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Use of Zidovudine-Sparing HAART in Pregnant HIV-Infected Women in Europe: 2000–2009

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Abstract

Background—Increasing numbers of women in resource-rich settings are prescribed zidovudine (ZDV)-sparing highly active antiretroviral therapy (HAART) in pregnancy. We compare ZDV-sparing with ZDV-containing HAART in relation to maternal viral load at delivery, mother-to-child transmission (MTCT) of HIV, and congenital abnormality.

Methods—This is an analysis of data from the National Study of HIV in Pregnancy and Childhood and the European Collaborative Study. Data on 7573 singleton births to diagnosed HIV-infected women between January 2000 and June 2009 were analyzed. Logistic regression models were fitted to estimate adjusted odds ratios (AORs).

Results—Overall, 15.8% (1199 of 7573) of women received ZDV-sparing HAART, with increasing use between 2000 and 2009 ($P < 0.001$). Nearly a fifth (18.4%) of women receiving ZDV-sparing HAART in pregnancy had a detectable viral load at delivery compared with 28.6% of women on ZDV-containing HAART [AOR 0.90; 95% confidence interval (CI): 0.72 to 1.14, $P = 0.4$]. MTCT rates were 0.8% and 0.9% in the ZDV-sparing and ZDV-containing groups, respectively (AOR 1.81; 95% CI: 0.77 to 4.26, $P = 0.2$). The congenital abnormality rate was the same in both groups (2.7%, AOR 0.98; 95% CI: 0.66 to 1.45, $P = 0.9$), with no significant difference between the groups in a subanalysis of pregnancies with first trimester HAART exposure (AOR 0.79; 95% CI: 0.48 to 1.30, $P = 0.4$).

Conclusions—We found no difference in risk of detectable viral load at delivery, MTCT, or congenital abnormality when comparing ZDV-sparing with ZDV-containing HAART. With increasing use of ZDV-sparing HAART, continued monitoring of pregnancy outcomes and long-term consequences of in utero exposure to these drugs is required.

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Keywords

antiretroviral agents; highly active antiretroviral therapy; HIV; pregnancy outcome; viral load; congenital abnormalities

INTRODUCTION

In recent years, there has been a steady increase in the United Kingdom and Ireland in the number of pregnancies among women diagnosed with HIV, from under 100 a year in the early 1990s to approximately 1400 in 2006¹; a similar pattern has been observed elsewhere in Europe.² Appropriate management of delivery, avoidance of breastfeeding, and effective use of antiretroviral therapy have reduced mother-to-child transmission (MTCT) rates in women diagnosed with HIV in the United Kingdom and the rest of Europe from approximately 20% in the early 1990s^{3,4} to less than 2% in recent years.⁵⁻⁷

Zidovudine (ZDV) is the only antiretroviral drug licensed in pregnancy and has been key in preventing mother-to-child transmission (PMTCT) of HIV.^{8,9} In non-pregnant adults in resource-rich settings, use of ZDV is declining due to well-recognized side effects, including hematologic and mitochondrial toxicity. Both tenofovir (TDF) and abacavir (ABC) are currently recommended as first-line treatment for HIV-infected adults in Europe.^{10,11}

Consequently, an increasing number of women are already taking highly active antiretroviral therapy (HAART) that does not contain ZDV when they conceive or initiate ZDV-sparing HAART during pregnancy (mainly containing TDF or ABC). Small descriptive studies have shown no evidence of an increased risk of MTCT associated with ZDV-sparing HAART,^{12,13} but there is insufficient evidence from large-scale data sets to support its noninferiority compared with ZDV-containing regimens. With respect to safety, the Anti-retroviral Pregnancy Registry data do not indicate an increased risk of congenital abnormality with drugs commonly used in ZDV-sparing regimens, except for didanosine.¹⁴ However, data on individual drugs and newer drug combinations remain sparse. Most animal and in vitro studies have not demonstrated any teratogenic effects of either ABC or TDF.¹⁵⁻¹⁷ However, there are case reports of congenital pyelectasis with in utero TDF exposure,¹⁸ and there are concerns about its effect on bone development.^{19,20} Analyses of data on ZDV-sparing regimens in pregnancy, although largely reassuring, therefore remain inconclusive.

As a randomized controlled trial comparing ZDV-sparing with ZDV-containing regimens for PMTCT is unfeasible, analysis of observational data is required to provide evidence to guide clinical practice. We carried out an analysis of individual patient data from 2 large European prospective observational studies to explore the use of ZDV-sparing HAART in pregnancy; quantify the extent to which ZDV-sparing HAART in pregnancy is increasing; and compare ZDV-sparing and ZDV-containing HAART with respect to detectable maternal HIV RNA viral load (viral load) at delivery, MTCT, and congenital abnormality. The risk of MTCT and congenital abnormality has previously been explored in these studies, but analyses did not specifically focus on ZDV-sparing regimens.^{5,21-23}

METHODS

This analysis was based on data from the National Study of HIV in Pregnancy and Childhood (NSHPC) and the European Collaborative Study (ECS), 2 prospective observational studies managed within the same institution. Comparable data are collected and have previously been combined.²⁴

The NSHPC, established in 1986, carries out comprehensive population-based surveillance of obstetric and pediatric HIV in the United Kingdom and Ireland. Pregnancies in HIV-infected women diagnosed by the time of delivery, and infants born to infected women, are reported through 2 active parallel schemes managed in collaboration with the Royal College of Obstetricians and Gynaecologists and the British Paediatric Surveillance Unit²⁵; full methods are described elsewhere.¹

The ECS, established in 1985, is an ongoing observational cohort study in which HIV-infected pregnant women diagnosed by the time of delivery are enrolled, and their infants are followed up according to standard clinical and laboratory protocols.²² In ECS sites, pregnant women are routinely offered HIV testing and all infected women are invited to participate in the study; there are 29 centers in 10 European countries (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden, the United Kingdom, and Ukraine). Pregnancies reported from Ukraine were excluded from this analysis due to the limited use of antenatal HAART.²⁶ Pregnancies from UK centers were excluded to avoid duplication of cases reported to the NSHPC.

This analysis was reviewed and approved by the research ethics committee of the London School of Hygiene and Tropical Medicine. The NSHPC has London MultiCentre Research Ethics Committee's approval (MREC/04/2/009). The ECS has been approved by the Great Ormond Street Hospital for Children NHS Trust/Institute of Child Health Ethics Committee.

Eligibility

We included all reported live singleton births to women who received HAART for at least 14 days before delivery between January 2000 (by which time HAART was widely available) and June 2009. Seventy-two mother-child pairs lacked information on all 3 outcomes of interest and were therefore excluded.

Variables

HAART was defined as a regimen of 3 or more antiretroviral drugs, including a protease inhibitor (PI) and/or nonnucleoside transcriptase inhibitor (NNRTI), and for simplicity, we use it in this article to include regimens taken solely for PMTCT and those prescribed as treatment for the mother herself. HAART was categorized as ZDV containing if use of ZDV was reported at any stage of pregnancy and as ZDV sparing if not. Only antepartum treatment was considered. Type of HAART was categorized as PI, NNRTI, or PI + NNRTI based and duration of HAART as 2–7, 8–11, 12–23, and ≥ 24 weeks.

Delivery viral load was defined as the closest reported viral load to delivery measured between 28 days before and 7 days after delivery. Delivery viral load was categorized as undetectable or detectable; “undetectable” was defined as <50 or <400 copies per milliliter, according to the assay detection limits used at the time of report. Baseline viral load was categorized as undetectable (according to the criteria above), 50–999, 1000–9999, and $\geq 10,000$ copies per milliliter. Baseline CD4 count and viral load were defined as the first reported measurement in pregnancy whether before or after treatment initiation.

Injecting drug use (IDU) referred to current or past history of injecting drug use in the ECS and to probable mode of HIV acquisition in the NSHPC. Maternal age at delivery was grouped as <25 , 25–29, 30–34, and ≥ 35 years. Gestational age was grouped as <34 , 34–36, and ≥ 37 completed weeks. Infant infection status was classified as uninfected or infected on the basis of reported polymerase chain reaction or HIV antibody results⁵ or indeterminate for infants whose infection status had not yet been reported. Congenital abnormalities (major and minor) were classified according to the World Health Organization's International

Classification of Diseases, Tenth Revision,²⁷ from information provided by clinicians at infant notification or at follow-up. Year refers to year of delivery.

Statistical Methods

Data were analyzed using Stata 10.0 (Stata Corporation, College Station, TX). Secular trends in exposure were assessed using χ^2 trend tests. The ZDV-sparing HAART group was compared with the ZDV-containing HAART group using univariable and multivariable logistic regression models to estimate odds ratios and adjusted odds ratios (AORs), with 95% confidence intervals (CIs). A priori confounders and variables found to have a confounding effect were included in the final multivariable model. Effect modification by study population (NSHPC or ECS) was assessed to verify the appropriateness of presenting summary odds ratios. Duration of HAART could not be modelled as a continuous variable due to lack of such data in women who conceived on treatment. Two prespecified subgroup analyses were carried out: The analysis of maternal viral load was stratified by whether women had conceived on HAART or started HAART post conception, and the analysis of congenital abnormality was restricted to pregnancies with first trimester HAART exposure. For the analysis of delivery viral load in women starting HAART post conception, we controlled for baseline CD4 and viral load as they potentially reflected pretreatment status; this was not the case in women who conceived on HAART.

RESULTS

Baseline Characteristics of Mother–Child Pairs

This analysis was based on 7573 mother–child pairs reported to the ECS (n = 1263) or NSHPC (n = 6310) with delivery between January 2000 and June 2009. Over three quarters (77.6%) of pregnancies were in women of black ethnicity and less than 5% were in women with a current or previous history of IDU. Median maternal age at delivery was 30.6 years (interquartile range 26.9–34.6 years). Only 15.6% of women had an initial CD4 count of <200 cells per cubic millimeter. About 30% of women were on HAART at conception. HAART was PI based in 56.3%, NNRTI based in 37.0% and PI + NNRTI based in 6.7% of pregnancies. Boosted PIs accounted for nearly two-thirds (3199 of 5204) of PI-based and PI + NNRTI-based HAART regimens. Over half of all deliveries (56.1%) were by elective caesarean section, and 13.9% of infants were preterm (<37-week gestation).

Patterns of ZDV-Sparing HAART Use

Overall, 15.8% of women (1199 of 7573) received ZDV-sparing HAART in pregnancy. Of these, 65% (778 of 1199) took lamivudine during pregnancy. Almost half of women (537 of 1199) received regimes containing TDF, 35% (417 of 1199) ABC, 25% (300 of 1199) didanosine, 18% (216 of 1199) stavudine, and 1% (12 of 1199) other nucleoside reverse transcriptase inhibitors (a substantial minority of women took more than one of these drugs). There were clear baseline differences between women on ZDV-containing and ZDV-sparing HAART particularly with reference to timing of HAART initiation. Women were more likely to be prescribed ZDV-containing HAART than ZDV-sparing HAART if they initiated treatment during pregnancy rather than before [4882 of 5226 (93%) versus 1477 of 2331 (64%); $P < 0.001$] (Table 1). There was also an association between country of report and ZDV-sparing HAART use ($P < 0.001$) with Spain having the highest rate at 25% (46 of 187) compared with 15% (956 of 6310) in the United Kingdom.

Exposure to ZDV-sparing HAART in pregnancy increased over time from 14.7% (48 of 326) in 2000 to 31.6% (68 of 215) in the first half of 2009 (χ^2_{trend} test $P < 0.001$), with most of the increase occurring between 2006 and 2009 (Figure). Among women who started HAART post conception, use of ZDV-sparing HAART in pregnancy increased from 4% in

2006 to 12% in 2009 (χ^2_{trend} test, $P < 0.001$). The proportion of women who were on ZDV-sparing HAART at conception doubled from 15% in 2000 to 31% in 2009 (χ^2_{trend} test, $P < 0.001$).

Detectable Maternal HIV Viral Load at Delivery

Maternal viral load at delivery was reported for 54.4% (4123 of 7573) of pregnancies and was detectable in 26.9% of these (1110 of 4123; 95% CI: 25.6% to 28.3%). In those who had a detectable viral load at delivery, the median viral load was 192 copies per milliliter (interquartile range 90–910 copies/mL). Only a small proportion (8%, 91 of 1110) of detectable viral loads were obtained after delivery. In a univariable analysis, ZDV-sparing HAART was associated with reduced odds of undetectable viral load at delivery (Table 2). After adjusting for duration of HAART and study, we found no difference in risk of detectable viral load at delivery between women receiving ZDV-sparing and ZDV-containing HAART (AOR 0.90; 95% CI: 0.72 to 1.14; Table 2).

Among women who started HAART post conception with available data on confounding variables ($n = 2178$), there was no evidence of a difference in the risk of detectable viral load at delivery between treatment groups after adjusting for baseline HIV viral load, baseline CD4 count, and study (AOR 1.25 for ZDV-sparing versus ZDV-containing HAART; 95% CI: 0.87 to 1.80; $P = 0.24$). There was also no difference in viral load at delivery among women who conceived on HAART ($n = 1196$) (AOR 0.79 for ZDV-sparing versus ZDV-containing HAART, adjusting for study; 95% CI: 0.56 to 1.09; $P = 0.17$).

Mother-to-Child Transmission

Infection status was available for 80% of infants (6130 of 7645) by the cutoff date for this analysis; 0.9% of infants were infected (56 of 6130; 95% CI: 0.7% to 1.0%). There was no evidence of a difference in odds of MTCT in women receiving ZDV-sparing HAART compared with those receiving ZDV-containing HAART after adjustment for duration of HAART, study, and mode of delivery (AOR 1.81; 95% CI: 0.77 to 4.26; Table 3).

Congenital Abnormality

Overall, 2.7% (197 of 7404; 95% CI: 2.4% to 3.1%) of infants were reported to have a congenital abnormality. After adjusting for study and maternal age group, the odds of congenital abnormality in pregnancies exposed to ZDV-sparing HAART was similar to the odds in those exposed to ZDV-containing HAART (AOR 0.98; 95% CI: 0.66 to 1.45; Table 4).

In 2554 pregnancies reported to have first trimester exposure to HAART, 42.2% of the regimens were ZDV sparing (1077 of 2554; 95% CI: 40.3 to 44.1). Subgroup analysis of these pregnancies showed no evidence of a difference in the risk of congenital abnormality between ZDV-sparing and ZDV-containing groups (AOR 0.79 for ZDV-sparing versus ZDV-containing HAART; 95% CI: 0.48 to 1.30; $P = 0.35$; adjusted for study and maternal age; data not shown in table).

Missing and Unreported Data

Information on viral load at delivery was missing for 45.6% (3450 of 7573) of mother–child pairs. Women with missing viral load at delivery had a lower risk of MTCT than those with viral load reported, but the difference was not statistically significant (0.7% versus 1.1%; 95% CI: 0.4 to 1.2; $P = 0.2$). Women with missing viral loads at delivery were more likely to be white than non-white, have a history of IDU, have an undetectable baseline viral load in pregnancy, have been on treatment for at least 24 weeks (including preconception), have delivered earlier in the study period, and have had a vaginal delivery ($P < 0.001$ for all,

based on χ^2 test). However, the proportion with missing data on viral load at delivery was similar in ZDV-sparing and ZDV groups (44.1% and 45.8%, respectively, $P = 0.28$).

Infant HIV status was indeterminate in 19.1% (1443 of 7573) of pregnancies at the time of this analysis; these infants were more likely to have been born in later years ($P < 0.001$), with most (61%) born between 2007 and 2009. Their mothers had higher CD4 counts ($P < 0.001$) and had been on HAART for longer ($P < 0.001$), suggesting that these infants would be at low risk of infection. Nearly a quarter of infants (24.7%) exposed to ZDV-sparing HAART in utero had indeterminate status compared with 18.0% exposed to ZDV ($P < 0.001$).

Information on congenital abnormality was missing in 2.2% (169 of 7573) of pregnancies and did not differ in ZDV-sparing and ZDV-containing groups (2.8% and 2.1%, respectively, $P = 0.12$).

DISCUSSION

In this analysis of combined observational data from 2 European studies involving 7573 mother-child pairs exposed to HAART in pregnancy, we found no evidence of a difference in risk of detectable maternal viral load at delivery, MTCT, or congenital abnormality when comparing ZDV-sparing with ZDV-containing HAART. Overall, 16% of women were prescribed ZDV-sparing HAART during pregnancy in this population. The fact that most women initiated ZDV-containing HAART during pregnancy even in 2009 was not surprising in light of the evidence base for use of ZDV in pregnancy; however, we saw an increase in initiation of ZDV-sparing HAART during pregnancy between 2000 and 2009. In general, use of ZDV-sparing HAART increased over time between 2000 and 2009, particularly among women conceiving on HAART, with approximately 1 in 3 HIV-infected pregnant women receiving ZDV-sparing HAART in 2009.

About 27% of women had a detectable viral load at delivery, similar to rates reported elsewhere,^{7,28} and there was no difference whether ZDV was used. The estimated overall rate of MTCT was 0.9%, consistent with other European data,⁷ and we found no association with ZDV-sparing HAART. We found no increased risk of congenital abnormality with use of ZDV-sparing HAART. This finding is in line with data from the Antiretroviral Pregnancy Registry, which has not detected an increased risk of congenital abnormality among infants exposed to stavudine, ABC, or TDF.¹⁴ The rate of congenital abnormality reported here was similar to that previously reported in the NSHPC.²¹

This is the first large-scale analysis of observational data sets looking specifically at adverse maternal and infant outcomes after use of ZDV-sparing HAART in pregnancy. Comparison with other sources of population surveillance data for HIV²⁹ suggests that virtually all diagnosed HIV-infected women in the United Kingdom and Ireland are reported to the NSHPC through its complementary reporting systems.³⁰ Nonenrolment in the ECS is approximately 5% and is due to migration rather than refusal, with no systematic exclusion.³¹

Although there was a substantial amount of missing data (46%) for delivery viral load, these data were more frequently missing for women on long-term treatment; because virologically suppressed women on long-term treatment probably had less frequent monitoring, and hence less chance of having viral load measured close to delivery, we are likely to have overestimated the proportion of women with detectable viral load at delivery. This is supported by the decreased risk of MTCT in women with missing delivery viral load although this difference was not statistically significant. Given that there was no difference in the proportion of missing data in the ZDV-sparing and ZDV-containing groups, missing

data would have resulted in reduced precision but not necessarily biased estimates. In a fifth of cases, infant HIV status had not yet been reported. This was strongly associated with delivery in later years, between 2007 and 2009, and is mainly a result of delay in reporting final laboratory results. Previous sensitivity analyses have shown that this is likely to have a minimal effect on MTCT estimates for the United Kingdom and Irish data.⁵

In this analysis, ZDV-containing HAART was defined as any ZDV exposure in pregnancy and included regimen switches to or from a ZDV-sparing regimen during pregnancy. More detailed information on regimen switches and discontinuation during pregnancy was not available for this analysis. There were no data on other potential confounders such as adherence to antiretroviral therapy, socioeconomic status, smoking, and alcohol use in pregnancy. Data on pregnancy complications and maternal coinfections have only recently been routinely collected in the studies and were not available for this analysis.

We were unable to conduct drug-specific analysis with regard to ZDV-sparing regimens due to small numbers. With increasing use of both TDF and ABC and consequently improved power to detect differences in outcomes, drug-specific analysis is a priority in the future. In this analysis, we were unable to explore long-term consequences of in utero exposure to ZDV-sparing HAART. This is of importance given recent data on TDF and long-term renal and bone toxicity in adults, children, and animal models.^{19,20,32,33} Data on children reported to the NSHPC are linked to routinely collected cancer and death registrations in England, but information on other health outcomes is not currently available.^{34,35} Although long-term follow-up of uninfected children exposed to ZDV-sparing HAART in utero would be desirable, it is a challenging undertaking.³⁶ Given the possible adverse effects of in utero exposure to ZDV^{37–39} and concerns regarding other drugs, continued pharmacovigilance of all antiretroviral drugs in pregnancy should remain a priority. As clinical trials in pregnancy are not feasible, observational data are needed to provide evidence of the equivalence of newer antiretroviral agents that are not currently licensed for use in pregnancy.

In conclusion, this large-scale analysis of European observational data including more than 7500 mother–child pairs showed that overall outcomes for women on ZDV-sparing HAART in pregnancy are similar to those in women on ZDV-containing regimens. This is reassuring given that a third of women delivering in these studies are now receiving ZDV-sparing HAART in pregnancy, with the trend towards increasing use likely to continue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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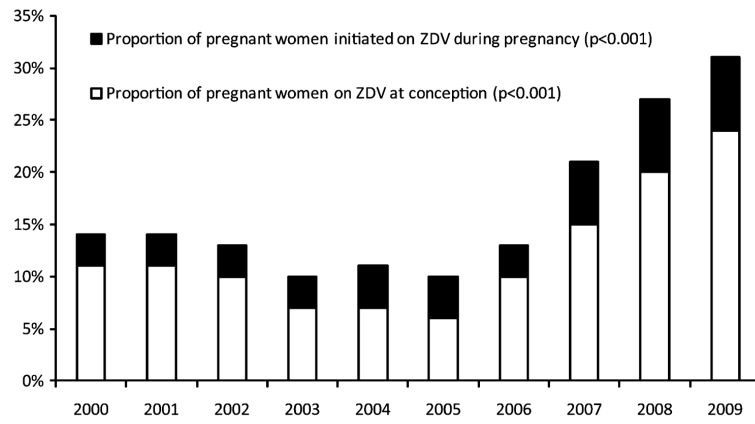


FIGURE.
Use of ZDV-sparing HAART over time.

TABLE 1

Baseline Characteristics of Mother–Child Pairs (n = 7573)

Maternal Characteristic	ZDV-Containing HAART (n = 6374), n (%)	ZDV-Sparing HAART (n = 1199), n (%)	P
Ethnicity (n = 7550)			<0.001
Black	4974 (78.3)	882 (73.8)	
White	1086 (17.1)	269 (22.5)	
Asian/others	294 (4.6)	45 (3.8)	
IDU (n = 7360)			<0.01
No	5960 (96.1)	1088 (93.9)	
Yes	241 (3.9)	71 (6.1)	
Maternal age at delivery (n = 7547), y			<0.001
<25	1072 (16.9)	110 (9.2)	
25–29	1979 (31.2)	257 (21.6)	
30–34	2006 (31.6)	738 (61.7)	
≥35	1293 (20.4)	92 (7.7)	
Mode of delivery (n = 7488)			0.12
Elective CS	3564 (56.5)	634 (54.0)	
Emergency CS	1151 (18.2)	243 (20.7)	
Vaginal	1599 (25.3)	297 (25.3)	
Baseline viral load (n = 4963), copies/mL			<0.001
Undetectable	1009 (24.6)	503 (58.5)	
50–999	626 (15.3)	101 (11.7)	
1000–9999	1071 (26.1)	115 (13.4)	
≥10,000	1397 (34.1)	141 (16.4)	
Baseline CD4 count (n = 6993), cells/mm ³			0.14
≥500	1520 (25.9)	316 (28.4)	
200–499	3427 (58.3)	636 (57.2)	
<200	934 (15.9)	160 (14.4)	
Type of HAART (n = 7573)			<0.001
PI	3624 (56.9)	640 (53.4)	
NNRTI	2366 (37.1)	439 (36.7)	

Maternal Characteristic	ZDV-Containing HAART (n = 6374), n (%)	ZDV-Sparing HAART (n = 1199), n (%)	P
PI + NNRTI	384 (6.0)	120 (10.0)	<0.001
Preconception HAART (n = 7557)			
Yes	1477 (23.2)	854 (71.3)	
No	4882 (76.8)	344 (28.7)	
Duration of HAART (n = 7573), wks			<0.001
≥24	1754 (27.5)	906 (75.6)	
12–23	2823 (44.3)	197 (16.4)	
8–11	1121 (17.6)	59 (4.9)	
2–7	676 (10.6)	37 (3.1)	
Gestational age (n = 7557), wks			0.02
≥37	5504 (86.6)	1002 (83.6)	
34–36	589 (9.3)	131 (10.9)	
<34	266 (4.2)	65 (5.4)	
Year of delivery (n = 7573)			<0.001
2000–2002	1246 (19.6)	205 (17.1)	
2003–2005	2490 (39.1)	290 (24.2)	
2006–2009	2638 (41.4)	704 (58.7)	

CS, cesarean section.

TABLE 2
Crude and AORs for Detectable Maternal HIV Viral Load at Delivery Comparing ZDV-Sparing With ZDV-Containing HAART in Pregnancies

	Univariable Model (n = 4123)			Multivariable Model (n = 4123)*		
	n (%)	OR (95% CI)	P	n (%)	AOR (95% CI)	P
ART group			<0.001			0.33
ZDV-containing HAART	3453 (28.6)	1		3524 (28.6)	1	
ZDV-sparing HAART	670 (18.4)	0.56 (0.46 to 0.69)		670 (18.4)	0.90 (0.72 to 1.11)	
Study			<0.001			<0.001
NSHPC	3452 (28.6)	1		3452 (28.6)	1	
ECS	671 (18.2)	0.55 (0.45 to 0.68)		671 (18.2)	0.62 (0.50 to 0.78)	
Duration of HAART (wks)						
≥24	1341 (15.5)	1	—	1341 (15.5)	1	—
12-23	1653 (23.0)	1.70 (1.42 to 2.05)	<0.001	1653 (23.0)	1.59 (1.31 to 1.94)	<0.001
8-11	672 (38.7)	3.44 (2.77 to 4.26)	<0.001	672 (38.7)	3.18 (2.54 to 3.99)	<0.001
2-7	457 (54.3)	6.46 (5.10 to 8.18)	<0.001	457 (54.3)	6.07 (4.74 to 7.77)	<0.001

* Adjusted for study and duration of HAART.

ART, antiretroviral therapy; OR, odds ratio.

TABLE 3
Crude and AORs for Maternal-to-Child Transmission Comparing ZDV-Sparing With ZDV-Containing HAART in Pregnancies

	Univariable Model (Numbers Vary Due to Missing Data)			Multivariable Model (n = 6111)*		
	n (%)	OR (95% CI)	P	n (%)	AOR (95% CI)	P
ART group			0.64			0.18
ZDV-containing HAART	5227 (0.9)	1		5214 (0.9)	1	
ZDV-sparing HAART	903 (0.8)	0.83 (0.37 to 1.83)		897 (0.8)	1.81 (0.77 to 4.26)	
Study			0.68			0.72
NSHPC	5261 (0.9)	1		5247 (0.9)	1	
ECS	869 (1.0)	1.16 (0.57 to 2.38)		864 (0.9)	1.15 (0.53 to 2.47)	
Mode of delivery						
Elective CS	3515 (0.8)	1	—	3515 (0.8)	1	—
Emergency CS	1095 (1.7)	2.28 (1.26 to 4.12)	<0.01	1095 (1.7)	2.07 (1.13 to 3.76)	0.02
Vaginal	1051 (0.9)	0.78 (0.37 to 1.66)	0.52	1051 (0.9)	0.80 (0.38 to 1.72)	0.58
Duration of HAART (wks)						
≥24	2087 (0.2)	1	—	2078 (0.2)	1	—
12–23	2416 (0.7)	2.95 (1.09 to 8.01)	0.03	2410 (0.7)	3.44 (1.20 to 9.86)	0.02
8–11	1020 (1.0)	4.12 (1.41 to 12.09)	0.01	1017 (1.0)	5.10 (1.65 to 15.77)	0.01
2–7	607 (4.0)	17.14 (6.51 to 45.12)	<0.001	606 (4.0)	20.09 (7.22 to 55.93)	<0.001

* Adjusted for study, mode of delivery, and duration of HAART.

ART, antiretroviral therapy; CS, cesarean section; OR, odds ratio.

TABLE 4
Crude and AORs for Congenital Abnormality Comparing ZDV-Sparing With ZDV-Containing HAART in Pregnancies

	Univariable Model (Numbers Vary Due to Missing Data)			Multivariable Model (n = 7383)*		
	n (%)	OR (95% CI)	P	n (%)	AOR (95% CI)	P
ART group			1.00			0.90
ZDV-containing HAART	6239 (2.7)	1		6220 (2.7)	1	
ZDV-sparing HAART	1165 (2.7)	1.00 (0.68 to 1.48)		1163 (2.7)	0.98 (0.66 to 1.45)	
Study			0.81			0.91
NSHPC	6210 (2.6)	1		6210 (2.6)	1	
ECS	1194 (2.8)	1.05 (0.72 to 1.53)		1173 (2.7)	1.02 (0.70 to 1.50)	
Maternal age group (wks)						
<25	1160 (2.6)	1	—	1160 (2.6)	1	—
25–29	2182 (2.2)	0.87 (0.55 to 1.37)	0.54	2182 (2.2)	0.87 (0.55 to 1.37)	0.54
30–34	2369 (3.0)	1.16 (0.76 to 1.79)	0.49	2369 (3.0)	1.17 (0.76 to 1.80)	0.49
≥35	1672 (2.8)	1.07 (0.67 to 1.70)	0.79	1672 (2.8)	1.07 (0.67 to 1.71)	0.78

* Adjusted for study and maternal age.

ART, antiretroviral therapy; OR, odds ratio.