Published in final edited form as:
J Acquir Immune Defic Syndr. 2010 February 1; 53(2): 176–185. doi:10.1097/QAI.0b013e3181c5c81f.

Maternal Antiretroviral Use during Pregnancy and Infant Congenital Anomalies: The NISDI Perinatal Study

Esau C. Joao, MD[1], **Guilherme A. Calvet, MD, MS**[1], **Margot R. Krauss, MD, MPH**[2], **Laura Freimanis Hance, MD, PhD**[2], **Javier Ortiz, MD**[3], **Silvina A. Ivalo, MD**[4], **Russell Pierre, DM, MPH**[5], **Mary Reyes, MD**[6], **D. Heather Watts, MD**[7], and **Jennifer S. Read, MD, MS, MPH [on behalf of for the NISDI Perinatal Study Group]**[7,*]

[1] Hospital dos Servidores do Estado, Rio de Janeiro, Brazil

[2] Westat, Rockville, MD, USA

[3] Instituto Nacional de Perinatologia, Mexico City, Mexico

[4] Hospital José María Ramos Mejía, Buenos Aires, Argentina

[5] University of the West Indies, Kingston, Jamaica

[6] Universidad National Mayor de San Marcos, Lima, Peru

[7] Pediatric, Adolescent, and Maternal AIDS Branch, CRMC, NICHD, National Institutes of Health, DHHS, Bethesda, MD, USA

Abstract

Background—We evaluated the association between maternal antiretrovirals (ARVs) during pregnancy and infant congenital anomalies (CAs), utilizing data from the NISDI Perinatal Study.

Methods—The study population consisted of first singleton pregnancies on study, ≥ 20 weeks gestation, among women enrolled in NISDI from Argentina and Brazil who delivered between September 2002 and October 2007. CAs were defined as any major structural or chromosomal abnormality, or a cluster of two or more minor abnormalities, according to the conventions of the Antiretroviral Pregnancy Registry. CAs were identified from fetal ultrasound, study visit, and death reports. The conventions of the Antiretroviral Pregnancy Registry were used. Prevalence rates [number of CAs per 100 live births (LBs)] were calculated for specific ARVs, classes of ARVs, and overall exposure to ARVs.

Results—Of 1229 women enrolled, 995 pregnancy outcomes (974 LBs) met the inclusion criteria. Of these, 60 infants (59 LBs and 1 stillbirth) had at least one CA. The overall prevalence of CAs (per 100 LBs) was 6.2 (95%CI = 4.6, 7.7). The prevalence of CAs after first trimester ARVs (6.2; 95% CI = 3.1, 9.3) was similar to that after second (6.8; 95%CI = 4.5, 9.0) or third trimester (4.3; 95%CI = 1.5, 7.2) exposure. The rate of CAs identified within seven days of delivery was 2.36 (95%CI: 1.4–3.3).

Corresponding author: Esaú Custódio João, MD, Infectious Diseases Department – Hospital dos Servidores do Estado, Rua Sacadura Cabral 178, 4° andar – anexo IV - Pesquisa Clínica, Saúde - Rio de Janeiro, RJ, Brazil, CEP: 20221-903, Tel.: 55.21.2518-1594; FAX: 55.21.2263-7135, esau@uninet.com.br.
*See Appendix for listing of study group members.

Presented in part: at the 48th Annual ICAAC/IDSA 46th Annual Meeting; Washington, DC; October 25–28, 2008 [abstract 964]

Conflict of interest: There are no conflicts of interest to disclose.

Conclusions—The prevalence of CAs following first trimester exposure to ARVs was similar to that following second or third trimester exposure. Continued surveillance for CAs among children exposed to ARVs during gestation is needed.

Keywords

HIV-1; pregnancy; antiretrovirals; congenital anomalies

INTRODUCTION

The increasing complexity of antiretroviral (ARV) regimens used during pregnancy for treatment of HIV-1-infected women and for prevention of mother-to-child transmission of HIV-1 raises concerns regarding potential ARV-related adverse events such as low birth weight, preterm birth, stillbirth, and teratogenicity.[1–5] Also, many HIV-1-infected women use other drugs (in addition to ARVs) during pregnancy with potentially teratogenic effects, such as trimethoprim/sulfamethoxazole prescribed for *Pneumocystis jiroveci* pneumonia prophylaxis.

The estimated proportion of children in Latin America with congenital anomalies (CAs) ranges from 0.4% to 8.4%.[6–11] There are few data addressing the relationship between maternal ARVs during pregnancy and infant CAs in Latin America. Therefore, we analyzed data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Study, a prospective cohort study of HIV-1-infected women and their children conducted at multiple sites in Latin America and the Caribbean, in order to determine the prevalence of CAs in this population, overall and according to *in utero* exposure to ARVs.

METHODS

The NISDI Perinatal Study

The NISDI Perinatal Study is a prospective cohort study conducted at Latin American and Caribbean clinical sites where, at a minimum, ARV prophylaxis and alternatives to breastfeeding are available. The primary objectives include characterizing adverse events among infants born to HIV-1-infected women.[12] Enrollment began in September 2002, and is ongoing. Prior to enrollment, all women provide signed informed consent for enrollment of themselves and their infants. Infant study visits are conducted before hospital discharge after birth, at 6–12 weeks, and six months of age. During each of these study visits, the infant's parent or guardian is interviewed, a physical examination is conducted, and laboratory samples are obtained. The protocol was approved by the ethical review boards of each clinical site enrolling subjects, the sponsoring institution (NICHD), and the data management and statistical center (Westat).

Clinical, immunologic, and virologic characteristics of the women are assessed during pregnancy, at the time of hospital discharge after delivery, and at the 6–12 week postpartum visit. Maternal clinical disease staging[13] is performed at each study visit. A maternal history of substance use during the index pregnancy is ascertained through maternal interview at enrollment. Infant gestational age at birth (in completed weeks) is determined either by obstetric estimation (dates of last menstrual period with or without ultrasonography)or by pediatric newborn examination (Ballard et al[14], Dubowitzet al[15] or Capurro et al[16]).

Study Population

The study population was restricted to women enrolled in the NISDI Perinatal Protocol as of October 2007 for the first time (second pregnancies on-study excluded) who delivered a singleton infant (live born or stillborn) ≥ 20 weeks gestation. Additionally, the study population was restricted to infants of mothers from Brazil and Argentina, since the great majority of subjects were enrolled in these two countries.

Primary Exposure and Outcome Variables for This Analysis

ARV regimens were determined by the subject's clinician, independent of participation in the NISDI Perinatal Study. Both Argentinean and Brazilian guidelines for the use of antiretrovirals during pregnancy[17–18] indicate that all HIV-infected women should be evaluated for the need of ARV treatment during pregnancy. ARV treatment should be continued or initiated according to the HIV disease stage of the pregnant woman. For those women who do not require ARV treatment, ARV prophylaxis should be administered throughout pregnancy and continued intrapartum. If prophylaxis is not initiated during pregnancy, intrapartum zidovudine should be administered intravenously.

We first described the overall receipt of ARVs during pregnancy. ARV regimens received during pregnancy were categorized in the following manner: none; one or two nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs; two NRTIs with one non nucleoside reverse transcriptase inhibitor (NNRTI) (HAART-NNRTI); two NRTIs with one protease inhibitor (PI) (HAART-PI), and other. If two HAART regimens were received for 28 days or more during pregnancy, the regimen received later in pregnancy took precedence overa regimen received earlier during pregnancy.

We analyzed the relationship between ARV use during the first trimester of pregnancy and CAs, since this is the trimester of fetal organogenesis. For these analyses, we focused on the earliest regimen used for at least 28 days during the first trimester of pregnancy and specific ARVs used during the first trimester.

A CA was defined as any major structural or chromosomal abnormality, or any cluster of two or more minor (conditional) abnormalities, occurring in infants or fetuses of at least 20 weeks gestational age based on the same criteria as used by the Antiretroviral Pregnancy Registry (APR)[19] and the Metropolitan Atlanta Congenital Defects Project (MACDP).[20] CAs were identified through fetal ultrasound, study visit, and death reports up to the child's six month follow-up visit. Infants with multiple congenital anomalies were counted as a single outcome for analysis, and CAs were grouped according to organ system[21] for reporting.

Other Variables

In addition to the primary exposure and outcomes variables of interest (maternal ARV use during pregnancy, especially during the first trimester, and infant CAs), we examined other variables in relation to the presence or absence of CAs. These variables were: maternal demographic characteristics (marital status; country of residence; age; years of formal education; gainful employment outside of the home); maternal HIV disease stage (CD4 count and CD4 percentage; plasma HIV-1 RNA concentration; clinical disease stage – both at enrollment and prior to delivery); obstetrical characteristics (gravidity; parity), other medical characteristics (body mass index; toxoplasmosis, rubella, cytomegalovirus, *Herpes simplex* virus, and syphilis during pregnancy; sexually transmitted infections; diabetes; hypertension; infectious and non-infectious renal disease during pregnancy); maternal alcohol, tobacco, and illicit drug use during pregnancy; folate antagonist and other class D drug exposures during pregnancy; and folic acid supplementation during pregnancy.

Statistical Analysis

The prevalence of CAs was calculated by dividing the number of CAs reported among pregnancy outcomes ≥ 20 weeks of gestation (stillborn and live born) by the total number of live births (LBs). Prevalence of CAs were calculated for those ARV exposures with more than 200 mother-infant pairs, following the APR convention.[19] Ninety-five percent confidence intervals (95%CIs) were calculated using a Poisson distribution. Fisher's exact test was used to assess associations between CAs and study characteristics, in particular ARV and folate antagonist use during pregnancy. Variables at least marginally associated with CA ($p < 0.20$) were considered candidates for multivariable logistic regression modeling. SAS software (Cary, NC) was used for all analyses.

RESULTS

Derivation of the Study Population

As of October 2007, 1229 women had enrolled in the NISDI Perinatal Study, of whom 1079 (87.8%) were enrolled in Argentina or Brazil. Of these enrollments, two women were not followed to delivery (one died, one was lost to follow-up). Of the remaining 1077 enrollments, 55 (5.1%) represented the second (or greater) pregnancy on study, and were excluded. Of the 1022 first pregnancies on study, 21 (2.1%) multiple gestation pregnancies were excluded. Of the remaining 1001 women with singleton outcomes, six (0.6%) experienced pregnancy losses before 20 weeks gestation, and were excluded. Among the remaining 995 pregnancy outcomes ≥ 20 weeks gestation, there were 974 (97.9%) LBs, one (0.1%) therapeutic abortion, and 20 (2.0%) stillbirths.

Maternal Antiretroviral Use during Pregnancy

Overall, 988 (99.3%) of the 995 women in the study population received one or more ARVs during pregnancy, with 249 (25.0%) receiving at least one ARV during the first trimester of pregnancy. The seven women categorized as not receiving ARVs during pregnancy included four women who received ARVs only at the time of delivery and three who had no record of receiving ARVs during the index pregnancy. Six of the seven women had a live birth.

Congenital Anomalies among Infants

CAs were detected among 60 infants (59 LBs and one stillbirth) *in utero* or postnatally through the six month study visit, for an overall prevalence of 6.16 per 100 LBs (95%CI = 4.60–7.72). Excluding infants with only minor (conditional) anomalies, the prevalence was 5.75 per 100 LBs (95%CI = 4.24–7.24). The prevalence of CAs detected within the first seven days of life only was 2.36 per 100 LBs (95%CI = 1.40–3.33), including two infants with patent foramen ovale (PFO). There were no infants included only because of minor (conditional) anomalies. Of the 60 infants with CAs, 41 had a single anomaly, 16 had two anomalies, and three had multiple anomalies. The specific CAs detected, grouped by organ system and first ARV exposure, are listed in Table 1. As shown in this table, the cardiovascular and musculoskeletal systems were most often affected.

Characteristics of the Study Population, and Associations with Congenital Anomalies

Characteristics of the study population, overall and according to the presence or absence of CAs, are shown in Tables 2 and 3. Of the covariates examined, only marital status of the mother ($P = 0.01$) was associated with CAs. The remaining variables were not associated with CAs, including: use of ARVs at conception or at enrollment; the number of ARV regimens used for 28 days or more during pregnancy, the first ARV regimen used for 28 days during the first trimester and the last ARV regimen used for 28 days or more during pregnancy. There was no statistically significant association between the trimester of first ARV exposure and infant CAs

(P = 0.52). Multivariable analyses were not performed since the main exposures of interest were not statistically associated with infant CAs, and did not meet our minimal entry criteria of P < 0.20 for multivariable modeling.

Prevalence of Congenital Anomalies, Overall and According to In Utero Exposure to Antiretrovirals

The prevalence of CAs among HIV-1-infected women who first received ARVs at the time of conception or during the first trimester was 15 of 242 LBs (6.20 per 100 LBs; 95% CI = 3.06–9.34); second trimester exposure: 35 of 518 LBs (6.76 per 100 LBs, 95% CI = 4.52–9.00); third trimester exposure: nine of 208 LBs (4.33 per 100 LBs, 95% CI = 1.50–7.15); and, no ARV exposure during pregnancy: one of 6 LBs (16.67 per 100 LBs, 95%CI = 0–49.33) (Table 4). Prevalence of CAs according to ARV class, specific ARVs, and any ARV exposure, by trimester, are shown in Table 5. The 95% confidence interval estimates for the prevalence rates generally overlap, suggesting that there are no significant differences in the prevalence of CAs according to ARV class or specific ARVs.

DISCUSSION

In this study of HIV-1-infected women and their infants in Argentina and Brazil, the overall prevalence of CAs was 6.16/100 LBs. The prevalence of CAs following first trimester exposure to ARVs (6.20/100 LBs) did not appear significantly different from that following second (6.76/100 LBs) or third trimester (4.33/100 LBs) exposure. In addition, the prevalence of CAs did not appear to differ significantly according to ARV class, specific ARVs, and any ARV exposure. Marital status, associated with CAs in univariate analysis, presumably is a proxy for other environmental and/or socioeconomic factors.

The prevalence of CAs within seven days of birth (2.4%) in our study population is similar to that at delivery (2.8%) reported by the Latin American Collaborative Study of Congenital Malformations (ECLAMC)[10], a hospital-based program for the clinical and epidemiological investigation of CAs. ECLAMC reports on CAs among approximately 200,000 births per year, including both major and minor anomalies diagnosed prior to hospital discharge after birth for infants weighing 500 grams or more. Participating countries include Argentina, Brazil, Chile, Ecuador, Peru, and Venezuela.

The overall prevalence of CAs in our study population is within the range reported among the general population in Latin America. Very low rates have been reported in studies utilizing birth certificate data or medical records: 0.4% in Vitoria, Brazil[6], 0.8% in Rio de Janeiro[7], and 1.4% in Pelotas, Brazil[8]. In relatively small, retrospective cohort studies of HIV-1-infected women, the observed prevalence of CAs was 2.3% in Buenos Aires, Argentina[22] and 2.2% in Rio de Janeiro, Brazil.[23] Other studies have reported CA rates ranging from 1.7% in Rio de Janeiro, Brazil[9]; 2.2% in Argentina (personal communication, Silvina Ivalo); 4.7% in Brazil[24]; and 8.4% in Chile.[11]

The overall prevalence of CAs in our study population is higher than that reported in other, large studies of HIV-1-infected women and their infants[19, 25–27], and the higher prevalence of CAs observed in our study could be attributed to its prospective design, with follow-up of infants until six months after birth and with reporting of both minor and major anomalies. However, the prevalence of CAs detected within the first seven days of life (2.36/100 LBs) is similar. Most importantly, our results showed no difference in the prevalence of CAs according to trimester of exposure to ARVs, consistent with previous studies of *in utero* ARV exposure and infant CAs.

One of the largest sources of data regarding *in utero* ARV exposure and CAs is the APR (130 CAs among 4530 LBs, or 2.9 CAs/100 LBs)[19], a voluntary registry, including data from the U.S. and other countries, with prospective assessment of exposure. The great majority of data utilized within the APR are collected at the time of birth or shortly thereafter. However, in some cases data collected through the first 1–6 years after birth are used for categorizing infant CAs. For the overall population exposed to ARVs in this registry, no increase in risk of either CAs overall or specific CAs has been detected to date when compared with observed prevalence for "early diagnoses" in population-based birth defects surveillance systems or with prevalence among those with earliest ARV exposure in the second trimester or third trimester. In analyzing individual drugs with sufficient data to warrant separate analyses, an increased frequency for CAs has been detected for didanosine, but without an increase in the prevalence of a specific anomaly.[19] Analyses of data collected within the first 18 months of life for HIV-exposed infants enrolled in the Women and Infants Transmission Study (WITS) (90 CAs among 2527 LBs, or 3.6 CAs/100 LBs) revealed a statistically significant elevated rate of hypospadias after first trimester exposure to zidovudine.[25] For the National Study of HIV in Pregnancy and Childhood (NSDHPC) in the United Kingdom and Ireland, most reports of CAs are collected with the first few weeks of life.[26] The observed rate of CAs was 232 CAs per 8242 LBs, or 2.8%.[26] No increased risk of CAs after *in utero* exposure to specific ARVs or different classes of ARVs was observed in this study[26], nor in the European Collaborative Study (55 CAs among 3740 children, or 1.5%).[27]

HIV-1-infected women may take other potentially teratogenic drugs besides ARVs. Dihydrofolate reductase inhibitors, such as trimethoprim, pyrimethamine, and sulfadiazine, and other folate antagonists, such as carbamazepine, phenytoin, and phenobarbital, may increase the risk of neural tube defects as well as cardiovascular, oral clefts, urinary tract and limb-reduction defects.[28–30] A retrospective study concluded that there was no evidence of teratogenicity of ARVs if given alone during the first trimester, but exposure to the combination of ARVs and folate antagonists (n=13) was associated with a significantly higher risk of CA when compared to no exposure (n=198). [31] In the present study, CAs were not associated with exposure to ARVs alone or in combination with folate antagonists. This could be partially explained because 86% of women in the study population were asymptomatic and because of food fortification policies (extra synthetic folic acid in wheat flour) established in several South American countries in recent years.[32]

Our observed stillbirth rate of 2% is consistent with the rate observed among 859,750 Latin American hospital births from 1982–1986 (2.0%).[33] Our 2% stillbirth rate also is consistent with published stillbirth rates among HIV-infected mothers in the US (2%)[34] and in Argentina (1.7%).[22]

This was the first large prospective study in Latin America to address the prevalence of CAs among HIV-1-exposed infants, and to accurately collect data regarding not only *in utero* exposure to ARVs, but also exposure to folic acid and folate antagonists. However, despite the large sample size, there was limited power to pursue detailed analyses of the prevalence of CAs according to specific ARV exposures, and to analyze specific types of CAs. The results of our analyses do not support changes to current recommendations for the use of ARVs during pregnancy for treatment of HIV-1-infected women and for prevention of mother to child transmission. Continued monitoring of the prevalence of CAs among children of HIV-1-infected women should be pursued.

Acknowledgments

Source of Financial Support: NICHD Contract # N01-HD-3-3345 and # HHSN267200800001C (NICHD Control # N01-DK-8-0001).

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APPENDIX: NISDI Perinatal Study Group

*Principal investigators, *co-principal investigators*, study coordinators, coordinating center representatives, and NICHD staff include: **Argentina:** ***Buenos Aires***: Marcelo H. Losso, Adriana S. Durán, Silvina Ivalo (Hospital General de Agudos José María Ramos Mejía); **Brazil:** ***Belo Horizonte:*** Jorge Pinto, *Victor Melo*, Fabiana Kakehasi (Universidade Federal de Minas Gerais); ***Caxias do Sul:*** Ricardo da Silva de Souza, *Nicole Golin*, Machline Paim Paganella (Universidade de Caxias do Sul/Secretaria Municipal de DST/AIDS de Caxias do Sul - Ambulatorio Municipal DST/AIDS); ***Nova Iguaçu:*** Jose Pilotto, *Beatriz Grinsztejn, Valdilea Veloso (*Hospital Geral Nova de Iguaçu Setor de DST/AIDS; ***Porto Alegre:*** Ricardo

da Silva de Souza, *Breno Riegel Santos*, Rita de Cassia Alves Lira (Universidade de Caxias do Sul/Hospital Conceição); Ricardo da Silva de Souza, *Mario Peixoto*, Marcelo Almeida (Universidade de Caxias do Sul/Hospital Fêmina); Regis Kreitchman, Debora Coelho Fernandes (Irmandade da Santa Casa de Misericórdia de Porto Alegre); ***Ribeirão Preto:*** Marisa M. Mussi-Pinhata, *Geraldo Duarte, Carolina Sales V. Macedo*, Maria A. do Carmo Rego (Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo); ***Rio de Janeiro:*** Ricardo Hugo S. Oliveira, *Elizabeth S. Machado*, Maria C. Chermont Sapia (Instituto de Puericultura e Pediatria Martagão Gesteira); Esau Custodio Joao, Leon Claude Sidi, Guilherme Amaral Calvet, Claudete Araújo Cardoso (Hospital dos Servidores do Estado); ***São Paulo:*** Regina Celia de Menezes Succi, Prescilla Chow Lindsey (Federal University of São Paulo); **Peru:** ***Lima:*** Jorge Alarcon (Instituto de Medicina Tropical "Daniel Alcides Carrion"-Division de Epidemiología), *Carlos Velásquez Vásquez* (Instituto Materno Perinatal), César Gutiérrez Villafuerte (Instituto de Medicina Tropical "Daniel Alcides Carrion"-Division de Epidemiología); **Data Management and Statistical Center:** Yolanda Bertucci, Laura Freimanis Hance, René Gonin, D. Robert Harris, Roslyn Hennessey, James Korelitz, Margot Krauss, Sharon Sothern, Sonia K. Stoszek (Westat, Rockville, MD, USA); **NICHD:** Rohan Hazra, Lynne Mofenson, Jack Moye, Jennifer S. Read, Heather Watts, Carol Worrell (Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland, USA). Supported by NICHD Contract # HHSN267200800001C (NICHD Control # N01-DK-8-0001)

Table 1

Congenital Anomalies by Organ System Affected and Earliest Antiretroviral Exposure

Organ system[†]	**Earliest Antiretroviral Exposure**	
List of specific congenital anomaly(ies)	**1st trimester (249)**	**2nd or 3rd trimester (746)**
Cardiovascular & circulatory (23 infants with 31 CV anomalies)	6 (2.4%)	17 (2.3%)
Ventricular septal defect (VSD)	1[1]	7[2,14]
Atrial septal defect (ASD)	2	1
Patent foramen ovale (PFO)	1[3]	2
Patent ductus arteriosus (PDA)	1[8]	2[4,18]
Peripheral pulmonary artery stenosis	1	1
Arrhythmia	0	1
Truncus arteriosus	0	1
Hemangioma ≥ 4cm	0	2
Musculoskeletal (26 infants with 28+ anomalies)	5 (2.0%)	21(2.8%)
Accessory finger (postaxial polydactyly, Type A)	0	3
Hip dysplasia	0	2
Accessory thumb (preaxial polydactyly)	0	1
Syndactyly (toes)	1	0
Genu valgum	0	1
Plagiocephaly	0	1
Congenital scoliokyphosis	1	0
Congenital dislocation of the hip	0	1
Talipes equinovarus	1	0
Talipes calcaneovarus	0	1
Valgus (outward) malformation of the foot	0	1
Premature closure of cranial sutures	1	0
Multiple anomalies of musculoskeletal system, including omphalocele (1[@])[7]	0	0
Inguinal hernia [female]	1	1
Inguinal hernia [male][*]	0	2[16]
Umbilical hernia[*]	0	6[9,10,11,15,17,18]
Genitourinary (10 infants with 12 GU anomalies)	2 (0.8%)	7 (0.9%)

Organ system†	Earliest Antiretroviral Exposure	
List of specific congenital anomaly(ies)	**1st trimester (249)**	**2nd or 3rd trimester (746)**
Congenital hydronephrosis	1[6]	0
Primary hypospadias	0	1
Congenital chordee (with hypospadias)	1[13]	0
Hydroureter	0	1
Ectopic kidney	0	1[5]
Hydrocele, congenital *	0	2[16]
Undescended testicle *	0	1[14]
Fusion of vulva *	0	1[17]
Central nervous system (5 infants with 5 CNS anomalies)	1 (0.4%)	4 (0.5%)
Anencephaly	0	1
Microcephaly	0	1
Agenesis of the of corpus callosum	0	1[9]
Horner's Syndrome	1	0
Ventricular cysts (ependymal)	0	1[12]
Skin (4 infants with 4 skin anomalies)	1 (0.4%)	3 (0.4%)
Cutis aplasia	0	2[10]
Nevus*	1[8]	0
Port wine stain*	0	1[12]
Other (4 infants with 4 anomalies)	1 (0.4%)	3 (0.4%)
Microphthalmos, bilateral	0	1[11]
Hirschsprung's disease	0	1[5]
Cleft palate	1	0
Menkes Syndrome	0	1

† Number of infants: counted once per organ system, and may be counted in multiple organ systems

@ No ARV exposure

* Minor (conditional) anomaly

[1] male with VSD and ASD

[2] female with VSD and ASD

[3] female with PFO, pulmonary value stenosis, pulmonary value hypoplasia, mitral value hypoplasia, and hypoplastic left ventricle

[4] female with tricuspid stenosis, PDA and ASD

[5] male with Hirschsprung's and ectopic kidney

[6] male with hydronephrosis and vesicouretreral reflux

[7] multiple anomalies of musculoskeletal system including omphalacele (unknown gender)- No ARV exposure

[8] female with PDA and nevus*

[9] male with agenesis of corpus callosum and umbilical hernia*

[10] male with cutis aplasia and umbilical hernia*

[11] male with bilateral micropthalmos and umbilical hernia*

[12] female with ependymal cysts and port wine stain*

[13] male with hypospadiasis (with chordee) and cryptorchidism*

[14] male with VSD and cryptorchidism*

[15] male with peripheral pulmonary artery stenosis and umbilical hernia*

[16] both males with inguinal hernia* and hydrocele*

[17] female umbilical hernia* and fusion of the vulva*

[18] female with umbilical hernia* and PDA resolved by 6 months*

Table 2

Maternal Characteristics, Overall and According to Presence or Absence of Congenital Anomaly (ies)

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	*P**
Receiving ARVs at conception				
Yes	182	10 (5.5)	172 (94.5)	0.86
No	812	50 (6.2)	762 (93.8)	
Missing	1	0	1	
Receiving ARVs at enrollment				
Yes	785	46 (5.9)	739 (94.1)	0.63
No	210	14 (6.7)	196 (93.3)	
Number of ARV regimens used ≥ 28 days during pregnancy				
0	47	3 (6.4)	44 (93.6)	0.56
1	775	44 (5.7)	731 (94.3)	
2	157	13 (8.3)	144 (91.7)	
3	15	0	15 (100.0)	
4	1	0	1 (100.0)	
First ARV regimen received for ≥ 28 days during the 1st trimester				
2NRTIs + 1NNRTI	100	9 (9.0)	91 (91.0)	0.51
2NRTIs + 1PI	94	4 (4.3)	90 (95.7)	
Other combinations of ≥ 3 ARVs	20	0	20 (100)	
1–2 NRTIs	19	2 (10.5)	17 (89.5)	
None received for ≥ 28 days	18	0	18 (100)	
No ARV	744	45 (6.0)	699 (94.0)	
Last ARV regimen received for ≥ 28 days during pregnancy				
2NRTIs + 1NNRTI	305	25 (8.2)	280(91.9)	0.27
2NRTIs + 1PI	511	25 (4.9)	486 (95.1)	
Other combinations of ≥ 3 ARVs	21	3 (14.3)	18 (85.7)	
1–2 NRTIs	100	4 (4.0)	96 (96.0)	
None received ≥ 28 days	40	2 (5.0)	38 (95.0)	

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	P*
No ARVs received	7	1 (14.3)	6 (85.7)	
Timing of first ARV exposure				
First trimester	249	15 (6.0%)	234 (94.0%)	0.52
Second trimester	530	35 (6.6%)	495 (93.4%)	
Third trimester	209	9 (4.3%)	200 (95.7%)	
No exposure	7	1 (14.3%)	6 (85.7%)	
Marital status				
Married or with partner	755	43 (5.7)	712 (94.3)	0.01
Single	206	11 (5.3)	195 (94.7)	
Divorced/Separated	23	2 (8.7)	21 (91.3)	
Widowed	11	4 (36.4)	7 (63.6)	
Country of residence				
Argentina	344	23 (6.7)	321(93.3)	0.58
Brazil	651	37 (5.7)	614 (94.3)	
Age (years) at enrollment				
<20	69	5 (7.2)	54 (92.8)	0.81
20–29	545	33 (6.1)	512 (93.9)	
>29	381	22 (5.6)	368 (94.4)	
Years of formal education at enrollment				
0–6	319	15 (4.7)	304 (95.3)	0.46
7–12	635	43 (6.8)	592 (93.2)	
≥ 13	41	2 (4.9)	39 (95.1)	
Gainfully employed[a] outside the home				
Yes	214	13 (6.1)	201 (93.9)	1.0
No	781	47 (6.0)	734 (94.0)	
Maternal CD4 count at enrollment (cells/mm^3)				
< 200	125	9 (7.2)	116 (92.8)	0.34
200–499	543	36 (6.6)	507 (93.4)	

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	P*
≥ 500	313	14 (4.5)	299 (95.5)	
Missing	14	1	13	
Maternal CD4 count prior to delivery (cells/mm^3)				
< 200	107	6 (5.6)	101 (94.4)	0.82
200–499	479	31 (6.5)	448 (93.5)	
≥ 500	399	22 (5.5)	377 (94.5)	
Missing	10	1	13	
Maternal CD4 percentage at enrollment				
< 14	76	7 (9.2)	69 (90.8)	
14–28	396	21 (5.3)	375 (94.7)	0.33
≥ 29	435	22 (5.1)	413 (94.9)	
Missing	88	10	78	
Maternal CD4 percentage prior to delivery				
< 14	61	6 (9.8)	55 (90.2)	0.32
14–28	350	18 (5.1)	332 (94.9)	
≥ 29	508	27 (5.3)	481 (94.7)	
Missing	76	9	67	
Maternal plasma viral load at enrollment (copies/mL)				
< 1000	553	35 (6.3)	518 (93.7)	0.46
1000 – <10,000	211	9 (4.3)	202 (95.7)	
≥ 10,000	216	15 (6.9)	201 (93.1)	
Missing	15	1	14	
Maternal viral load prior to delivery (copies/mL)				
< 1000	768	46 (6.0)	722 (94.0)	0.88
1000 – <10,000	131	7 (5.3)	124 (94.7)	
≥ 10,000	86	6 (7.0)	80 (93.0)	
Missing	10	1	9	
Maternal CDC clinical stage at enrollment				

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	P^*
A	859	50 (5.8)	809 (94.2)	0.29
B	53	2 (3.8)	51 (96.2)	
C (AIDS)	83	8 (9.6)	75 (90.4)	
Maternal CDC clinical stage prior to delivery				
A	857	50 (5.8)	807 (94.2)	0.30
B	54	2 (3.7)	52 (96.3)	
C (AIDS)	84	8 (9.5)	76 (90.5)	
Gravidity				
1	147	9 (6.1)	138 (93.9)	1.0
>1	848	51 (6.0)	797 (94.0)	
Parity				
0	223	11 (4.9)	212 (95.1)	0.6
1	312	18 (5.8)	294 (94.2)	
>1	460	31 (6.7)	429 (93.3)	
Body Mass Index[b] at enrollment				
<20	169	8 (4.7)	161 (95.3)	0.64
20–25	594	40 (6.7)	554 (93.3)	
>25	218	12 (5.5)	206 (94.5)	
Missing	14	0	14	
Maternal toxoplasmosis during pregnancy				
Yes	8	2 (25.0)	6 (75.0)	0.08
No	987	58 (5.9)	929 (94.1)	
Maternal rubella or cytomegalovirus infection during pregnancy				
Yes	0	0	0	1.0
No	995	60 (6.0)	935 (94.0)	
Maternal *Herpes simplex* virus infection during pregnancy				
Yes	22	2 (9.1)	20 (90.9)	0.39
No	973	58 (6.0)	915 (94.0)	

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	P*
Maternal syphilis infection during pregnancy				
Yes	29	3 (10.3)	26 (89.7)	0.41
No	966	57 (5.9)	909 (94.1)	
Any sexually transmitted infection[c] during pregnancy				
Yes	62	7 (11.3)	55 (88.7)	0.09
No	933	53 (5.7)	880 (94.3)	
Diabetes[d] during pregnancy				
Yes	23	2 (8.7)	21 (91.3)	0.64
No	972	58 (6.0)	914 (94.0)	
Hypertension[e] during pregnancy				
Yes	36	1 (2.8)	35 (97.2)	0.72
No	959	59 (6.2)	900 (93.8)	
Infectious renal disease[f] during pregnancy				
Yes	64	7 (10.9)	57 (89.1)	0.10
No	931	53 (5.7)	878 (94.3)	
Non-infectious renal disease[g]				
Yes	2	0	2	1.0
No	993	60 (6.0)	933 (94.0)	
Alcohol use during pregnancy				
Yes	89	2 (2.2)	87 (97.8)	0.16
No	906	58 (6.4)	848 (93.6)	
Tobacco use during pregnancy				
Yes	261	15 (5.7)	246 (94.3)	0.88
No	734	45 (6.1)	689 (93.9)	
Illicit drug use during pregnancy				
Yes	42	2 (4.8)	40 (95.2)	1.0

Characteristic	Overall [n]	Congenital anomaly (ies) [n (%)]	No Congenital anomaly (ies) [n (%)]	P*
No	953	58 (6.1)	895 (93.9)	
Folate antagonist[h] use during 1st trimester				
Yes†	21	2 (9.5%)	19 (90.5%)	0.36
No	974	58 (6.0%)	916 (94.0%)	
Other Class D drugs[i] during 1st trimester				
Yes‡	3	0	3 (100)	1.0
No	992	60 (6.0)	932 (94.0)	
Folic acid supplementation[j] during pregnancy				
≥800 mcg	170	10 (5.9)	160 (94.1)	
< 400 mcg	21	2 (9.5)	19 (90.5)	0.31
Folinic acid	5	1 (20.0)	4 (80.0)	
No folic or folinic acid	799	47 (5.9)	752 (94.1)	
Use of ARVs and/or folate antagonists during the 1st trimester				
Both ARVs and folate antagonists†	17	2 (11.8)	15 (88.2)	
Either ARVs or folate antagonists† alone	236	13 (5.5)	223 (94.5)	0.45
No exposure to either type of drugs	742	45 (6.1)	697 (93.9)	

*P value calculated using Fisher exact test. (Missing values not included in calculation of *P* value).

†No folic acid supplementation received

‡Exposure to doxycyline (1), alprazolam(1) or lorazepam(1)

[a]Homemakers, unemployed individuals, and students were classifiedas not gainfully employed outside of the home; all others were classified as gainfully employed outside of the home.

[b]Body mass index (BMI) adjusted for length of gestation usingan algorithm available from the Ministry of Health of Argentina.[22]

[c]Sexually transmitted infections included the following: syphilis, gonorrhea, chancroid, lymphogranuloma, salpingitis/pelvic inflammatory disease, urethritis, chlamydial infection, trichomoniasis or cervicitis (*Ureaplasma* sp., *Chlamydia* sp., *Mycoplasma* sp., or *Neisseria* sp.)

[d]Diabetes included the following conditions prior to or during pregnancy: type I or type II diabetes, pregestational or gestational diabetes

[e]Hypertension included eclampsia, pre-eclampsia, pregnancy-induced hypertension, or chronic hypertension if women were taking anti-hypertensive medications during pregnancy

[f] Infectiousrenal disease included bacteriuria (asymptomatic or symptomatic), pyelonephritis and urinary tract infection.

[g] Non-infectiousrenal disease included interstitial nephritis, nephropathy, proximal renal tubular acidosis, renal failure, nephrotic syndrome, renal tubular acidosis, renal Fanconi syndrome and renal disorder not otherwise specified

[h] Use of folate antagonists (dihydrofolate reductase inhibitors and other drugs) were defined as follows: (1) intake lasting 15 days or more, and occurring 90 days prior to or after conception; (2) interruption of drug intake for less than seven days was considered continuous intake; (3) exposure was classified according to first occurrence; and (4) if no medication was taken or any was taken for less than 15 days, exposure was classified as “none”.

[i] Use of other FDA pregnancy category class D drugs were defined as follows: (1) intake lasting 15 days or more, and occurring 90 days prior to or after conception; (2) interruption of drug intake for less than seven days was considered continuous intake; (3) exposure was classified according to first occurrence; and (4) if no medication was taken or any was taken for less than 15 days, exposure was classified as “none”.

[j] Folic acid supplementation was defined as follows: (1) intake lasting 15 days or more during pregnancy; (2) interruption of drug intake for less than seven days was considered continuous intake; (3) the form/dose of folic acid taken for the longest period of time during the first trimester was used (categorized as either 800 mcg/day or 400mcg/day); (4) if no folic acid supplementation was taken or if taken for less than 15 days, exposure was classified as “none”. Folinic acid was categorized as “yes” or “no”.

Table 3

Infant Characteristics, Overall and According to Presence or Absence of Congenital Anomaly (ies)

Characteristics	Overall [No.]	Congenital anomaly (ies) present [No. (%)]	No Congenital anomaly (ies) present [No. (%)]	*P* value*
Gender				
Female	467	29 (6.2)	438 (93.8)	
Male	502	29 (5.8)	473 (94.2)	0.79
Missing	26	2	24	
Gestational age (completed weeks)				
<37	95	8 (8.4)	87 (91.6)	
≥ 37	873	50 (5.7)	823 (94.3)	0.26
Missing	27	2	25	
Birth weight (grams)				
<2500	135	13 (9.6)	122 (90.4)	
≥ 2500	833	45 (5.4)	788 (94.6)	0.08
Missing	27	2	25	

**P* value using Fisher exact test. (Missing values not included in calculation of *P* value.)

Table 4

Prevalence of congenital anomalies per 100 live births by trimester of first ARV exposure

Timing of first ARV exposure	Congenital anomalies (outcomes ≥20 weeks)	Women first exposed to ARVs during this period	Women exposed to ARVs during this period who had live births	Congenital anomalies per 100 live births (95% CI)*
1st trimester	15	249	242	6.20 (3.06–9.34)
2nd trimester	35	530	518	6.76 (4.52–9.00)
3rd trimester	9	209	208	4.33 (1.5–7.15)
No exposure	1	7	6	16.67 (0–49.33)
TOTAL	60	995	974	6.16 (4.60–7.72)

Table 5

Classes of Antiretrovirals, Specific Antiretroviral Drugs and Any Antiretroviral Drug Exposure by Trimester and Prevalence of Congenital Anomalies

Antiretrovirals	Trimester of Exposure			Congenital anomalies [No.]	Total number of women [No.]	Women with LBs [No.]	Prevalence * (95% CI)
	1st Trimester [No. (%)]	2nd Trimester [No. (%)]	3rd Trimester [No. (%)]				
Any PI							
Yes	**115 (11.6)**	**434 (43.6)**	**561 (56.4)**	**30**	**579**	**567**	**5.29 (3.40–7.18)**
No	880 (88.4)	561 (56.4)	434 (43.6)	30	416	407	7.37 (4.73–10.01)
Amprenavir							
Yes	2 (0.2)	2 (0.2)	2 (0.2)	0	3	3	
No	933 (99.8)	933 (99.8)	933 (99.8)	60	992	971	
Atazanavir							
Yes	7 (0.7)	2 (0.2)	2 (0.2)	0	8	8	
No	988 (99.3)	933 (99.8)	933 (99.8)	60	987	966	
Indinavir							
Yes	10 (1.0)	8 (0.8)	5 (0.5)	0	13	13	
No	985 (99.0)	987 (99.2)	990 (99.5)	60	982	961	
Lopinavir							
Yes	21 (2.1)	46 (4.6)	72 (7.2)	5	74	74	
No	974 (97.9)	949 (95.4)	923 (92.8)	55	921	900	
Nelfinavir							
Yes	**76 (7.6)**	**375 (37.7)**	**489 (49.2)**	**25**	**508**	**497**	**5.03 (3.06–7.00)**
No	919 (92.4)	620 (62.3)	506 (50.8)	35	487	477	7.34 (4.91–9.77)
Ritonavir							
Yes	22 (2.2)	46 (4.6)	72 (7.2)	5	74	74	
No	973 (97.8)	949 (95.4)	923 (92.8)	55	921	900	
Saquinavir (hard gel)							
Yes	3 (0.3)	6 (0.6)	6 (0.6)	0	6	6	
No	992 (99.7)	989 (99.4)	989 (99.4)	60	989	968	
Saquinavir (soft gel)							
Yes	2 (0.2)	4 (0.4)	6 (0.6)	0	7	6	
No	993 (99.8)	991 (99.6)	989 (99.4)	60	988	968	
Any NRTI							

Antiretrovirals	Trimester of Exposure			Congenital anomalies [No.]	Total number of women [No.]	Women with LBs [No.]	Prevalence * (95% CI)
	1st Trimester [No. (%)]	2nd Trimester [No. (%)]	3rd Trimester [No. (%)]				
Yes	**248 (24.9)**	**769 (77.3)**	**978 (98.3)**	**59**	**987**	**967**	**6.10 (4.54–7.66)**
No	747 (75.1)	226 (22.7)	17 (1.7)	1	8	7	14.29 (0–42.3)
Abacavir							
Yes	21 (2.1)	18 (1.8)	22 (2.2)	3	32	31	
No	974 (97.9)	977 (98.2)	973 (97.8)	57	963	943	
Stavudine							
Yes	58 (5.8)	51 (5.1)	44 (4.4)	5	81	78	
No	937 (94.2)	944 (94.9)	951 (95.6)	55	914	896	
Zalcitabine							
Yes	2 (0.2)	1 (0.1)	0	0	2	2	
No	933 (99.8)	994 (99.9)	995	60	993	972	
Didanosine							
Yes	33 (3.3)	37 (3.7)	31 (3.1)	4	52	51	
No	962 (96.7)	958 (96.3)	964 (96.9)	56	943	923	
Tenofovir							
Yes	4 (0.4)	3 (0.3)	12 (1.2)	1	13	13	
No	991 (99.6)	992 (99.7)	983 (98.8)	59	982	961	
Lamivudine							
Yes	**204 (20.5)**	**680 (68.3)**	**906 (91.1)**	**54**	**921**	**901**	**5.99 (4.39–7.59)**
No	791 (79.5)	315 (31.7)	89 (8.9)	6	74	73	8.2 (1.64–14.80)
Zidovudine							
Yes	**182 (18.3)**	**731 (73.5)**	**942 (94.7)**	**57**	**954**	**936**	**6.09 (4.51–7.67)**
No	813 (81.7)	264 (26.5)	53 (5.3)	3	41	38	7.89 (0–16.83)
Emtricitabine							
Yes	1 (0.1)	0	0	0	1	1	
No	994 (99.9)	995	995	60	994	973	
Any NNRTI							
Yes	**130 (13.1)**	**278 (27.9)**	**350 (35.2)**	**32**	**407**	**398**	**8.04 (5.25–10.83)**
No	865 (86.9)	717 (72.1)	645 (64.8)	28	590	576	4.86 (3.06–6.66)
Efavirenz							
Yes	43 (4.3)	13 (1.3)	3 (0.3)	4	44	44	

Antiretrovirals	Trimester of Exposure			Congenital anomalies [No.]	Total number of women [No.]	Women with LBs [No.]	Prevalence * (95% CI)
	1st Trimester [No. (%)]	2nd Trimester [No. (%)]	3rd Trimester [No. (%)]				
No	952 (95.7)	982 (98.7)	992 (99.7)	56	951	930	
Nevirapine							
Yes	**95 (9.5)**	**269 (27.0)**	**348 (35.0)**	**30**	**383**	**374**	**8.02 (5.15–10.89)**
No	900 (90.5)	726 (73.0)	647 (65.0)	30	612	606	4.95 (3.18–6.72)
Any ARV							
Yes	**249 (25.0)**	**779 (78.3)**	**988 (99.3)**	**59**	**988**	**968**	**6.10 (4.54–7.65)**
No	746 (75.0)	216 (21.7)	7 (0.7)	1	7	6	16.67 (0–49.33)

*Prevalence rates calculated when ≥ 200 live born infants exposed *in utero*