National Institute for Child Health and Human Development, Bethesda, MD, USA

²Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, USA

³National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

⁴Frontier Science and Technology Research Foundation, Inc., Amherst, NY, USA

⁵Tesserae Genetics, Dallas, TX, USA

⁶University College London Institute of Child Health, London, UK and Africa Centre, University of KwaZulu-Natal, South Africa

⁷Université Paris-Diderot, Colombes, France

⁸Agence Nationale de Recherches sur le SIDA, Paris, France

⁹Department of Pediatrics, Duke University Medical Center, Durham, NC, USA

Abstract

Objective—To determine rate of and risk factors for birth defects in infants born to HIV-infected women receiving nucleoside and protease inhibitor antiretroviral (ARV) therapy.

Methods—Birth defects were evaluated among infants on the Pediatric AIDS Clinical Trials Group 316 trial that studied addition of peripartum nevirapine to established ARV regimen for prevention of mother-to-child transmission. Maternal therapy was categorized by trimester of earliest exposure. Birth defects were coded using conventions of the Antiretroviral Pregnancy Registry.

Results—Birth defects were detected in 60/1414 (4.2%; 95% CI 3.3–5.4%) infants including 30/636 (4.7%; 95% CI 3.2–6.7%) with first trimester ARV exposure and 30/778 (3.9%; 95% CI 2.6–5.5%) with exposure only after the first trimester ($P=0.51$). Rates of classes of defects were similar between first trimester compared to later exposure groups except heart defects which occurred in 16 (2.5%; 95% CI 1.4–4.1%) with first trimester ARV exposure and in six (0.8%; 95% CI 0.3–1.7%) infants with later exposure ($P=0.02$). Exposure to ARV was not associated with specific types of heart defects. Two cases of cardiomyopathy were noted.

Conclusion—ARV use in early pregnancy was not associated with an increased risk of birth defects overall. The possible association of ARV exposure with heart defects requires further surveillance.

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*Corresponding author: D. Heather Watts, MD, PAMA/CRMC/NICHD, 6100 Executive Blvd, Room 4B11, Bethesda, MD 20892-7510, USA, Tel.: +1 301-435-6874, hw59i@nih.gov.

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Keywords

Antiretrovirals; birth defects; HIV

Introduction

An increasing number of pregnant women are receiving antiretroviral (ARV) therapy both for their own treatment and for prevention of maternal-to-child transmission of HIV. In addition, many HIV-infected women conceive while receiving ARV treatment [13]. Data on the risk of birth defects after ARV exposure are limited and varied, with some studies reassuring and others finding increased risks after specific exposures. Data from the Antiretroviral Pregnancy Registry (APR) have been reassuring without overall increased risk of birth defects compared to population-based surveillance data or when comparing rates after first trimester exposure to those after ARV exposure only later in pregnancy [19], although biases in reporting may occur. A small study from England did not find an increased risk of birth defects with ARV exposure or folate antagonist exposure alone, but did find an increased risk of defects when the combination of ARV therapy and folate antagonists, such as trimethoprim/sulfa were used in the first trimester [10]. An analysis of data from the Pediatric AIDS Clinical Trials Group (PACTG) study 185 suggested an increased risk of ventricular septal heart defects after zidovudine exposure in the first trimester [19]. This study was unable to control for concomitant medications, such as trimethoprim/sulfa for pneumocystis pneumonia (PCP) prophylaxis, that were likely more common among women with first trimester exposure because of increased disease severity. An analysis from the Women and Infants Transmission study detected an increased risk of hypospadias after first trimester zidovudine exposure but again was unable to control for concomitant medication exposures [22]. Data from the European Collaborative Study (ECS) and the UK National Study of HIV in Pregnancy and Childhood did not detect an increased risk of defects with ARV exposure [16,20]. Animal data suggest a potential increased risk for central nervous system and facial defects among cynomolgus monkeys after first trimester exposure to efavirenz, but human data are inconclusive [15,19]. Thus, evaluation of the rates of and risks for birth defects after well-characterized exposure to ARV agents and other drugs during pregnancy is needed to assist in selecting appropriate treatment regimens for pregnant and reproductive age women.

The objectives of this study were to assess the rate of and risk factors for birth defects among infants born after *in utero* ARV exposure in the PACTG protocol 316, which evaluated the potential benefit in reduction of mother-to-child transmission of HIV of adding intrapartum and neonatal single-dose nevirapine to an established ARV regimen [7]. Participating women were well-characterized as to the timing and content of ARV during pregnancy, and infants were followed regularly for assessment of outcomes, including birth defects [21].

Methods

PACTG 316 study was a phase III, international, multicenter, randomized, placebo-controlled, double-blind study of intrapartum and newborn nevirapine in addition to standard ARV therapy for prevention of HIV transmission for HIV-infected pregnant women. Women were enrolled at PACTG sites in the US, Brazil, the Bahamas and at European sites participating in the Agence Nationale de Recherches sur le SIDA (ANRS) and the ECS networks between May 1997 and June 2000. The methods and primary outcome of this study have been described [7]. Women were eligible for enrollment if they were 13 years of age or older, were receiving a stable ARV regimen not including a non-

nucleoside reverse transcriptase inhibitor, and were able and willing to sign informed consent for participation. Enrollment was allowed anytime after 20 weeks of gestation. Gestational age was estimated using either reliable menstrual history that correlated with physical examination or sonogram performed before 20 weeks of gestation. Women were excluded if already enrolled in other treatment trials, if they had elevated alanine aminotransferase levels, if they had hypersensitivity to benzodiazepines, had received non-nucleoside ARV drugs in the past, or if they had a fetus with an anomaly incompatible with life in the current pregnancy.

Women and their infants were randomized to receive a single-dose of nevirapine or placebo to the mother at the onset of active labor and to the infant between 48 and 72 h after birth. Infants were evaluated with a complete history and physical examination at birth, between 48 and 72 h after birth, at 6–9 days, between four and six weeks, and at three and six months of age. Any abnormalities were reported on case report forms, and any ancillary evaluations done as part of clinical care, such as echocardiograms were captured. During the study, adverse events in the infants were reviewed on a monthly basis by the study team, and additional information was requested if needed to clarify diagnoses.

Women were required to be on ARV therapy for prevention of mother-to-child transmission of HIV at the time of enrollment. Timing of first exposure was categorized as first trimester if the woman conceived on or began ARV therapy within the first 12 completed weeks of pregnancy. Therapy begun after 12 completed weeks of gestation was categorized as second/third trimester exposure only.

For this analysis, all physical examination findings and diagnoses were reviewed by members of the protocol team who were blinded to the timing and type of ARV exposure. Defects were coded using the Metropolitan Atlanta Congenital Defect Program coding scheme, following the conventions of the APR to include infants with two or more conditional or minor defects as defect cases even in the absence of a major defect [4,19]. After an initial review by the PACTG 316 team, defects were further reviewed by one author (A.S.), defect reviewer for the APR. Defects were then grouped according to organ-system classification to allow grouping of defects with similar pathogenesis [17]. After classification of defects, the overall rate of defects, the rate of defects by trimester of earliest ARV drug exposure, and the rate of defects by organ/system were evaluated.

Of the 1506 women enrolled to the trial, 92 were excluded from the current analysis: 84 because the delivery date and data were missing, two because they lacked the start and stop dates for ARV therapy, and six because they did not receive ARVs during pregnancy, leaving 1414 for analysis.

Characteristics of women with first trimester vs. later ARV drug exposure were compared. The χ^2 -test and Fisher's exact test were used for comparisons of categorical variables. The Wilcoxon non-parametric test was used for comparison of continuous variables. Logistic models were developed using forward logistic regression.

Results

Enrollment characteristics of the 1414 women, 1408 with livebirths and six with stillbirths, categorized according to timing of earliest ARV drug use during pregnancy are shown in Table 1. Women with first trimester ARV exposure were older, more likely to be Caucasian, of lower parity, had lower CD4+ lymphocyte counts, and were more likely to receive combination therapy with protease inhibitors compared to single or dual nucleoside therapy. HIV RNA levels and rates of illicit drug use did not differ at enrollment between the groups.

Data on smoking, alcohol use, and first trimester opportunistic infection prophylaxis were not consistently available and are not reported here.

A total of 73 defects were detected among 59 liveborn infants and one stillborn infant, with nine infants having two defects, and two infants having three defects. The rate of infants with defects was 60 (4.2%, 95% CI 3.3–5.4) of 1414 infants. Four cases were included as defects based on the presence of two conditional, or minor, defects only (one plagiocephaly and severe nasal crease, two with nevus and umbilical hernia, and one with patent ductus arteriosus and peripheral pulmonic stenosis). Excluding these cases, the rate of infants with defects was 56 (4.0%) of 1414.

The rate of defects among infants with first trimester exposure was 30 (4.7%) of 636 and among infants with only later exposure was 30 (3.9%) of 778 ($P=0.43$). A variety of characteristics and exposures were evaluated to determine factors associated with the detection of a birth defect in the cohort (Table 2). ARV exposure in the first trimester, including any exposure, any nucleoside agent, zidovudine, or any protease inhibitor, was not associated with an increased risk of defects. Only maternal HIV RNA at enrollment was associated with risk of birth defects on univariate analysis and remained the only significant factor on multivariate logistic regression (results not shown).

The organ-system classification of defects according to trimester of first ARV drug exposure is shown in Table 3. The occurrence of defects was balanced between the first trimester compared to later exposure groups except that any type of heart defect occurring in 16 (2.5%) of 636 infants with first trimester ARV exposure and in six (0.8%) of 778 infants with later exposure ($P=0.02$). The overall rate of any heart defect was 1.6% (95% CI 1.0–2.4%).

All infant heart defects are listed in Table 4 according to trimester of earliest ARV exposure along with specific drug exposures and organ/system classification. The heterogeneity of the defects makes assessment of ARV risk difficult. Whereas both cases of conotruncal defects occurred in infants with first trimester exposure to ARVs, one case was associated with trisomy 21, a known risk factor for heart defects. The three anatomic right-sided obstructive defects occurred after second or third trimester exposure to ARVs. The right-sided obstructive defects seen after first trimester exposure were peripheral pulmonic stenosis, a functional defect noted along with other structural heart defects. Two different left-sided obstructive defects were noted after first trimester exposure. The “heart-other” group of defects included a variety of cases, most commonly septal defects. Evaluating the rate of septal defects in this group, including the case of persistent patent foramen ovale, we found seven cases among 636 (1.1%) infants with first trimester exposure whereas four cases (0.5%) occurred among 778 infants with later exposure ($P=0.21$). The overall rate of ventricular septal defects was 0.6%. Of note, two cases of cardiomyopathy were diagnosed along with a case of septal hypertrophy, which may be indicative of cardiomyopathy. All three of these infants were HIV-uninfected.

Discussion

The overall rate of birth defects of 4.2% is somewhat higher than the rate of 2.7% detected in a population of HIV-infected women with similar demographic characteristics in the prospective report of the APR [19]. It is not surprising that infants enrolled to a clinical trial with intensive newborn follow-up may have a higher rate of detected defects than those with only routine care, which is the case for most infants reported to the APR. While no specific additional testing was mandated by the protocol, subjects on study may be more likely to receive ancillary testing to clarify physical findings, such as heart murmurs. In addition,

reports to the APR are made primarily by the prenatal care provider who may not be aware of defects detected in infant after the birth, whereas infants were followed on study for 6 months. Among infants reported to the APR from clinical trials during pregnancy, the rate of defects is 3.1%, with a rate of 5.6% with first trimester drug exposure, suggesting differential follow-up in clinical trials [19]. In a report of infant outcomes from the PACTG 076 study of zidovudine vs. placebo for prevention of maternal-to-child transmission, major defects were diagnosed among 36 (8.6%) of the 417 live born infants, although no ARV exposure occurred before the second trimester [18]. All women in PACTG076 had CD4+ lymphocyte counts above 200 cells/ μ L, so were unlikely to be receiving trimethoprim/sulfa prophylaxis. Thus, while the overall rate of defects in this study is higher than in the APR and probably related to enhanced ascertainment, the lack of association of defects with ARV exposure is reassuring.

Using the organ/system classification to group defects expected to have similar pathogenesis revealed an increased rate of heart defects overall among infants with first trimester ARV exposure compared to only later exposure, but not in specific subgroups of defects. Conotruncal defects and obstructive left-sided defects occurred only after first trimester exposure but were too infrequent to allow assessment of an association with ARV exposure. Conotruncal heart defects reported to the APR are reviewed specifically as part of the semi-annual review of data, and no association with ARV exposure has been reported to date [19]. Continuing surveillance is warranted.

The other heart defects category is heterogeneous, making it difficult to associate with ARV's. In the current study, cardiac septal defects were common but the rate of septal defects was not significantly different by trimester of exposure. The rate of ventricular septal defects, 0.6%, was slightly higher than the rates of 0.25–0.5% reported in the literature, again likely related to increased ascertainment related to study participation [2,14]. Of note, the prevalence of congenital heart disease has been found to be increasing in the US overall, most likely due to improved ascertainment [2]. In addition, wide variability in rates of mild atrial and ventricular septal defects has been noted, probably related to regional or temporal differences in use of diagnostic techniques [11]. An increased rate of atrial and ventricular septal defects after first trimester zidovudine exposure was reported to the APR from two clinical studies, the PACTG 185 randomized clinical trial of hyperimmune globulin for prevention of mother-to-child transmission and a German multicenter clinical study [19]. A recent detailed analysis of all ventricular septal cases reported among prospective cases in the APR did not find an association between these defects and ARV exposure, but surveillance continues [19].

The finding of two cases of cardiomyopathy and a case of septal hypertrophy among HIV-infected infants with *in utero* exposure to ARVs is concerning. While HIV infection alone in the infant is a known risk factor for cardiomyopathy [8], exposure to nucleoside analogs has also been associated with the development of cardiomyopathy in HIV-uninfected children [6]. One case of cardiomyopathy was noted among the 122 infants who received zidovudine in the PACTG 076 study and were followed in PACTG219 [5]. In a study of both HIV-infected and HIV-exposed, uninfected children compared to HIV and ARV unexposed controls, infants born to HIV-infected women were had lower fractional shortening at birth suggestive of left ventricular dysfunction, which persisted up to four months in HIV-exposed but uninfected infants [12]. Mitochondrial damage in cardiac and skeletal muscle has been shown in mice and monkeys after dosing schedules with nucleosides *in utero* and in the newborn period similar to human prophylaxis regimens [1,9]. Cardiomyopathy has myriad causes. The repeated reporting of cardiomyopathy cases in studies of ARV agents in pregnancy indicates the need for ongoing long-term surveillance.

A limitation of our study is the lack of complete data on smoking, alcohol use, and opportunistic infection prophylaxis exposure during pregnancy. A previous study suggested that the combination of ARV agents and folate antagonists in the first trimester, most commonly trimethoprim-sulfa used for prevention of PCP, increased the risk of birth defects [3]. While we were unable to evaluate this directly, CD4+ lymphocyte count at enrollment <200 cells/ μ L, an indication for PCP prophylaxis, was not associated with an increased risk of birth defects. Women with fetuses with defects incompatible with life were excluded from enrollment, thus severe defects, such as anencephaly may be underrepresented in this study. A recent study from Europe found that pregnancy termination occurred in 88% of cases after prenatal diagnosis of trisomy 21 or neural tube defects, and we do not have data on such cases that may have been diagnosed before enrollment [3]. We do not have complete data on women who were screened but found not to be eligible for enrollment. Another limitation is the lack of exposure to non-nucleoside reverse transcriptase inhibitors including efavirenz by study design and the limited array of protease inhibitors available during the study period.

The data presented here from a large clinical trial provide reassuring evidence that first trimester exposure to ARV agents does not increase the risk of non-lethal birth defects. However, the increased rate of heart defects with early exposure, suggested in previous analyses as well, underscores the need for continuing evaluation, especially as newer ARV agents are approved and increasingly complex regimens are used. All providers are urged to report cases of women with ARV exposure during pregnancy as early in pregnancy as possible to the APR (details at www.APRegistry.com) to allow continued surveillance.

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Dr. Myron J. Levin and Dr. Adriana Weinberg (The Denver Medical Center), Susan Laverty, RN and Dr. Geoffrey A. Weinberg (University of Rochester), Dr. Hannah Gay and Netta Boudreaux, RN (University of Mississippi Medical Center), Dr. Susanne R. Lavoie and Tima Y. Smith, RN (Medical College of Virginia), Dr. Edwin Thorpe and Ms. Nina Sublette (The Regional Medical Center), Dr. Dan Lancaster and Dr. Debra Terry (Methodist Hospital Central), Dr. Gregory J. Wilson and Peggy Bender, FNP (Vanderbilt University Medical Center), I. Heyer, RN, BSN and Dr. L. Lugo (University of Puerto Rico), Harold W. Lischner, MSN and Kelly R. Hassey, MSN, CRNP (St. Christopher's Hospital for Children), Deb Goldman, ARNP and Dr. Jane Hitti (Children's Hospital and Medical Center), Dr. Robert Maupin and Dr. Thomas Alchediak (Tulane University Hospital), Dr. Katherine Luzuriaga and Sheila Noone, RN, PhD (University of Massachusetts Medical School), Dr. Juan C. Salazar and Dr. Winston Campbell (University of Connecticut), Gail Karas, RN and Dr. Juan C. Salazar (Connecticut Children's Medical Center), Dr. George Wendel and Dr. Janet Squires (Children's Medical Center), Dr. Theodore Jones and Dr. Ellen Moore (Children's Hospital of Michigan), Dr. Mobeen Rathore and Dr. Isaac Delke (University of Florida Health Sciences Center), Dr. Jaime Deville and Maryanne Dillon, BSN (University of California Medical Center), Dr. Ruth Tuomala (Brigham and Women's Hospital), Dr. Sandra Burchett (Children's Hospital), Dr. John Farley and Barbara Davis, RN, M Ed. (University of Maryland), Dr. Kenneth Rich and Dr. Mark Vajaranant (University of Illinois), Dr. Indu Pathak and Dr. Hamida Khakoo (Metropolitan Hospital Center), Dr. Nancy Wade and Dr. Renee Samelson (Children's Hospital at Albany Medical Center), Emily Barr and Dr. John Nosovitch (State University of New York Upstate Medical University), Pam Daniel and Patty Kohler, RN (University of Cincinnati), Dr. Margaret Keller and Marie Beall (Harbor University of California Medical Center), Angela Ranzini and Marian Lake (St. Peter's Medical Center), Dr. Robert Pass and Dr. Marilyn Crain (University of Alabama), Dr. Valerie Whiteman and Dr. Ellen Tidaldi (Temple University School of Medicine), Carla Duff, RN and Dr. John Sleaseman (University of Florida, Gainesville), Dr. Hector Cintron and Wanda Figueroa (Ramon Ruiz), Dr. George Johnson and Moya Clarkson, RN (Medical University of South Carolina), Dr. Savita Pahwa (North Shore LIJ Research Institute), Dr. Sunanda Gaur and Patricia Whitley Williams (Robert Wood Johnson AIDS Program), Dr. Michael Hughes and Dr. David Shapiro (Statistical and Data Analysis Center, Harvard School of Public Health). **European Collaborative Study:** Dr. I. Grosch-Wörner, Dr. K. Seel (Charite Virchow-Klinikum, Berlin, Germany); Dr. J. Jimenez (Hospital 12 De Octubre, Madrid, Spain); Dr. A.B. Bohlin, Dr. S. Lindgren (Huddinge and Karolinska Hospitals, Sweden); Dr. A. Mür, Dr. A. Paya (Hospital del Mar, Barcelona, Spain); Dr. O. Coll, Dr. C. Fortuny (Hospital Clinic, Barcelona, Spain); Dr. M. Casellas Caro (Hospital Vall D'Hebron, Barcelona, Spain); Dr. M. Leyes, Dr. L. Ciria (Hospital Son Dureta, Mallorca); Prof. P. Martinelli, Dr. W. Buffolano, Dr. M. Sansone (II Policlinico, Naples, Italy); Dr. C. Tibaldi, Dr. N. Ziarati (S Anna Hospital, Torino, Italy); Dr. S. Alberico, Dr. C. Salvatore (Burlo Garofolo Hospital, Trieste, Italy); Prof. M. Temmerman (University of Ghent); Dr. I. Hoesli, Dr. C. Rudin (University of Basel); Dr. X. Carnet, Dr. J. Pich (Clinical Pharmacology Unit, University of Barcelona); Dr. M. Ravizza, Prof. G. Pardi, Dr. L. Mangiarotti (San Paolo Hospital, Milan, Italy); Dr. V. Savasi, Dr. A.E. Semprini, Prof. E. Ferrazzi (Sacco Hospital, Milan, Italy); Dr. M. Sharland, Ms. T. Chester (St. George's Hospital, London UK), Dr. A. Fakoya (Newham General Hospital, London, UK), Dr. G. Scaravelli (PUI, Rome, Italy), Dr. W. Coroleou, Dr. Cavalle Gelabret (H. Germans Trias I pujol, Badalona, Spain) Prof. C. Loveday (University College London, UK); **France:** Scientific Committee: Annie Metro (ANRS), Marie-Jeanne Mayaux, Stephane Blanche, Christine Rouzioux, Marc Tardieu [Enquete Pediatrique Francaise (EPF)]; Jean-Pierre Aboulker (Service Commun 10, INSERM); Bertrand Baumelou (Boehringer Ingelheim, France); Clinicians: Veronique Chambrin, Hassina Razafimahefa (Hopital Antoine Beclere, Clamart), Laurent Mandelbrot, Guislaine Firtion (Hopital Cochin-Port Royal, Paris), Nicole Ciraru-Vigneron, Claudine Bruner (Hopital Lariboisiere, Paris), Alain Berrebi, Joelle Tricoire (Hopital Purpan, Toulouse), Claude Hocke, Daniele Douard (Hopital Pellegrin, Bordeaux), Catherine Crenn-Hebert, Corinne Floch-Tulal (Hopital Louis-Mourier, Colombes), Etienne Wilmer, Annick Ottenvalter (Hopital Robert Debre, Paris), Marie-Aude Khuong, Jean-Marc Retbi (Hopital Delafontaine, Saint-Denis), Vincent Jeantils, Eric Lachassine (Hopital Jean-Verdier, Bondy), Sophie Matheron, Jean-Louis Benifla (Hopital Bichat-Claude-Bernard, Paris), Cristianne Huraux-Rendu, Joelle Teboul (Hopital Henri-Mondor, Creteil), Deborah Fried, Brigitte Heller-Roussin (Hopital Intercommunal Montreuil), Brigitte Clavier, Veronique Brossard (Hopital Charles Nicolle, Rouen), Andre Bongain, Fabrice Monpoux (Hopital de l'Archet, Nice), Michel Levardon, Fabienne Mazy (Hopital Beaujon, Clichy), Veronique Cayol, Catherine Dolfus (Hopital Saint-Antoine-Trousseau, Paris), Paul Benos, Joelle Nicolas (Hopital Arnaud De Villeneuve, Montpellier), Daniel Raudrant, Laurent Cotte (Hopital de l'Hotel Dieu, Lyon), Cecile Francois, Françoise Mechinaud (Hopital de l'Hotel-Dieu, Nantes), Rose Nguyen, Adrien May (Hopital Louise Michel, Evry), Benedicte Mougeon, Alain Devidas (Hopital Gilles de Corbeil, Corbeil); **Brazil:** Dr. Susie Andries Nogueira, Dr. Márcia Bondarowsky (Federal University of Rio de Janeiro, Brazil), Esaú Custódio João Filho, MD, Marcos Machado D'Ippolito, MD (Hospital dos Servidores in Rio de Janeiro, Brazil); **Bahamas:** Dr. M. Perry Gomez, Dr. P. McNeil (Princes Margaret Hospital, Bahamas).

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Table 1

Characteristics at enrollment of the mothers and their pregnancies according to timing of earliest antiretroviral therapy during pregnancy

Characteristic	First trimester (n=636)	Second/third trimester (n=778)	P-value	Total (n=1414)
Mean age (years)	29.2	27.4	<0.0001 ^a	28.2
Race/ethnicity				
Caucasian, non-Hispanic	179 (28%)	138 (18%)	<0.0001 ^b	317 (22%)
Black, non-Hispanic	347 (55%)	480 (62%)		827 (58%)
Hispanic	100 (16%)	153 (20%)		253 (18%)
Other	10 (2%)	7 (1%)		17 (1%)
Illicit drug use this pregnancy	84 (13%)	107 (14%)	0.77 ^c	191 (14%)
CD4+ lymphocyte count ^d				
≥400 cells/μL	322 (51%)	468 (60%)	0.001 ^c	790 (56%)
200–399 cells/μL	220 (35%)	230 (30%)		450 (32%)
<200 cells/μL	93 (15%)	80 (10%)		173 (12%)
HIV RNA level (copies/mL) ^d				
<400	220 (35%)	245 (32%)	0.68 ^c	465 (33%)
400–2499	230 (36%)	281 (36%)		511 (36%)
2500–4999	53 (8%)	75 (10%)		128 (9%)
5000–10,000	40 (6%)	55 (7%)		95 (7%)
>10,000	91 (14%)	120 (15%)		211 (15%)
Most complex ARV regimen				
Single nucleoside	62 (10%)	270 (35%)	<0.0001 ^c	332 (24%)
Dual nucleoside	224 (35%)	273 (35%)		497 (35%)
Combination with PI	350 (55%)	235 (30%)		585 (41%)
Pregnancy outcome				
Live birth	635 (99.8%)	773 (99.4%)	0.23 ^b	1408 (99.6%)
Stillbirth	1 (0.2%)	5 (0.6%)		6 (0.4%)
Spontaneous loss	0 (0%)	0 (0%)		0 (0%)
Termination	0 (0%)	0 (0%)		0 (0%)

ARV=antiretroviral, PI=protease inhibitor.

Note: All percentages are column percentages.

^a Wilcoxon two-sample test

^b Fisher exact test

^c χ^2 -test

^d One woman did not have a CD4+ lymphocyte count result, and two women did not have HIV RNA results available.

Table 2

Evaluation of factors associated with any defect

Characteristic	Defect (n=60)	No defect (n=1354)	P-value
Mean age (years)	29.3	28.2	0.18 ^a
Race/ethnicity			
Caucasian	21 (7%)	296 (93%)	0.10 ^b
Black	30 (4%)	797 (96%)	
Hispanic	8 (3%)	245 (97%)	
Other	1 (6%)	16 (94%)	
Illicit drug use this pregnancy	10 (5%)	181 (95%)	0.44 ^b
CD4+ lymphocyte count			
≥400 cells/μL	34 (4%)	756 (96%)	0.99 ^c
200–399 cells/μL	19 (4%)	431 (96%)	
<200 cells/μL	7 (4%)	166 (96%)	
HIV RNA level (copies/mL)			
<400	28 (6%)	437 (94%)	0.05 ^c
400–5000	22 (3%)	618 (97%)	
>5000	9 (3%)	296 (97%)	
Any ARV drug			
First trimester	30 (5%)	606 (95%)	
Second/third trimester	30 (4%)	748 (96%)	0.43 ^b
Any zidovudine			
First trimester	23 (4%)	494 (96%)	
Second/third trimester	20 (3%)	576 (97%)	0.35 ^b
Any protease inhibitor			
First trimester	17 (5%)	351 (95%)	
Second/third trimester	11 (4%)	244 (96%)	
None	32 (4%)	759 (96%)	0.89 ^b

ARV=antiretroviral.

Note: All percentages are row percentages.

^a Wilcoxon two-sample test
^b Fisher (or Fisher-Freeman-Halton) exact test
^c χ^2 -test.

Table 3
Organ/system listing of birth defects (not infants) detected according to antiretroviral (ARV) exposure

Birth defect	Earliest ARV exposure	
	First trimester	Second/third trimester
Heart and circulatory defects	18 defects in 16 infants	7 defects in 6 infants
Conotruncal heart defects	2	0
Obstructive heart defects-right-sided	3	3
Obstructive heart defects-left-sided	2	0
Heart-other defects ^a	11	4
Other circulatory defects	0	0
Central nervous system	0	1
Face/neck	2	2
Cleft lip or palate	0	2
Respiratory	1	0
Upper gastrointestinal	1	1
Lower gastrointestinal system	0	1
Male genitalia	3	3
Female genitalia	0	1
Renal and urinary system	2	4
Limb reduction/addition	2	1
Other musculoskeletal defects	2	10
Skin and skin derivatives	0	4
Chromosome anomaly	1	2
Total defects	34	39

^aHeart-other defects includes atrial septal defects other than primum, ventricular septal defects, single coronary artery, and cardiomyopathy.

Table 4
Listing of specific heart defects in infants according to trimester of ARV exposure

Defect	Exposure	Organ/system category
First trimester exposure		
Tetralogy of Fallot, trisomy 21	ZDV, 3TC, saquinavir	Cono-truncal
Double outlet right ventricle, transposition of the great vessels	ZDV, 3TC	Cono-truncal
Persistent PDA, PPS	ZDV, 3TC, nelfinavir	Obstructive right-sided
VSD, PPS	D4T, DDI, nelfinavir	Heart-other; obstructive right-sided
Muscular VSD, PPS	ZDV	Heart-other; obstructive right-sided
Bicuspid aortic valve	3TC, nelfinavir	Obstructive left-sided
Aortic coarctation	ZDV, 3TC, indinavir	Obstructive left-sided
Single coronary artery, neonatal death	ZDV	Heart-other
ASD	ZDV, 3TC, nelfinavir	Heart-other
Symptomatic patent foramen ovale	ZDV, 3TC	Heart-other
VSD	ZDV, 3TC	Heart-other
VSD	D4T, 3TC	Heart-other
VSD	ZDV, indinavir	Heart-other
VSD	ZDV, 3TC	Heart-other
Cardiomyopathy	D4T, 3TC, ZDV	Heart-other
Cardiomyopathy	ZDV, 3TC	Heart-other
Second/third trimester exposure		
Septal hypertrophy, pulmonary branch stenosis	ZDV	Obstructive right-sided
Valvular pulmonic stenosis	ZDV, 3TC, indinavir	Obstructive right-sided
ASD, VSD, pulmonic stenosis	ZDV, 3TC, nelfinavir	Heart-other, obstructive right-sided
Persistent foramen ovale (>6 months)	ZDV	Heart-other
VSD	ZDV, 3TC, nelfinavir	Heart-other
VSD	ZDV	Heart-other

ZDV=zidovudine, 3TC=lamivudine, PDA=patent ductus arteriosus, PPS=peripheral pulmonic stenosis, D4T=stavudine, DDI=didanosine, VSD=ventricular septal defect, ASD=atrial septal defect.