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Antiretroviral Therapy Use during Pregnancy and the Risk of Small-for-Gestational-Age Birth in a Medicaid Population

Kelesitse Phiri, MS, ScD¹, Paige L. Williams, BSPH, MS, PhD², Kate B. Dugan, MPH¹, Michael A. Fischer, MS, MD³, William O. Cooper, MD, MPH⁴, George R. Seage III, ScD¹, and Sonia Hernandez-Diaz, MD, MPH, DrPH¹

¹Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

²Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA

³Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

⁴Department of Preventive Medicine and Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

Abstract

Background—Several studies have assessed the association between antiretroviral (ARV) therapy use during pregnancy and small for gestational age (SGA), but the evidence remains incompletely elucidated.

Methods—We linked data from Tennessee Medicaid files and vital records to evaluate pregnancies among human immunodeficiency virus (HIV)-infected women who delivered between 1994 and 2009. Maternal HIV status was defined based on diagnosis codes, ARV prescriptions, and laboratory codes for CD4 count or HIV RNA assays. ARV use was identified from pharmacy claims. Risk of SGA (defined as birthweight below the 10th percentile for gestational age) and preterm birth were evaluated using logistic regression models.

Results—477 HIV- infected pregnant women contributing 604 singleton pregnancies were identified; 156 (26%) delivered SGA infants. ARV use during pregnancy was not associated with SGA (adjusted odds ratio [aOR] = 0.93; 95% confidence interval [CI], 0.56-1.56) or preterm birth (aOR = 0.74; 95% CI, 0.42-1.32). Exposure to a protease inhibitor (PI) during the first trimester was associated with a lower risk of SGA (OR, 0.54; 95% CI, 0.29-1.01) compared to non-exposure to a PI throughout pregnancy.

Conclusions—We observed no evidence of an association between ARV exposure during pregnancy and SGA delivery in this Medicaid cohort of HIV-infected women.

Corresponding author, address & email: Kelesitse Phiri 677 Huntington Avenue, Dept. of Epidemiology, Boston, MA 02115, USA, Tel: 617-432-7917, Fax: 617-566-7805, kphiri@hsph.harvard.edu.

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Keywords

HIV; antiretroviral; pregnancy; small-for-gestational age; Medicaid

The use of antiretroviral (ARV) therapy during pregnancy is the standard of care for human immunodeficiency virus (HIV)-infected pregnant women.^{1, 2} Some epidemiologic studies have indicated that maternal ARV use during pregnancy may be associated with significant increases in adverse pregnancy outcomes,³⁻¹⁰ including small for gestational age (SGA),^{7, 10} but the evidence remains inconclusive as other studies did not observe such associations.^{5, 11-15} The conflicting evidence regarding SGA may be due to differences in the definition of SGA or ARV comparison groups between studies; also, comparison of SGA risk by ARV drug class has not been adequately explored. Our study used a variety of exposure classifications, including classification by drug class, to evaluate the effect of ARV use during pregnancy on the risk of SGA in the newborn (using the standard definition of birth weight below the 10th percentile for gestational age) among HIV-infected pregnant women in the US.

Methods

Study cohort

From a source population of females aged 10-55 years who were enrolled in Tennessee Medicaid (TennCare) from January 1, 1994 through December 31, 2009, we identified a cohort of pregnant women with evidence of HIV infection, based on an algorithm that required codes for HIV diagnosis, HIV related laboratory testing (CD4 count or HIV viral load), or prescription dispensing for ARVs.¹⁶ Only HIV-infected pregnant women for whom Medicaid and vital records databases could be linked were included. Linkage of mothers to their infants was achieved by using an already established linkage algorithm for women enrolled in TennCare as described elsewhere.¹⁷

We restricted our study cohort to women who were continuously enrolled in Medicaid with drug coverage from at least 30 days before their last menstrual period (LMP) through the date of delivery or fetal death. This restriction was done in order to identify ARV prescriptions that were dispensed prior to the LMP and had a supply that extended into pregnancy in order to ensure complete follow-up of women and complete ascertainment of exposure information throughout pregnancy. We also required infants to have been enrolled in Medicaid within the first 30 days of life and for at least 90 days in order to ascertain adverse fetal outcomes. Since for some women the first diagnosis of HIV infection may occur only during pregnancy or after delivery, we further restricted the cohort to pregnancies that had evidence of HIV infection at any time from up to one year before the LMP through to the delivery date [Figure 1]. All singleton pregnancies that occurred during the study period and were recorded in TennCare were included in our final cohort. Our analysis was restricted to pregnancies for which there was a live birth and a recorded LMP on the birth certificate.

Validation of HIV infection

To validate our definition of HIV-infected women from claims data, we reviewed a random sample of medical charts for the women identified as HIV-infected who were not exposed to any ARVs throughout pregnancy. We then calculated the positive predictive value of our definition based on these chart reviews to assess how well our algorithm for HIV correctly classified infected women.

Antiretroviral exposure

We identified prescriptions for ARVs from the women's Medicaid pharmacy claims. A woman was considered exposed to a specific ARV drug or ARV drug class during pregnancy if she had at least one prescription dispensed for that ARV from 30 days prior to the LMP through delivery; trimester exposures were also based on at least one prescription dispensed during the specific trimester. Exposure was classified in three different ways: (1) exposure to any ARV during pregnancy; (2) exposure to ARV treatment containing a protease inhibitor (PI), or a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or a nucleoside reverse-transcriptase inhibitor (NRTI), categorized hierarchically for the entire pregnancy (regardless of any treatment switch during pregnancy); and (3) first exposure to a PI-containing treatment in the first, second, or third trimester, or no exposure to a PI-containing treatment during pregnancy.

Classification of small for gestational age (SGA)

Information on gestational age at birth and birthweight was obtained from the birth certificate files. The gestational age recorded in birth certificates is typically calculated from an algorithm that uses information on LMP (based on maternal recall), ultrasound and clinical assessment; a study that used data from the same population (TennCare, 1985-2002) and data system as the one used for our study showed a concordance of 94% between the date of the LMP in birth certificates and medical records;¹⁸ We determined the percentile for birthweight for each infant based on the gestational age using sex-specific references.¹⁹ SGA infants were defined as those with a birthweight below the 10th percentile for their gestational age.

Definition of study covariates

Information on potential risk factors for SGA (maternal age, race, education and parity; trimester in which prenatal care began; and alcohol, tobacco and illicit drug use during pregnancy) was obtained from birth certificate files; clinical information came from Medicaid inpatient and outpatient diagnosis claims, and information on non-ARV medications used during pregnancy was obtained from Medicaid pharmacy claims.

Statistical analysis

We compared the characteristics of women who were exposed versus those unexposed to ARVs during pregnancy using χ^2 and Fisher's exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables. Univariable logistic regressions were performed to identify potential risk factors for SGA. All variables with a 2-sided P-value <0.10 were included in the multivariable logistic regression models to estimate the effect of

ARV use on the risk of SGA. To assess whether there were temporal changes in the effect of ARVs on SGA resulting from the evolving clinical management of HIV during pregnancy over the course of the study period (including the temporal availability of ARVs), we performed analyses stratified by four birth cohorts; the cutoffs for the birth cohorts were determined from observed patterns of ARV use in the Medicaid population nationwide.²⁰ We found no significant differences in the effect estimates by birth cohort and therefore all study years were included in our analyses. Unadjusted and adjusted regression models were fit using generalized estimating equations (GEE) to account for clustering of multiple pregnancies by a woman during the study period. All final models were adjusted for the year of delivery and HIV-related maternal illnesses in order to minimize the potential impact of confounding by temporal trends in ARV use and maternal HIV disease stage. Similar logistic regression models were used in a secondary analysis to estimate the association of ARV use with the risk of preterm delivery (gestational age <37 completed weeks).

We also conducted a sensitivity analysis using an alternative definition of SGA to make a distinction between SGA infants who were preterm to those who were full term since the risk of morbidity and mortality may differ between these two groups. For the preterm infants we retained the same definition of SGA (birthweight below the 10th percentile for gestational age) while for full term infants SGA was redefined as birthweight < 2,500g. Statistical significance was defined as two-sided p-values < 0.05. All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

Results

From 1994 to 2009, 3228 women in TennCare had evidence of HIV and at least one pregnancy; 2408 of them were enrolled in Medicaid with drug coverage from 30 days prior to the LMP through delivery and 2284 women (3,793 pregnancies) had their infants enrolled within the first 30 days of life and for at least 3 months. After excluding 1944 pregnancies in which women had their first recorded HIV diagnosis only after delivery and restricting our cohort to mothers with an indication of HIV or ARV from one year before the LMP through delivery, 820 pregnancies remained. A further exclusion of 25 multiple gestation pregnancies (3 of which included fetal deaths), and an additional 5 singleton fetal deaths left 790 pregnancies in our study cohort contributed by 623 women [Figure 1].

Among the 790 pregnancies, 151 (19.1%) were unexposed to ARVs from one year before the LMP through delivery. We reviewed medical records for a random sample of these 151 ARV unexposed pregnancies. Out of 31 medical charts reviewed, there were 14 from women with only 1 HIV claim in the dataset; we confirmed the HIV positive status for 3 women (positive predictive value: 21%); the other 11 pregnancies were HIV negative. Of 17 medical records with 2 or more HIV claims in the dataset, we confirmed the HIV positive status for 16 women (positive predictive value: 94%), and the one HIV negative woman had positive enzyme immunoassay (EIA) but no HIV RNA detected in plasma. Therefore, we excluded women with only one HIV claim from our cohort of HIV positive women, leaving 597 women contributing 764 singleton pregnancies that resulted in live births. Finally, we excluded pregnancies with missing information on the LMP date (N = 157) and gestational age (N = 3) since our primary outcome of interest was SGA.

The characteristics of the final cohort of 477 HIV- infected pregnant women contributing 604 pregnancies are shown on the Table1. A total of 93 pregnancies (15%) were unexposed to ARVs throughout pregnancy. Compared to ARV exposed pregnancies, those unexposed had a higher proportion of women with late (third trimester) or absent prenatal care (24% vs. 6%); overall prevalence of absent or late access to prenatal care was approximately 9% before 2002, and remained at about 8% by 2009 [Figure 2]. There was a slight decrease over time in the prevalence of ARV unexposed pregnancies (19%, before 2002; 16%, 2002 – 2004; 13%, 2005 – 2007; 12%, 2008 – 2009). Among the 511 (85%) pregnancies exposed to ARVs, 222 (37%) were exposed to a PI-containing treatment, 78 (13%) to NNRTI-containing treatment, 109 (18%) to NRTI dual or triple therapy, and 102 (17%) to NRTI monotherapy [Table 2].

There were 156 (26%) deliveries of SGA infants. The prevalence, which remained above 20% throughout the study years [Figure 2], was 26% for ARV-exposed and 25% for ARV-unexposed pregnancies; those exposed to NNRTI-containing treatment had significantly higher prevalence of SGA births (36%) compared to all other groups [Table 2]. Maternal characteristics associated with SGA were prescription of medications other than ARVs during pregnancy, smoking, alcohol and drug use. After adjusting for these variables, and for the year of delivery and HIV-related maternal illnesses, we found no association between any ARV exposure during pregnancy and the risk of SGA (aOR, 0.93; 95% CI, 0.56-1.56) [Table 3]. Similarly, for ARV exposure by drug class, we observed no statistically significant associations between use of ARV regimens containing a PI, a NNRTI, or only NRTIs (one, two or three NRTIs) and the risk of SGA. However, pregnancies that were exposed to ARV treatment containing a PI in the first trimester compared to those with no PI throughout pregnancy had marginally lower risk of SGA (aOR, 0.54; 95% CI, 0.29-1.01).

The prevalence of SGA was sensitive to the definition used. When we used an alternative definition of SGA for full term births (defined as birthweight < 2,500g) the prevalence of SGA decreased to 14%. However, results for the association between ARV exposure and SGA using this alternative definition were similar to those observed using the primary definition of SGA. For our secondary analysis assessing the association between ARV exposure and the risk of preterm delivery, we observed an overall preterm delivery prevalence of 21%; 20% among ARV-exposed pregnancies and 29% among unexposed [Table 2]. The adjusted OR for the association between any ARV exposure during pregnancy and the risk of preterm birth was 0.74 (95% CI, 0.42-1.32).

Discussion

In this cohort of 477 HIV-infected women who were enrolled in Tennessee Medicaid and had a total of 604 pregnancies between 1994 and 2009, we found no association between ARV exposure and the risk of both SGA and preterm delivery. However, women who were exposed to a PI-containing treatment in the first trimester had a marginally significant lower risk of SGA compared to those who were unexposed to a PI throughout pregnancy.

The prevalence of SGA infants was high in our study population (26%) compared to the US general population (11%),²¹ and to studies conducted in France (4%),²² in Botswana

(18%),¹⁰ and in other US populations (16% and 7%, respectively).^{14, 23} These differences are most likely due to the different definitions of SGA and the reference populations used. We used US sex-specific references to define SGA as infants below the 10th percentile for their gestational age at birth. This resulted in 71 full term infants (gestational age ≥ 37 weeks) with a birthweight > 2500g being classified as SGA, comprising 46% of all SGA infants in our cohort. Our observed slight increase in the prevalence of SGA infants during the study period may be a reflection of changes in clinical management decisions over time (such as performing an indicated preterm delivery, induction, or cesarean delivery) based on the presence of fetal growth restriction and subsequent SGA.

Unlike previous studies, our main reference group was HIV-infected women who were unexposed to ARVs throughout pregnancy. Overall, we observed a similar prevalence of SGA for ARV exposed women compared to those who were unexposed. The main differences were among the specific drug classes, with the highest SGA prevalence among women who were exposed to NNRTIs.

The high proportion of HIV-infected pregnant women who were not exposed to ARVs throughout pregnancy (15%) is a notable finding of our study. This could be a result of women entering prenatal care late (3rd trimester) or not receiving prenatal care throughout pregnancy as seen in the Table 1. To verify that we did not miss some ARV information in the pharmacy claims data, we searched for any mention of ARV use in the random sample of the 31 medical charts reviewed and found that while indeed some of the women did not receive any ARV during pregnancy, administration of prophylactic therapy during labor and delivery to avoid maternal-fetal transmission was recorded. The chart reviews and medical profiles further revealed a high proportion of mental health disorders, drug abuse, incarceration, and other social problems in this population which could act as barriers to treatment. We note that the high occurrence of social problems that we observed from the chart reviews could have been accentuated by our study design since we restricted the cohort to women eligible for Medicaid before LMP. That is, to be eligible, these women had to be either multiparous or have disabilities. Our methods may overestimate ARV exposure during pregnancy if HIV-infected women without Medicaid coverage during their pregnancy have worse access to ARV medications. On the other hand, our methods may underestimate ARV exposure during pregnancy if those on Medicaid before pregnancy are the most disadvantaged populations and have worse access (including poor adherence) to prenatal care and ARVs. This would imply that if ARVs increased the risk of SGA as shown in a few studies,^{7, 10} our results would be biased towards the null as the exposure group in our analysis would be misclassified by including those with poor adherence as being exposed; poor ARV adherence during pregnancy has been shown to be high among adolescents, substance users, and women with mental illnesses.²⁴⁻²⁷ In addition, changes in Medicaid eligibility and enrollment over time may have also led to different populations in the context of HIV severity and obstetric interventions, a phenomenon we accounted for in all our analyses by adjusting for calendar year of birth.

Our study had several limitations. First, our exposure measure only considered when prescriptions were dispensed and not necessarily when the women took the medications which could lead to exposure misclassification. Second, we were unable to assess the effect

of specific combination regimens, which is the standard of care for HIV infected pregnant women in resource-rich nations and often the main exposure of interest in studies assessing the effect of ARV use on birth outcomes. This is because we could not ascertain that prescriptions for individual ARVs were taken concomitantly, but nonetheless our analysis using any ARV exposure provides a valid statistical test for the null hypothesis that no combination therapy has an effect on SGA. Third, since we only used a proxy for HIV severity and could not directly adjust for the women's CD4 cell counts and viral loads, we cannot rule out potential confounding by indication. Furthermore, we did not have information on the HIV status of the infant at birth which has been shown to be associated with SGA and preterm delivery.^{28, 29} However, both maternal HIV severity and fetal HIV acquisition might be intermediates on the pathway between ARV exposure and SGA, in which case adjusting for them in the analyses would require advanced methods and more granular information of the intermediates.³⁰ Also, greater than 30% pregnancies had missing information on illicit drug and alcohol use, both of which are major risk factors for SGA and may be important confounders of the association between exposure to ARVs and SGA. Furthermore, while our sample size was small to detect smaller yet clinically significant increases in risk of SGA, we did have the power to detect an increase in SGA from 25% among ARV-unexposed to 40% (OR = 2.0) in women who were exposed to ARVs during pregnancy. Finally, since women may only become eligible for Medicaid as a result of their pregnancy, and many women only find out they are HIV-infected when they become pregnant, our eligibility criteria requiring continuous enrolment in Medicaid from 3 months prior to LMP through delivery oversampled multiparous women or those with disabilities. In addition, excluding pregnancies with missing information on the LMP date and gestational age may have resulted in a biased sample; however, we would expect this to be the case only if those excluded were systematically different from those included in ways that correlate with both ARV exposure and unmeasured risk factors for SGA.

A major practical strength of our study is the use of a valid, existing database over a long period of time (1994-2009). Our cohort represents a population that is disproportionately affected by HIV infection compared to women of other races/ethnicities³¹ and therefore might be closer to the real population of ARV users or those in need of ARVs. The characteristics of the cohort minimize the possibility of missing data since Medicaid enrollees are unlikely to have other resources to pay for their medical care and thus virtually all treatment prescriptions, lab measurements, and health outcomes are captured in the data files. Generalizability to populations in developing countries and also to populations not in the low income category in developed countries, however, will have to be made with caution. The conflicting results from previous studies^{7, 10, 14, 22, 23} possibly reflect geographic differences in the populations studied including different baseline risks, availability of obstetrical care, concomitant morbidities and treatments, and confounding by indication for ARV use. Our findings of no effect of ARV use on the risk of SGA are concordant with results from studies conducted in the U.S.^{14, 23}

In conclusion, we found no association between ARV exposure and both SGA and preterm delivery. Our results showed evidence of a high proportion of HIV-infected pregnant women who did not use any ARVs throughout pregnancy despite 77% of them initiating prenatal care in the first or second trimester. This has important implications for appropriate perinatal

and maternal HIV treatment during pregnancy, suggesting greater prioritization of obstetric and gynecologic services in Medicaid recipients of childbearing age.

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Figure 1. Cohort structure

HIV = human immunodeficiency virus; LMP = last menstrual period; ARV = antiretroviral

^aThese are pregnancies that were either (1) not enrolled with drug coverage from LMP-30 through delivery (N=364) or (2) had an HIV claim only prior to LMP-365 (N = 639) or (3) had an HIV claim only prior to LMP-365 and after delivery (N=26)

^bIncludes women with the following indication(s) for HIV: (a) one (or more) inpatient diagnoses (prior to the birth hospitalization), or (b) two (or more) outpatient diagnoses separated by at least 30 days, or (c) two (or more) prescriptions for ARVs on different dates, or (d) any combination of two indications (one or more of each of the following indications – birth hospitalization diagnosis plus outpatient diagnosis, or birth hospitalization diagnosis plus prescription, or birth hospitalization diagnosis plus procedure, or outpatient diagnosis plus prescription, or outpatient diagnosis plus procedure, or prescription plus procedure)

Figure 2. Trends over time - Late access to prenatal care and SGA among HIV-infected pregnant women in Tennessee Medicaid: 1994 – 2009

SGA: small-for-gestational age (defined as birthweight below the 10th percentile for the gestational age).

The number of pregnancies for each birth cohort is as follows: <2002 = 154; 2002 – 2004 = 198; 2005 – 2007 = 150; 2008 – 2009 = 102

Note: Late access to prenatal care was defined as starting prenatal care in the 3rd trimester or not having any prenatal care throughout pregnancy. A slight increase in SGA births among those with late access to prenatal care over time was observed (<2002, 5.8%; 2002 – 2004, 7.8%; 2005 – 2007, 9.7%; 2008 – 2009, 12%)

Table 1
Characteristics of HIV-Infected Pregnant Women Enrolled in TennCare between 1994 and 2009 (N = 604 Pregnancies)

Characteristic	Women with ARV prescriptions during pregnancy (N = 511)	Women without ARV prescriptions during pregnancy (N = 93)
Year of delivery		
1994 – 1998	124 (24)	30 (32)
1999 – 2002	167 (33)	31 (33)
2003 – 2006	130 (25)	20 (22)
2007 – 2009	90 (18)	12 (13)
Age, median (range)	26 (14 – 43)	25 (17 – 40)
Race, no. (%)		
Black	412 (81)	77 (83)
White	99 (19)	16 (17)
Years of Education 12 years, no. (%)	427 (84)	80 (86)
Parity, mean (25 th – 75 th)	2 (1 – 3)	2 (1 – 4)
Trimester prenatal care began, no. (%)		
1 st	304 (61)	46 (52)
2 nd	162 (32)	22 (25)
3 rd	22 (4)	7 (8)
None	11 (2)	14 (16)
Missing	12	4
Number of prenatal visits among those with at least one visit, median (range)	10 (1 – 33)	10 (2 – 18)
Hypertension diagnosis, no. (%)	56 (11)	12 (13)
Mental health disorder diagnosis, no. (%)	57 (11)	16 (17)
Substance abuse diagnosis, no. (%)	22 (4)	3 (3)
Other chronic health diagnoses ^a , no. (%)	56 (11)	13 (14)
Maternal Illnesses, no (%)		
Possibly HIV-related ^b	6 (1)	1 (1)
Other ^c	237 (46)	13 (14)
None	268 (52)	79 (85)
AIDS diagnosis, no. (%)	279 (54)	16 (17)
Non-ARV medication use during pregnancy ^d , no (%)	209 (41)	15 (16)
Alcohol use, no. (%)		
Yes	22 (7)	4 (6)
No	306 (93)	58 (94)
Tobacco use, no. (%)		
Yes	124 (24)	27 (29)
No	387 (76)	66 (71)
Illicit drug use, no. (%)		
Yes	34 (10)	9 (15)

Characteristic	Women with ARV prescriptions during pregnancy (N = 511)	Women without ARV prescriptions during pregnancy (N = 93)
No	295 (90)	53 (85)

HIV = human immunodeficiency virus; ARV = antiretroviral

^a epilepsy, sickle cell disease, asthma, renal disease, neoplastic disease, cardiac disease, cystic fibrosis, alcohol abuse, cerebrovascular disease, obesity, migraine, sexually transmitted infection, or hepatitis

^b pneumocystis pneumonia, tuberculosis, kaposi sarcoma, cytomegalovirus infection, toxoplasmosis, HIV encephalopathy, cryptosporidiosis, isosporiasis, histoplasmosis, coccidiomycosis, or lymphoma.

^c weight loss, mycobacterial infection, nephropathy, cardiomyopathy, or diarrhea.

^d *No ARV fills* – Anti-hypertensives, 3 (3%); Mental health disorder, 5 (5%); Anti-infectives, 3 (3%); Asthma, 3 (3%); *ARV fills* – Anti-hypertensives: 38 (7%); Mental health disorder: 88 (17%); Anti-infectives: 76 (15%); Asthma: 69 (13%).

Note: Information on alcohol and illicit drug use was missing for >30% pregnancies, 214 missing observations for alcohol and 213 missing observations for illicit drug use.

Table 2
Pregnancy Outcomes by Type of ARV Prescriptions Received During Pregnancy (N=604 Pregnancies)

Outcome, no. (%)	ARV Prescriptions containing a:			
	PI ^a (n = 222)	NNRTI, ^b no PI (n = 78)	NRTI monotherapy (n = 102)	NRTI dual/triple therapy (n = 109)
Birth weight				
<1500	6 (3)	1 (1)	1 (1)	2 (2)
1500 – 2499	43 (19)	25 (32)	12 (12)	24 (22)
2500 – 4000	171 (77)	52 (67)	86 (84)	80 (73)
>4000	2 (1)	0 (0)	3 (3)	3 (3)
Gestational age at delivery ^c				
<32 weeks	9 (4)	3 (4)	0 (0)	3 (3)
32 – 36 weeks	41 (18)	14 (18)	12 (12)	21 (19)
≥37 weeks	172 (77)	61 (78)	90 (88)	85 (78)
SGA ^d	55 (25)	28 (36)	23 (23)	27 (25)
SGA by alternative definition ^e	29 (13)	20 (26)	8 (8)	16 (15)
C-section delivery	132 (59)	49 (63)	21 (21)	46 (42)
NICU admission	25 (11)	6 (8)	9 (9)	11 (10)

ARV = antiretroviral; NICU = neonatal intensive care unit; SGA = small-for gestational age; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

^a NRTI + PI (n = 191); NRTI + NNRTI + PI (n = 29; ; note these are possibly women who switched from a NNRTI-based regimen to an PI-based regimen or vice versa); PI only (2)

^b NRTI + NNRTI (n = 78)

^c Gestational age at delivery based on completed weeks.

^d SGA defined as birthweight below the 10th percentile for the gestational age.

^e SGA defined as birth weight below the 10th percentile for gestational age for preterm births, and birth weight <2500 g for full term births (37 weeks or later).

Table 3
Risk of SGA Comparing Different ARV Prescriptions, Tennessee Medicaid, 1994 - 2009

Exposure Group	N and Percent with prescription	Crude Models OR (95% CI)	P	Adjusted Models 1 ^a OR (95% CI)	P	Adjusted Models 2 ^b OR (95% CI)	P
Any ARV vs. No ARV	511 (85)	1.10 (0.68, 1.78)	0.70	1.04 (0.63, 1.72)	0.87	0.93 (0.56, 1.56)	0.79
<i>Prescriptions containing:</i>							
No ARV	93 (15)	Ref	---	ref	---	ref	---
PI ^c	222 (37)	0.99 (0.58, 1.69)	0.98	0.88 (0.50, 1.54)	0.65	0.74 (0.42, 1.32)	0.31
NNRTI ^d	78 (13)	1.60 (0.86, 2.97)	0.14	1.47 (0.78, 2.79)	0.23	1.21 (0.63, 2.33)	0.57
NRTIdual/triple therapy	109 (18)	1.08 (0.59, 1.96)	0.80	0.99 (0.53, 1.83)	0.97	0.88 (0.47, 1.66)	0.69
NNRTI monotherapy	102 (17)	0.99 (0.52, 1.88)	0.97	1.14 (0.58, 2.26)	0.69	1.19 (0.55, 2.57)	0.65
<i>First PI-containing prescription in:</i>							
1 st Trimester	71 (12)	0.67 (0.36, 1.24)	0.20	0.60 (0.33, 1.12)	0.11	0.54 (0.29, 1.01)	0.05
2 nd Trimester	96 (16)	1.05 (0.64, 1.70)	0.86	0.97 (0.57, 1.65)	0.91	0.86 (0.49, 1.50)	0.59
3 rd Trimester	55 (9)	0.88 (0.46, 1.68)	0.70	0.74 (0.37, 1.47)	0.39	0.74 (0.37, 1.46)	0.38
No PI	382 (63)	ref	---	ref	---	ref	---

SGA = small-for gestational age; ARV = antiretroviral; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; OR = odds ratio; CI = confidence interval

^a Adjusted for non-antiretroviral medication use during pregnancy (binary), smoking (binary) and alcohol use (binary).

^b Adjusted for all variables included in Model 1 plus birth year cohort (categorical – 4 levels) and HIV-related maternal illnesses during pregnancy (categorical – 3 levels)

^c NRTI + PI (n = 191); NRTI + NNRTI + PI (n = 29; note these are possibly women who switched from a NNRTI-based regimen to an PI-based regimen or vice versa); PI only (2)

^d NRTI + NNRTI (n = 78)

Note: Drug use was significant in the univariable analysis, but was highly correlated with alcohol use in the multivariable model; therefore we didn't adjust for it in the multivariable model.