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Factors Associated with Lack of Viral Suppression at Delivery among HAART-Naïve HIV-Positive Women in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1025 Study

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Abstract

Background—High delivery maternal plasma HIV-1 RNA level (viral load, VL) is a risk factor for mother to child transmission and poor maternal health.

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Objective—To identify factors associated with detectable VL at delivery despite initiation of highly active antiretroviral therapy (HAART) during pregnancy.

Design—Multicenter observational study.

Setting—67 US AIDS clinical research sites.

Patients—HIV-1-positive pregnant women who initiated HAART during pregnancy.

Measurements—Descriptive summaries and associations between socio-demographic, HIV disease, treatment and pregnancy-related risk factors and detectable VL (>400copies/mL) at delivery.

Results—Between October 2002 and December 2011, 671 women met inclusion criteria and 13% had detectable VL at delivery. Factors associated with detectable VL included multiparity (16.4% vs 8% nulliparous, $p=0.002$), black non-Hispanic ethnicity (17.6% vs 6.6% Hispanic and 6.6% white/non-Hispanic, $p<0.001$), 11th grade or less education (17.6% vs 12.1% high school graduate and 6.7% some college or higher, $p=0.013$), and initiation of HAART in third trimester (23.9% vs 12.3% second and 8.6% first, $p=0.002$), timing of HIV diagnosis prior to current pregnancy (16.1% vs 11% during current pregnancy, $p=0.051$), and timing of first prenatal visit in 3rd trimester (33.3% vs 14.3% second and 10.5% first, $p=0.002$). Women who experienced treatment interruptions or reported poor medication adherence during pregnancy were more likely to have detectable VL at delivery than women with no interruptions or who reported better adherence.

Limitations—Women entered the study at varying times during pregnancy and for this and other reasons there was incomplete data on many covariates.

Conclusions—In this large U.S.-based cohort of HIV-1 positive women, 13% of women who initiated HAART during pregnancy had detectable VL at delivery. The timing of HAART initiation and prenatal care along with medication adherence during pregnancy appear to be modifiable factors associated with detectable VL at delivery. Social factors such as Black/non-Hispanic ethnicity and less than high school education may help to identify women at highest risk who may benefit from focused efforts to promote early treatment initiation and adherence to HAART.

Clinical Trial Registration Number—NCT00028145

Keywords

Antiretroviral therapy; pregnancy; maternal to child transmission; HIV; women

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) estimates that 6,500 HIV-positive women give birth annually in the U.S. (1). High maternal plasma HIV-1 RNA level (viral load, VL) is a major risk factor for mother-to-child transmission (MTCT) (2–6). Use of Highly Active Antiretroviral Therapy (HAART) to suppress viral replication has become a mainstay in the management of HIV-positive pregnant women in developed nations, reducing MTCT rates at delivery to 1–2% (7–10).

Despite the widespread use of HAART in the U.S., some women still have detectable VL at delivery; every birth of an HIV-infected infant represents a missed prevention opportunity (11). Viral suppression reduces MTCT risk and confers important benefits to maternal health both during and after pregnancy (12, 13). Factors associated with detectable VL (VL >400 copies/mL) at delivery include advanced HIV disease, late initiation of HAART, and inability to adhere to treatment (14–16).

Results are mixed regarding the role of different antiretroviral (ARV) regimens. While one previous report showed virologic response to vary by regimen type (17), a large observational study found no difference in response by ARV regimen (18). A randomized trial of women with CD4+ 200 cells/μL in Botswana comparing the impact of a nucleoside reverse-transcriptase inhibitor [NRTI]-based regimen to a boosted protease-inhibitor [PI]-based regimen on VL at delivery observed high rates of virologic suppression at delivery and no difference between regimens (19).

The objective of this study was to identify risk factors associated with detectable VL at delivery among women who initiated HAART for the first time during pregnancy.

METHODS

Design

IMPAACT P1025 is a multicenter observational study in the U.S. (including Puerto Rico) designed to assess maternal and infant safety, and effectiveness of interventions prescribed for prevention of mother-to-child transmission (PMTCT) and women's health. Enrollment began in October 2002. HIV-positive women 13 years of age and older could enroll between 8 weeks gestation and 14 days after delivery and again for subsequent pregnancies. Additional details of P1025 study procedures have been published (20). Institutional review boards approved the protocol at all 67 clinical sites, and written informed consent was obtained from those enrolled.

Eligibility

The study population eligible for this analysis included women who enrolled in P1025 for the first time prior to delivery, with an estimated date of confinement (EDC) on or before December 31, 2011, who had available VL data between 14 days before and 7 days after delivery, were ARV-naïve prior to pregnancy, and initiated HAART during the index pregnancy. HAART was defined as a regimen of 3 antiretroviral drugs, including two NRTIs combined with either: 1) a non-nucleoside reverse transcriptase inhibitor (NNRTI); 2) an unboosted (without ritonavir) PI; 3) a boosted (with ritonavir) PI; or 4) a third NRTI.

Variable Selection

Analysis variable selection was driven by clinical hypotheses, using covariates known at baseline and others shown to be relevant in prior studies. The outcome of interest was detectable VL at delivery, defined as VL >400 copies/mL, the standard assay limit of quantification prior to 2008. Baseline characteristics were assessed at the time HAART was

initiated in pregnancy and characteristics of antiretroviral management and adherence assessed through the remainder of the pregnancy.

Baseline characteristics included maternal age, race/ethnicity, and highest education level attained; obstetric information, including parity and timing of first prenatal visit; HIV and treatment characteristics, including trimester of HAART initiation, first HAART regimen used in pregnancy, timing of HIV diagnosis, CDC clinical classification (21), and pre-treatment CD4+ count and VL measures.

Using ARV regimen information collected via chart abstraction, we calculated the number of and reasons for regimen changes and medication interruptions that occurred during pregnancy. We did not consider a formulation change, or IV Zidovudine at time of delivery to be a regimen change. A medication interruption was defined as >1 day interval between a regimen stop date and subsequent regimen start date. Adherence to HAART was self-reported at each study visit using an interviewer-administered questionnaire, which included questions about the current regimen, the number of doses missed for each antiretroviral of the regimen over the 3 days prior to the study visit, and a multi-choice question regarding the last time a dose was missed (22). We selected the interviews completed closest to delivery for this analysis.

Statistical Analyses

We summarized and compared the distribution of the covariates of interest by trimester of HAART initiation, and compared the proportion with detectable VL at delivery across levels of each covariate, using Chi-square tests. We explored associations between covariates and VL at delivery using logistic regression models. Many covariates were closely related and we selected one covariate from each group of related covariates (maternal age and parity; regimen composition and calendar year; and timing of first prenatal visit, HIV diagnosis and HAART initiation) for inclusion in multivariable logistic regression models.

We used multiple imputation to account for the fact that pretreatment VL data were not available for 29% of women, due to P1025's observational study design. Thirty imputations were used and the imputation model included all covariates from our final model, plus VL at delivery. Data were imputed using Proc MI under the assumption that missing pretreatment VL was missing at random (MAR), and final estimates were found using Proc MIANALYZE. Predicted probabilities, evaluated at the mean value of all other covariates in the model, were estimated from this model and reported as adjusted probabilities. To assess the sensitivity of our results to the multiple imputations, we also fit models on the subset of women with complete pretreatment VL data. We explored results by pre-treatment VL and timing of HAART initiation since we expected both factors would be strongly related to VL at delivery and to one another. Due to concerns that self-reported adherence data were missing non-randomly, we did not include adherence in our multivariable models and instead explored the association between adherence and VL at delivery more descriptively in women who had complete adherence data available. We considered a two-sided p-value <0.05 statistically significant and conducted all analyses with SAS version 9.2 software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 2294 women enrolled in P1025 with an EDC between 10/2002 and 12/2011, 1013 (44.2%) had not used ARVs prior to pregnancy. Of these, 15 women not on HAART during pregnancy, 186 who enrolled at or after delivery, and 141 with no delivery VL data were excluded, leaving 671 women eligible for this analysis. Women without delivery VL data were more likely to be black than women included in the analysis. The median number of participants per site was 6.5 (Q1–Q3: 4.0–14.0; range 1–63).

Table 1 describes baseline socio-demographic, HIV disease, and treatment characteristics of the cohort, by timing of HAART initiation. Of women with available data, most (88.1%) had VL >400 copies/mL prior to HAART initiation; 35.0% had VL between 10,000 – < 100,000 copies/mL, and 7.3% had VL ≤ 100,000 copies/mL. About half (52.6%) received a boosted PI-based regimen (79.3% received lopinavir/ritonavir and most of the remainder received atazanavir/ritonavir), 23.7% received an unboosted PI-based regimen (95.0% containing nelfinavir), 7.3% received an NNRTI-based regimen (85.7% containing nevirapine, and 14.3% efavirenz), and 16.4% received a triple NRTI-based regimen (majority with abacavir) as their initial regimen during pregnancy. Women who initiated HAART in the 3rd trimester were significantly more likely to be black, have started prenatal care and enrolled in P1025 later, been diagnosed with HIV more recently, and have a lower pre-treatment VL than those initiating HAART earlier in pregnancy. Multiparous women were older than nulliparous women (median age 28.8 vs 23.5, $p<0.001$) and those with more recent EDC (2008–2011) were more likely to have initiated use of boosted PI regimens (>70.9% vs <37.7% in years prior, $p<0.001$).

Table 2 summarizes treatment management and adherence during pregnancy. Thirty-nine (5.8%) women had at least one treatment interruption during pregnancy. The median interruption duration was 12 days (Q1–Q3: 5, 39). The most common reasons reported for treatment interruptions were toxicity, teratogenicity, or obstetric complications (59.0%) and non-compliance (28.2%). Six discontinued completely (3 due to non-compliance, and 3 due to toxicity). In addition, 137 (20.4%) changed regimens at least once during pregnancy; 96 were exposed to 2 regimens, 33 were exposed to 3 regimens, and 8 were on 4 regimens. Women initiated on NNRTI regimens were most likely to change regimens and women initiated on triple NRTI regimens were least likely to change regimens relative to the other regimen types. The reasons reported for medication changes were toxicity, teratogenicity, or obstetric complication (40.9%); clinician request (30.7%); non-compliance (5.8%); patient request (3.6%); and virologic failure or drug resistance (3.6%). Of the 541 women (80.6%) with ARV adherence data available, 22.0% and 20.2% reported non-adherence within the preceding two weeks or three days, respectively, of the last adherence assessment prior to delivery. The percentage of women without adherence data appeared to differ according to race (higher among Hispanics and Blacks relative to white non-Hispanic women), site, calendar year, type of regimen, and overall duration of HAART during pregnancy.

Table 3 summarizes pregnancy outcomes. Median gestational age at delivery was 38.3 weeks; 85.7% delivered at ≥ 37 weeks gestation. Of those with detectable VL at delivery, 64.8% delivered by Cesarean section and 35.2% delivered vaginally. In contrast, of those

with VL <400 copies/mL at delivery, a significantly higher proportion (50.8%) delivered vaginally. We did not observe a statistically significant difference in gestational age at delivery by VL. There was 1 confirmed MTCT (0.2%); the mother was diagnosed with HIV during the pregnancy, and received HAART for 12 weeks before delivery. She had detectable VL (between 1,000 – <10,000 copies/mL) both pre-treatment and at time of delivery, and at her visit closest to delivery, she reported missing ARVs during the previous 2 weeks.

Eighty-eight women (13.1%) had detectable VL at delivery. Of these, 59 (67.0%) had VL 1000 copies/mL; 13 (14.8%) had VL between 10,000 – < 100,000 copies/mL, and 3 (3.4%) had VL ≥ 100,000 copies/mL. In univariate comparisons, (Table 4), race/ethnicity, level of education, parity, timing of first prenatal visit, and timing of HAART initiation were associated with detectable VL at delivery. Data in women with pretreatment VL, suggested an association between higher proportions with detectable VL at delivery and higher (> 10,000 c/mL) pretreatment VL (15.8% vs. 10.2%, $p=0.065$). There was some evidence that the proportion with detectable VL at delivery was marginally higher with non-boosted PI-containing regimens compared with boosted PI-containing regimens (17.0% vs 11.6%, $p=0.098$). In the multivariable modelling following multiple imputation of missing pre-treatment VL (Table 4), the significant predictors in univariate analyses continued to be associated with VL at delivery. In addition, pretreatment viral load was significantly associated with VL at delivery. When the multivariable modeling was restricted to the subset of women with complete pre-treatment VL, results remained consistent.

In univariate analyses of treatment management characteristics, women with at least one treatment interruption were more likely to have detectable VL at delivery than those with no interruption (28.2% vs. 12.2%, $p=0.004$), but regimen changes were not significantly associated with detectable VL at delivery. When treatment interruption was added to the multivariable model, it remained statistically significant ($p=0.002$, adjusted probability 24.3%; 95% CI (13.0, 40.8) with interruptions vs. 9.0%; 95% CI: (6.7, 11.9) with no interruptions) and the p -values and adjusted probabilities for the pretreatment variables did not change substantially. In the subset of women with complete adherence data ($N=541$), the proportion with detectable VL at delivery was highest among women who reported non-adherence in the previous 2 weeks (19.3%) vs. earlier (12.3%) or never (9.6%) ($p=0.039$).

There was some variation in the adjusted probabilities of detectable VL at delivery by pretreatment VL and trimester of HAART initiation, though estimates were imprecise. Among women with pre-treatment VL ≥ 10,000 c/mL, the adjusted probability of detectable VL at delivery increased if HAART was initiated later in pregnancy (1st trimester: adjusted probability 4.2%, 95% CI (1.0%, 15.8%); 2nd trimester: 12.8% (8.1%, 19.7%); 3rd trimester: 32.5% (16.1%, 54.6%)). However, among women with pretreatment VL <10,000 c/mL, there was much less of an increase in the adjusted probability of detectable VL at delivery with later HAART initiation (1st trimester: 7.8% (2.4%, 22.4%); 2nd trimester: 7.6% (4.6%, 12.2%); 3rd trimester: 9.5% (3.9%, 21.6%)).

DISCUSSION

In this large U.S.-based cohort of HAART-naïve, HIV-1 positive women, 13% had detectable VL at delivery. While this percentage of women with persistent viremia at delivery is concerning, this estimate is lower than the 24% of HAART-naïve women with detectable VL at delivery observed in an earlier U.S. cohort (18). The timing of HAART initiation, along with consistent usage during pregnancy, were associated with VL at delivery. Among women who initiated HAART in the 3rd trimester nearly one-quarter 23.9% had detectable VL at delivery.

A recent retrospective study from the United Kingdom recommended women with VL >10,000 copies/mL should begin HAART by 20.4 weeks, while those with VL >100,000 copies/mL should start HAART without delay (23). In that study, women with VL <10,000 copies/mL could potentially begin HAART by 26.3 weeks to achieve an undetectable VL by delivery, but this should be balanced against the possible increased risk of *in-utero* transmission with a delayed start, or the risk of transmission should a premature delivery occur.

Our data suggest that the timing of HAART initiation may be more strongly associated with detectable viral load among women who have high pre-treatment VL (≥10,000 copies/mL) than among those who have lower pre-treatment VL (<10,000 copies/mL). The timing of HAART initiation during pregnancy deserves special attention, as vaginal delivery in HIV-positive pregnant women is recognized to be safer for women and equally safe as cesarean section for newborns if VL is non-detectable at delivery (24). For HAART-naïve women, the updated USA DHHS perinatal guidelines from July 2012 recommend starting the regimen in the first trimester or delaying until 12 weeks' gestation depending on CD4-cell count, HIV RNA levels, and maternal conditions such as nausea and vomiting. Earlier initiation of a combination regimen may be more effective in reducing transmission, but benefits must be weighed against potential fetal effects of first-trimester drug exposure (24).

One important consideration regarding when to start HAART extends beyond the benefits for maternal health and decreasing neonatal transmission rates. There is emerging literature focused on the effects of maternal viremia on long-term post-delivery outcomes in HIV-exposed, uninfected (HEU) children. Research from South Africa shows that both HIV-positive and HEU children under 1 year old were at increased risk of failing treatment for severe pneumonia (25). More recent findings corroborate the greater infectious morbidity among this population (26). Poor outcomes may relate to the fact that HEU infants have altered CD4 immunity during the first year of life (27). Infants born to immunosuppressed mothers have increased exposure to pathogens (28). Subsequent research has shown that HEU infants present a variety of immunological abnormalities, including impaired immune response to vaccines (29) as compared to non-exposed neonates, however it remains unclear if this is related to maternal HIV infection or to use of HAART (30).

Missing data precluded us from incorporating adherence data into a multivariable analysis, but it appears that women who reported suboptimal adherence had higher rates of detectable VL at delivery than women who reported optimal adherence. These findings are supported

by other studies that show the importance of early HAART initiation (31), as well as medication adherence both within (32), and outside the context of pregnancy (33), and suggest that HAART can only achieve its optimal efficacy in prevention of mother-to-child transmission (MTCT), morbidity, and mortality if HIV-positive individuals initiate treatment in a timely manner, and adhere to their medications (34–36). Our findings provide further evidence of the importance of early HAART initiation (37) and support of medication adherence throughout pregnancy.

Women with higher pre-treatment VL and those on less potent regimens containing unboosted PIs had higher probability of having detectable VL at delivery. The AIDS 2012 IAS-USA treatment guidelines stressed that initial therapy for all adults, including pregnant women, should optimize potency of the regimen and be based on a combination of 2 NRTIs and a third agent, generally consisting of an NNRTI, a ritonavir-boosted PI, an integrase strand transfer inhibitor (INSTI), or, rarely, an agent that blocks the CC chemokine receptor 5 (CCR5) (38). Unboosted PIs are not considered first line therapy at this time, and our findings reflect the fact that a regimen containing a PI without ritonavir boosting is suboptimal, and this was generally not prescribed after 2007.

We also identified several sociodemographic factors associated the detectable viral load at delivery: Black non-Hispanic ethnicity and attainment of an educational level less than high school graduation. Prior studies have identified race-associated disparities in maternal HIV disease outcomes including high VL at delivery (16, 39–41). It is possible that experiences of race-based discrimination or lack of trust in the medical care system may pose barriers to engagement in care, which in turn could be associated with unsuppressed VL. For example, Bogart et al. found that African-American women frequently reported race-based discrimination when seeking family-planning and contraceptive services (42). In a different study of a random cross-sectional sample of African Americans, up to 60% endorsed HIV conspiracy beliefs (43). There may also be racial variations in drug pharmacokinetics during pregnancy and risk of virologic failure (44) or ethnic differences in the sites where patients receive care and resources devoted to promoting adherence. Education is an important social determinant of health. As a marker of socioeconomic status, lower education has been linked to suboptimal engagement in care, non-adherence to antiretroviral therapy, and lower rates of survival in individuals with HIV infection (45, 46). While the mechanisms linking lower educational attainment to detectable VL at delivery remain unclear, it may reflect lower levels of health literacy, or possibly be a marker of overall poverty. Lower health literacy and greater poverty-related stress have been linked to medication non-adherence and other negative health outcomes (47–49).

A limitation of this observational study is that women could enroll at any time during their pregnancy. Thus, there is incomplete data on some covariates and study entry did not correspond with entry into pre-natal care or initiation of treatment. Women who enrolled in the study during their 3rd trimester were more likely to have missing pre-treatment VL and CD4+ data. Also, correlations between maternal age and parity, calendar year and treatment regimen, and timing of HAART initiation, first prenatal visit, and HIV diagnosis prohibited drawing conclusions about the independent effects of these factors on detectable VL at delivery. Additionally, a large amount of missing adherence data and reliance on self-report

for adherence precluded inclusion of adherence in multivariable analyses and results should be interpreted with caution. Despite this, our findings are consistent with prior studies related to medication adherence in a U.S.-based population of HIV-positive pregnant women (22).

Generalizability is uncertain because this study occurred at AIDS clinical trial sites and may not reflect patients in the community. These sites are geographically and demographically diverse, but small numbers of women at each site and lack of socio-demographic variation within sites inhibited our ability to account for site effects. Some sites enrolled mostly or all black Non-Hispanic women, while other sites enrolled mostly or all Hispanic women. This makes it possible that the association we found between ethnicity and VL was due to site factors rather than ethnicity. Finally, we did not have resistance data for most women. Despite these limitations, our study is one of the largest U.S.-based analyses evaluating the association between antiretroviral therapy and virologic suppression at delivery in the current era of HAART.

Our results suggest that women who initiate HAART in the 3rd trimester, have higher pre-treatment VL, or have suboptimal antiretroviral adherence are at increased risk for having detectable VL at delivery. Optimal care for HIV-positive, HAART-naïve pregnant women should focus on initiation of HAART according to pre-treatment VL, and prior to the third trimester. Additional interventions should focus on early prenatal care, early HIV testing, and measures to support adherence to treatment throughout pregnancy in order to promote both maternal and infant health.

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APPENDIX

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Table 1

Baseline characteristics of HAAART-naïve women in P1025 from 2002–2011

Sociodemographic Characteristics	By trimester of HAAART initiation				P-value ²
	Overall N=671	1st N=128	2nd N=455	3rd N=88	
Age (years)					
13–19	53 (7.9%)	10 (7.8%)	31 (6.8%)	12 (13.6%)	0.266
20–34	540 (80.5%)	101 (78.9%)	373 (82.0%)	66 (75.0%)	
35+	78 (11.6%)	17 (13.3%)	51 (11.2%)	10 (11.4%)	
Race/Ethnicity					
Black Non-Hispanic	397 (59.2%)	66 (51.6%)	270 (59.3%)	61 (69.3%)	0.032
Hispanic	198 (29.5%)	49 (38.3%)	127 (27.9%)	22 (25.0%)	
White Non-Hispanic/Other ³	76 (11.3%)	13 (10.2%)	58 (12.7%)	5 (5.7%)	
Highest level of education					
11th grade or less	239 (35.6%)	58 (45.3%)	148 (32.5%)	33 (37.5%)	0.041
High school graduate/equivalent	313 (46.6%)	50 (39.1%)	218 (47.9%)	45 (51.1%)	
Some college	119 (17.7%)	20 (15.6%)	89 (19.6%)	10 (11.4%)	
Parity					
Multiparous	409 (61.0%)	77 (60.2%)	284 (62.4%)	48 (54.5%)	0.38
Nulliparous	262 (39.0%)	51 (39.8%)	171 (37.6%)	40 (45.5%)	
Timing of first prenatal visit					
1st trimester	381 (56.8%)	117 (91.4%)	249 (54.7%)	15 (17.0%)	<.001
2nd trimester	244 (36.4%)	10 (7.8%)	190 (41.8%)	44 (50.0%)	
3rd trimester	27 (4.0%)	1 (0.8%)	1 (0.2%)	25 (28.4%)	
Timing of P1025 enrollment					
1st/2nd trimester	244 (36.4%)	52 (40.6%)	189 (41.5%)	3 (3.4%)	<.001
3rd trimester	427 (63.6%)	76 (59.4%)	266 (58.5%)	85 (96.6%)	
Calendar year					
2002–2005	195 (29.1%)	35 (27.3%)	131 (28.8%)	29 (33.0%)	0.195
2006–2008	238 (35.5%)	37 (28.9%)	168 (36.9%)	33 (37.5%)	
2009–2011	238 (35.5%)	56 (43.8%)	156 (34.3%)	26 (29.5%)	

By trimester of HAART initiation					
Sociodemographic Characteristics	Overall N=671	1st N=128	2nd N=455	3rd N=88	P-value ²
HIV & Treatment Characteristics					
HIV+ diagnosis timing					
During current pregnancy	392 (58.4%)	47 (36.7%)	277 (60.9%)	68 (77.3%)	<.001
Prior to pregnancy	279 (41.6%)	81 (63.3%)	178 (39.1%)	20 (22.7%)	
Reason not on ARV prior to pregnancy					
Recent HIV diagnosis	358 (53.4%)	45 (35.2%)	255 (56.0%)	58 (65.9%)	<.001
Never prescribed/Not indicated for health	180 (26.8%)	50 (39.1%)	119 (26.2%)	11 (12.5%)	
Refused/did not tolerate/non-compliant	22 (3.3%)	5 (3.9%)	15 (3.3%)	2 (2.3%)	
No medical care	15 (2.2%)	0 (0.0%)	13 (2.9%)	2 (2.3%)	
Missing	96 (14.3%)	28 (21.9%)	53 (11.6%)	15 (17.0%)	
Pre-treatment viral load (copies/mL) during pregnancy					
<10,000	275 (41.0%)	31 (24.2%)	200 (44.0%)	44 (50.0%)	0.021
10,000	202 (30.1%)	40 (31.3%)	139 (30.5%)	23 (26.1%)	
Missing	194 (28.9%)	57(44.5%)	116 (25.5%)	21 (23.9%)	
Pre-treatment CD4+ count (cells/mm ³) during pregnancy					
<200	57 (8.5%)	10 (7.8%)	37 (8.1%)	10 (11.4%)	0.314
200–349	153 (22.8%)	20 (15.6%)	117 (25.7%)	16 (18.2%)	
350–499	106 (15.8%)	19 (14.8%)	76 (16.7%)	11 (12.5%)	
500+	177 (26.4%)	31 (24.2%)	116 (25.5%)	30 (34.1%)	
Missing	178 (26.5%)	48 (37.5%)	109 (24.0%)	21 (23.9%)	
CDC ⁴ class					
A/B	640 (95.4%)	122 (95.3%)	433 (95.2%)	85 (96.6%)	0.843
C	31 (4.6%)	6 (4.7%)	22 (4.8%)	3 (3.4%)	
Initial HAART regimen ⁵					
2 NRTIs/NNRTI	49 (7.3%)	7 (5.5%)	35 (7.7%)	7 (8.0%)	0.877
2 NRTIs/PI	159 (23.7%)	30 (23.4%)	110 (24.2%)	19 (21.6%)	
2 NRTIs/PI/RTV	353 (52.6%)	73 (57.0%)	235 (51.6%)	45 (51.1%)	
3 NRTIs	110 (16.4%)	18 (14.1%)	75 (16.5%)	17 (19.3%)	

¹ HAART: Highly-active antiretroviral therapy.

² Chi square test comparing characteristics by the three trimesters of HAART initiation (among non-missing data).

³ Included all other race responses (Asian, Pacific Islander, American Indian, Alaskan Native, unknown, and refused to report).

⁴ CDC: Centers for Disease Control

⁵ NRTI: nucleoside/nucleotide reverse-transcriptase inhibitor; NNRTI: non-nucleoside/nucleotide reverse-transcriptase inhibitor; PI: protease inhibitor; RTV: ritonavir.

Table 2

Treatment management and adherence during pregnancy

By trimester of HAART ¹ initiation					P-value ²
Overall N=671	1st N=128	2nd N=455	3rd N=88		
Treatment management information from chart abstraction					
Treatment interruptions					
At least one interruption	39 (5.8%)	11 (8.6%)	27 (5.9%)	1 (1.1%)	0.069
No interruptions	632 (94.2%)	117 (91.4%)	428 (94.1%)	87 (98.9%)	
Regimen changes					
At least one change	137 (20.4%)	35 (27.3%)	90 (19.8%)	12 (13.6%)	0.041
No changes	534 (79.6%)	93 (72.7%)	365 (80.2%)	76 (86.4%)	
Interviewer administered self-reported adherence at the visit closest prior to delivery					
Last time missed HIV medication					
Never missed	292 (43.5%)	57 (44.5%)	189 (41.5%)	46 (52.3%)	0.103
>2 weeks ago	130 (19.4%)	30 (23.4%)	87 (19.1%)	13 (14.8%)	
During previous 2 weeks	119 (17.7%)	19 (14.8%)	90 (19.8%)	10 (11.4%)	
Missing	130 (19.4%)	22 (17.2%)	89 (19.6%)	19 (21.6%)	
Non-adherence in past 3 days					
Took all doses in last 3 days	424 (63.2%)	88 (68.8%)	279 (61.3%)	57 (64.8%)	0.083
Missed at least 1 dose	107 (15.9%)	17 (13.3%)	82 (18.0%)	8 (9.1%)	
Missing	140 (20.9%)	23 (18.0%)	94 (20.7%)	23 (26.1%)	

¹ HAART: Highly-active antiretroviral therapy

² Chi square test comparing characteristics by the three trimesters of HAART initiation (among non-missing data).

Table 3**Pregnancy/Delivery/Infant Outcomes**

Overall	N=671
Delivery outcome	
Live birth	666 (99.3%)
Stillbirth (IUFD ¹ 20 wks)	5 (0.7%)
Number of fetuses	
Singleton	663 (98.8%)
Twins	8 (1.2%)
Gestational age at delivery	
<37 weeks	96 (14.3%)
≥37 weeks	575 (85.7%)
Live Births²	
N=666	
Delivery type	
Vaginal Delivery	327 (49.1%)
Cesarean Section	338 (50.8%)
Missing	1 (0.2%)
Infant birth weight class	
<2.5 kg	80 (12.0%)
≥2.5 kg	576 (86.5%)
Missing	10 (1.5%)
Infant birth size class	
Large for gestational age	40 (6.0%)
Appropriate for gestational age	579 (86.9%)
Small for gestational age	44 (6.6%)
Intrauterine growth restriction	2 (0.3%)
Missing	1 (0.2%)
Infant HIV status ³	
Infected	1 (0.2%)
Uninfected	549 (82.4%)
Indeterminate	39 (5.9%)
Negative, based on best available data	77 (11.6%)

¹ IUFD: intra-uterine fetal demise.

² Certain information not evaluated or not available on still births.

³ Indeterminate: little to no test result information available; Negative, based on best available data: multiple negative tests, did not meet required timing of testing to meet the definition of uninfected.

Table 4

Association of Pretreatment Factors with VL >400 copies/mL at Delivery

Characteristics	Viral load at delivery >400 copies/mL			Multivariable Baseline Model (Pre-Treatment variables only)		
	Total	N	%	P-value ¹	Adjusted Probability ² (95% CI)	P-value ³
	671	88	13.1			
<hr/>						
Age (years)						
13–19	53	9	17.0%	0.25	13.6% (6.8, 25.3)	0.42
20–34	540	73	13.5%		10.5% (8.0, 13.7)	
35+	78	6	7.7%		5.1% (2.1, 11.7)	
Parity ⁴						
Nulliparous	262	21	8.0%	0.002		
Multiparous	409	67	16.4%			
Race/Ethnicity						
Black Non-Hispanic	397	70	17.6%	<0.001	15.1% (11.7, 19.3)	<0.001
Hispanic	198	13	6.6%		5.3% (3.0, 9.2)	
White Non-Hispanic/Other ⁵	76	5	6.6%		4.9% (1.9, 11.8)	
Highest level of education						
11th grade or less	239	42	17.6%	0.013	14.4% (10.3, 19.7)	0.002
High school graduate/equivalent	313	38	12.1%		9.7% (6.8, 13.6)	
Some college or more	119	8	6.7%		4.7% (2.2, 9.7)	
Pre-treatment viral load (copies/mL) during pregnancy						
<10,000	275	28	10.2%	0.065	8.1% (5.5, 11.8)	0.007
10,000	202	32	15.8%		12.9% (9.1, 18.0)	
Missing	194	28	14.4%			
HAART ⁶ initiation timing						
1st trimester	128	11	8.6%	0.003	6.6% (3.5, 12.0)	0.006
2nd trimester	455	56	12.3%		9.5% (7.0, 12.8)	
3rd trimester	88	21	23.9%		20.8% (13.4, 30.9)	
HIV diagnosis timing ⁴						

	Viral load at delivery >400 copies/mL			Multivariable Baseline Model (Pre-Treatment variables only)		
	Total	N	%	P-value ¹	Adjusted Probability ² (95% CI)	P-value ³
	671	88	13.1			
Prior to current pregnancy	279	45	16.1%	0.051		
During current pregnancy	392	43	11.0%			
First prenatal visit ⁴						
1 st trimester	381	40	10.5%	0.002		
2 nd trimester	244	35	14.3%			
3 rd trimester	27	9	33.3%			
Missing	19	4	21.1%			
Initial HAART ⁶ regimen ⁷						
2 NRTIs/NNRTI	49	3	6.1%	0.14	4.2% (1.3, 12.9)	0.088
2 NRTIs/PI	159	27	17.0%		13.4% (8.8, 19.9)	
2 NRTIs/PI/RTV	353	41	11.6%		9.0% (6.3, 12.6)	
3 NRTIs	110	17	15.5%		12.4% (7.5, 19.9)	
Calendar year ⁴						
2002–2004	116	18	15.5%	0.46		
2005–2007	241	34	14.1%			
2008–2011	314	36	11.5%			

¹ Chi square test comparing proportion of detectable VL across covariate levels (among non-missing data).

² For a given covariate, predicted probabilities were estimated at mean of the other covariates in the model.

³ Overall Wald Chi-square test from logistic regression modeling, pooled over 30 imputations

⁴ Variables not selected for multivariable modeling due to association with other covariates.

⁵ Included all other race responses (Asian, Pacific Islander, American Indian, Alaskan Native, unknown, and refused to report)

⁶ HAART: highly-active antiretroviral therapy

⁷ NRTI: nucleoside/nucleotide reverse-transcriptase inhibitor; NNRTI: non-nucleoside/nucleotide reverse-transcriptase inhibitor; PI: protease inhibitor; RTV: ritonavir.