Risk Factors for Detectable HIV-1 RNA at Delivery among Women Receiving Highly Active Antiretroviral Therapy in the Women and Infants Transmission Study

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Abstract

Background—Detectable HIV-1 RNA at delivery is the strongest predictor of mother-to-child transmission. The risk factors for detectable HIV, including type of regimen, are unknown. We evaluated factors, including highly active antiretroviral (HAART) regimen, associated with detectable HIV-1 RNA at delivery in the Women and Infants Transmission Study.

Methods—Data from 630 HIV-1 infected women who enrolled from 1998–2005 and received HAART during pregnancy were analyzed. Multivariable analyses examined associations between regimens, demographic factors, and detectable HIV-1 RNA (>400 cp/ml) at delivery.

Results—Overall, 32% of the women in the cohort had detectable HIV-1 RNA at delivery. Among the subset of 364 HAART-experienced women, a lower CD4+ cell count at enrollment (adjusted odds ratio [AOR]=1.20 per 100 cells/μl, CI 1.04–1.37) and higher HIV-1 RNA at enrollment (AOR=1.52 per log10 cp/ml, CI 1.32–1.75) were significantly associated with detectable HIV-1 RNA levels at delivery. For the 266 HAART-naïve women, both lower CD4+ cell count at enrollment (AOR=1.24 per 100 cells/μl, CI 1.05–1.48) and higher HIV-1 RNA at enrollment (AOR=1.35 per $\log_{10}$ cp/ml, CI 1.12–1.63) were associated with detectable HIV-1 RNA at delivery. In addition, age at delivery (AOR=0.92 per 10y older, CI 0.86–0.99), and maternal illicit drug use (AOR=3.15, CI 1.34–7.41) were significantly associated with detectable HIV-1 RNA at delivery among HAART-naïve women. Type of HAART regimen was not significant in either group.

Conclusions—Lack of viral suppression at delivery was common in the WITS cohort, but differences by antiretroviral regimen were not identified. Despite a transmission rate below 1% in

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the last 5 years of the WITS cohort, improved measures to maximize HIV-1 RNA suppression at term among high-risk women are warranted.

Keywords

antiretrovirals; HIV; pregnancy; MTCT; HAART

INTRODUCTION

More than 6000 women in the United States living with human immunodeficiency virus (HIV) become pregnant each year.[1] Prior to 1994, approximately 25% of their infants ultimately became infected with HIV. Results from the AIDS Clinical Trials Group study 076 (ACTG 076) established that administration of zidovudine (ZDV) to the mother during pregnancy and delivery, as well as to the infant post-partum reduced the rate of HIV transmission from mother to child (MTCT) by two-thirds.[2] Highly active antiretroviral treatment (HAART), elective caesarian sections for women with HIV-1 RNA >1,000 cp/ml, and avoidance of breastfeeding have subsequently been shown to reduce MTCT rates to < 1–2% for women identified early in pregnancy.[3] Unfortunately, the most recent surveillance data from the Centers for Disease Control (CDC) demonstrate up to 4% transmission at sentinel sites. [4] While these data may not be indicative of current trends, they suggest that we are not achieving optimal coverage of HIV-infected pregnant women. Despite the great success in the prevention of mother-to-child transmission (PMTCT) in the United States, more aggressive screening and implementation of effective interventions may be required.

The Women and Infants Transmission Study (WITS) cohort previously found that HIV-1 RNA at delivery is associated with risk for MTCT. [3] A prospective analysis from January 1990 to June 2000 showed the odds of transmission increased 2.4-fold (95% CI, 1.7–3.5) for every one $\log_{10}$ cp/ml increase in delivery viral load. Other studies support these findings, however, research to date has not correlated the use of HAART with the outcome of viral suppression.[5–9] While data support the use of HAART for PMTCT,[3, 10, 11] prior studies have not fully elucidated the impact of ritonavir boosting on maternal HIV-1 RNA at term. [12,13] In addition, few studies have examined the association between specific HAART regimens and HIV-1 RNA during pregnancy while controlling for socio-demographic, racial and behavioral factors. Instead, most prior research has focused on the impact of these factors on HIV infected women outside of the context of pregnancy.[14]

Using data from one of the largest and well-characterized prospective cohort studies of infected pregnant women in the United States, we conducted an analysis to determine the clinical, socio-demographic, and biological risk factors associated with lack of maternal virologic suppression at term in women who were either "HAART-experienced" or "HAART-naïve" prior to pregnancy. We chose to subdivide our sample into these two categories to provide proxy measures for "duration of treatment" and because the approaches for managing determinants of lack of suppression might differ between these two groups. Our primary aim was to determine the relationship between HIV-1 RNA levels at delivery and HAART regimen in these two groups. Our *a priori* hypothesis was that more potent regimens containing ritonavir would be associated with improved HIV-1 RNA suppression at delivery. Our secondary aim was to examine the impact of known sociodemographic risk factors on HIV-1 RNA while controlling for HAART regimen. We hypothesized that sociodemographic factors that have previously been associated with lower adherence would increase the risk of having a detectable HIV-1 RNA level at delivery, independent of HAART regimen.[15,16]

METHODS

The Women and Infants Transmission Study (WITS) is a multicenter, prospective, natural history cohort study of the perinatal transmission of HIV-1 and the natural history of HIV-1 infection in pregnant women and their infants.[17] Starting in December, 1989, HIV infected pregnant women and their infants were enrolled at centers in New York City, Boston, Worcester, San Juan, and Chicago. Additional sites were added in 1991 in Brooklyn and in 1993 in Houston. The study was approved by each site's institutional review board, and all women provided informed consent for enrollment of themselves and their newborns. The women were enrolled at any time during pregnancy or up to seven days postpartum.

HIV infected women were assessed, based upon their time of enrollment, at or before 20 weeks of gestation, at 25 +/− 2 weeks, at 32 +/− 2 weeks, at delivery, and at two and six month post-partum visits. At each visit, women completed detailed medical and behavioral questionnaires, underwent physical examination, and gave a sample of blood. CD4+ cell counts were determined in fresh blood by flow cytometry, in accordance with protocols developed by the Division of AIDS of the National Institute of Allergy and Infectious Diseases. Plasma HIV-1 RNA was measured in five laboratories from repository samples (stored at −70°C). Obstetric data were obtained from abstraction of the medical record. Antiretroviral therapy was not prescribed as part of the study. Start and stop dates for medications were recorded as the month and year of the first or last use. Only one regimen was categorized per pregnancy, based upon a woman's earliest regimen initiated.

The nested cohort used for this analysis consisted of the subset of women who received HAART during pregnancy and gave birth to infants between June 1998 and December 2005. We chose June 1998 to December 2005 because that corresponded to the funding periods for WITS III and IV, when there were larger numbers of women on 3 drug regimens for PMTCT. We restricted our primary analysis to women who had an HIV-1 RNA level available from delivery. We excluded all women whose "delivery HIV-1 RNA" was recorded as their "enrollment HIV-1 RNA," in order to eliminate any women who enrolled during or immediately prior to delivery. HAART was defined as a regimen of 3 or more antiretroviral drugs. In all cases, women received at least two nucleoside reverse-transcriptase inhibitors (NRTIs) combined with either: 1) a non-nucleoside reverse-transcriptase inhibitor (NNRTI); 2) an unboosted (without ritonavir) protease inhibitor (PI); 3) a boosted (with ritonavir) PI; or 4) a third NRTI. Two subpopulations of women were analyzed: those who were HAART-experienced prior to pregnancy and those who were HAART-naïve prior to pregnancy. This information was determined based upon self-report from patients. Women classified as HAART-naïve prior to pregnancy could have started on treatment prior to study enrollment (given they were allowed to enroll at any point during their pregnancy). Given this, a minority of the HAART-naïve subset (11%) had undetectable levels of HIV-1 RNA upon study enrollment.

Univariate analyses of associations were performed using the chi squared test, Fisher's exact test, Wilcoxon rank sum test, or F-test from analysis of variance, as appropriate. Covariates considered as potential risk factors for detectable HIV-1 RNA at delivery included sociodemographic characteristics (maternal age at delivery, race, insurance status), factors associated with birth (parity, number of live births), factors associated with disease acuity (CDC clinical classification[18] enrollment CD4+ count, and enrollment HIV-1 RNA level), maternal illicit drug use (defined as use of heroine/opiates, methadone, cocaine, or any injection drug use during the current pregnancy), timing of HIV diagnosis and of HAART initiation, and HAART regimen. Logistic regression models estimated the odds of having a detectable HIV-1 RNA level at delivery (>400 cp/ml) as a function of these characteristics.

We chose an HIV-1 RNA cutoff of >400 cp/ml because it was the standard assay limit of detection used during the WITS study.

We generated 2 separate multivariable models that examined women who were either HAART-experienced or HAART-naïve prior to pregnancy. For each multivariable model, we first used stepwise logistic regression with p<0.05 as the entry and stay criteria for variable selection. We then fit a model for each of the two populations which included all variables which were significant in one or both of the models identified using stepwise variable selection. Finally, as we were interested in evaluating potential differences between HAART regimens, we added this variable in the model. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of 935 HIV-1 infected women enrolled between June 1998 and December 2005, 630 (67%) met eligibility criteria for this analysis (Table 1). The majority of women in the analysis cohort were young (59% were < 30 years old), black (57%), on public insurance (80%), not illicit drug users (80%), and in either CDC class A or B (93%). Among all 630 women, 109 (17%) received a boosted PI-based regimen (64 women were on lopinavir/ritonavir and the remainder received either indinavir/ritonavir or saquinavir/ritonavir), 402 (65%) received an unboosted PI-based regimen (all containing nelfinavir), 87 (14%) received an NNRTI-based regimen (all containing nevirapine), and 25 (4%) received a triple NRTI-based regimen (the majority with abacavir). Most regimens contained zidovudine (ZDV) (89%) and lamivudine (95%) as part of the NRTI backbone.

Of these, 364 (58%) were HAART-experienced prior to pregnancy and 266 (42%) were HAART-naïve prior to pregnancy. A comparison of enrollment characteristics by history of HAART exposure is shown in Table 1. There were significant differences between HAART-experienced and HAART-naïve women in age, insurance status, parity, and time since HIV diagnosis (median of 5 years in the HAART-experienced group versus 6 months in the HAART-naïve group). The median CD4+ cell count overall was 435 cells/μl (IQR 294, 640), however, women who were naïve to HAART prior to pregnancy were more likely to have a first CD4+ cell count measurement >200 cells/μl (95% vs. 83%, p<0.001) and lower CDC class (73% vs. 54% Class A, p<0.001). Among both HAART-experienced and HAART-naïve women, 53% had a detectable HIV-1 RNA at first study measurement in pregnancy. There was a significant difference between HAART-experienced and HAART-naïve women in the proportion of women using the different types of regimens (p<0.001, Table 1). This primarily reflected a higher proportion of HAART-experienced compared to HAART-naïve women who received a boosted PI-regimen. We also examined the distribution of women by year of study enrollment (Figure 1). The proportion of women with detectable HIV-1 RNA at enrollment varied significantly by calendar year of enrollment, reflecting declining trends over time, both among women who were HAART-experienced prior to pregnancy (p<0.001) and among women who were naïve prior to pregnancy (p<0.001).

Among all 630 women, the overall rate of detectable HIV-1 RNA at delivery was 32%. In univariate analyses, significant predictors for detectable HIV-1 RNA at delivery included pre-pregnancy HAART exposure, younger age at delivery, black race, public insurance, maternal illicit drug use, HIV diagnosis prior to the current pregnancy, detectable HIV-1 RNA at enrollment, and earlier year of enrollment (Table 2). Parity was not significant and type of HAART regimen was of borderline significance (p=0.051). In separate analyses of HAART-experienced and HAART-naïve women, the directions of associations with these factors remained the same as in the overall analysis, but for HAART-experienced women,

only age, race, HIV-1 RNA at enrollment and year of enrollment remained significant, while for HAART-naïve women, only maternal illicit drug use, timing of HIV diagnosis and HIV-1 RNA at enrollment were significant. Of 295 women who entered the study with an undetectable HIV-1 RNA, 39 (13%) ultimately had detectable levels of HIV-1 RNA at delivery; 15% among women in the HAART-experienced group, and 11% among women in the HAART-naïve group. Conversely, 162 (48%) of the 335 women who were detectable at enrollment remained detectable at delivery; 57% among women in the HAART-experienced group and 36% among women in the HAART-naïve group.

Table 3 shows gestational age at delivery as well as number of women with detectable HIV-1 RNA at enrollment and delivery by treatment regimen for both HAART-experienced and HAART-naïve women. In both cohorts, women on PI-based therapies were more likely to have a detectable viral load both at enrollment and at delivery. In univariate analysis, there was no apparent advantage to boosting PI-based regimens with ritonavir.

Results from the multivariable analysis are displayed in Table 4. The variables that were selected for inclusion in the model (see Statistical Methods) are reported in the footnote in Table 4. Among HAART-experienced women, detectable levels of HIV-1 RNA levels at delivery were significantly associated with a higher enrollment HIV-1 RNA (adjusted odds ratio [AOR] 1.52 per $\log_{10}$ cp/ml, 95% confidence interval [CI] 1.32 to 1.75, p<0.001) and a lower enrollment CD4+ count (AOR 1.20 per 100 cells/μl, CI 1.04 to 1.37, p=0.009) at first study measurement. Among HAART-naïve women, detectable levels of HIV-1 RNA levels at delivery were also associated with a higher HIV-1 RNA at enrollment (AOR 1.35 per $\log_{10}$ cp/ml, CI 1.12 to 1.63, p=0.002) and a lower CD4+ count at enrollment (AOR 1.24 per 100 cells/μl, CI 1.05 to 1.48, p=0.014). In addition, maternal age (AOR 0.92 per 10y older, CI 0.86 to 0.99, p=0.022) and maternal illicit drug use (AOR 3.15, CI 1.34 to 7.41, p=0.008) were significantly associated with detectable HIV-1 RNA among HAART-naïve women. Type of regimen was not associated with detectable HIV-1 RNA at delivery for either HAART-experienced or HAART-naïve women. After adjustment for the other variables included in the model, there was a significant association among HAART-experienced women (p=0.001), but not among with HAART-naïve women (p=0.77), with calendar year of enrollment reflecting a decreasing trend over time in the odds of detectable HIV-1 RNA at delivery.

DISCUSSION

The use of HAART for PMTCT is one of the most successful public health interventions of the HIV era in the United States.[10] Despite rates of transmission remaining below 1% for the last 5 years of WITS,[19] we found that 32% of the women who received HAART between 1998 and 2005 had a detectable HIV-1 RNA at delivery. This discrepancy may indicate successful peripartum prophylaxis efforts of mothers and infants, but it also highlights the fact that one of the cornerstones of PMTCT – maternal virologic suppression–was difficult to achieve in this cohort. MTCT continues to occur in the United States, and this transmission is at least in part due to factors associated with detectable maternal HIV-1 RNA at delivery. While rates of detectable viral load declined over time, a finding which is also consistent with CDC data,[4] the high numbers of women on treatment with detectable HIV-1 RNA highlights the need for increased counseling of known HIV-infected women and aggressive treatment for the most vulnerable groups regardless of pregnancy status, both for PMTCT as well as overall maternal health.

In the current study, women who were most at risk were those who presented with a higher HIV-1 RNA and lower CD4+ count at enrollment. This was seen among women who were HAART–experienced and among women who were HAART-naïve prior to their pregnancy.

For women who were HAART-naïve prior to pregnancy, this may have reflected more advanced disease and/or initiation of therapy later in pregnancy. For women who were HAART-experienced prior to pregnancy, this may have reflected either more advanced disease possibly refractory to antiretrovirals, or suboptimal use of antiretrovirals prior to pregnancy that was ultimately more resistant to subsequent regimens. Younger age and illicit drug use also significantly increased the odds of having detectable HIV-1 RNA at delivery in women who were HAART-naïve prior to pregnancy.

The type of HAART treatment did not significantly impact HIV-1 RNA levels at delivery, both before and after adjusting for enrollment factors, including HIV-1 RNA and CD4+ count. This finding was consistent for all women. The lack of superiority for boosted PI's was a surprising finding in our evaluation of the impact of antiretroviral regimens on suppression of maternal HIV-1 RNA at term. While these findings are novel, it is important to interpret them with caution, given the relatively small numbers in each treatment group, and the observational design that may be prone to residual confounding. In addition, boosted PI's may have been used more commonly in patients with more advanced disease, in whom antiretrovirals may have diminished effectiveness. We therefore believe that current treatment practices that recommend the use of ritonavir boosting when using PI's in pregnancy should continue, pending further study of this question, ideally in randomized studies.

The loss of viral load suppression during pregnancy that occurred among 13% of women who initially had undetectable levels of HIV-1 RNA is of concern. It is unknown whether pregnancy itself increases the risk for loss of suppression. Factors specific to pregnancy may include increased medication intolerance (especially gastrointestinal), increased medication side effects (anemia's or other), or altered pharmacokinetics. [20],[21],[22] Several studies have reported lower area under the plasma concentration time curve (AUC) in the third trimester with both lopinavir/ritonavir [23],[24] and nelfinavir, [24] but the association between lower drug levels during pregnancy and virologic outcome at delivery has not been studied. Many experts, however, consider it to be reasonable to increase the dose of certain PI's during the third trimester when viral load remains unsuppressed in the setting of good medication adherence. [25] Whether or not such dose increases might have reduced the loss of suppression in this cohort is unknown. We believe our findings warrant further study in trials where information on medication adherence, pharmacokinetics, and resistance can be obtained.

Women who were HAART-experienced prior to pregnancy differed from those who were HAART-naïve prior to pregnancy, both in enrollment characteristics as well as likelihood of virologic suppression at delivery. In general, women who were HAART-experienced were significantly more likely to be older, on public insurance, parous, have a more advanced CDC class, a longer duration of HIV diagnosis, and a lower CD4 count at enrollment. HAART-naïve women appeared to have generally less advanced disease at enrollment and were more likely to be virologically suppressed at term. This may in fact reflect disease stage, but could also reflect unmeasured sociodemographic factors, or lower rates of resistant virus among HAART-naïve women.

There were some significant trends within the cohort over time. There appeared to be fewer women who were HAART-naïve at enrollment in later years. This may reflect expanded screening for HIV and earlier treatment outside of pregnancy or more known HIV-infected women choosing to get pregnant. An important observation seen in our multivariable model was that the odds of having a detectable HIV-1 RNA at delivery declined with calendar year in the HAART-experienced group, even after adjustment for HIV-1 RNA and CD4+ cell count at enrollment. This may be reflective of increasing knowledge of the importance of

viral load suppression at delivery and greater ability to achieve this in the HAART-experienced group as treatment options expanded, despite minimal changes over time with the HAART-naïve group. We did not find, however, that calendar year confounded associations with other factors included in the model.

This was an observational analysis, and prone to biases, including potential selection bias, and unmeasured confounding. We had limited information on medication dosage, patterns of resistance, adherence, and the exact timing of HAART initiation. In addition, we were only able to measure the initial regimen used in pregnancy, and viral suppression at delivery may have been affected by subsequent regimen changes. Because most women had started HAART before study entry, our first measured CD4+ cell count and HIV-1 RNA were not true "baseline" values, even for women who were HAART naïve prior to pregnancy. Despite these limitations, our study is one of the first U.S.-based observational analyses comparing the association between regimens and virologic suppression at delivery in the current era of HAART availability. Virologic suppression at delivery is an important risk factor for MTCT, and one that can be clinically measured. HIV-1 RNA suppression at delivery is a reasonable surrogate measure of success for antiretroviral therapy as an intervention to prevent MTCT.

In conclusion, our analysis suggests that women with lower CD4+ counts and higher HIV-1 RNA during pregnancy are at an increased risk for a detectable HIV-1 RNA at delivery. Persistently detectable HIV-1 RNA is particularly common among HAART-experienced women presenting with detectable HIV-1 RNA in pregnancy (57% of whom remained detectable at delivery). Of additional concern was the loss of virologic suppression by delivery among 13% of women with undetectable HIV-1 RNA at entry. Our findings suggest that efforts to improve suppression at term are warranted, particularly among women with lower CD4+ cell count and higher HIV-1 RNA.

Acknowledgments

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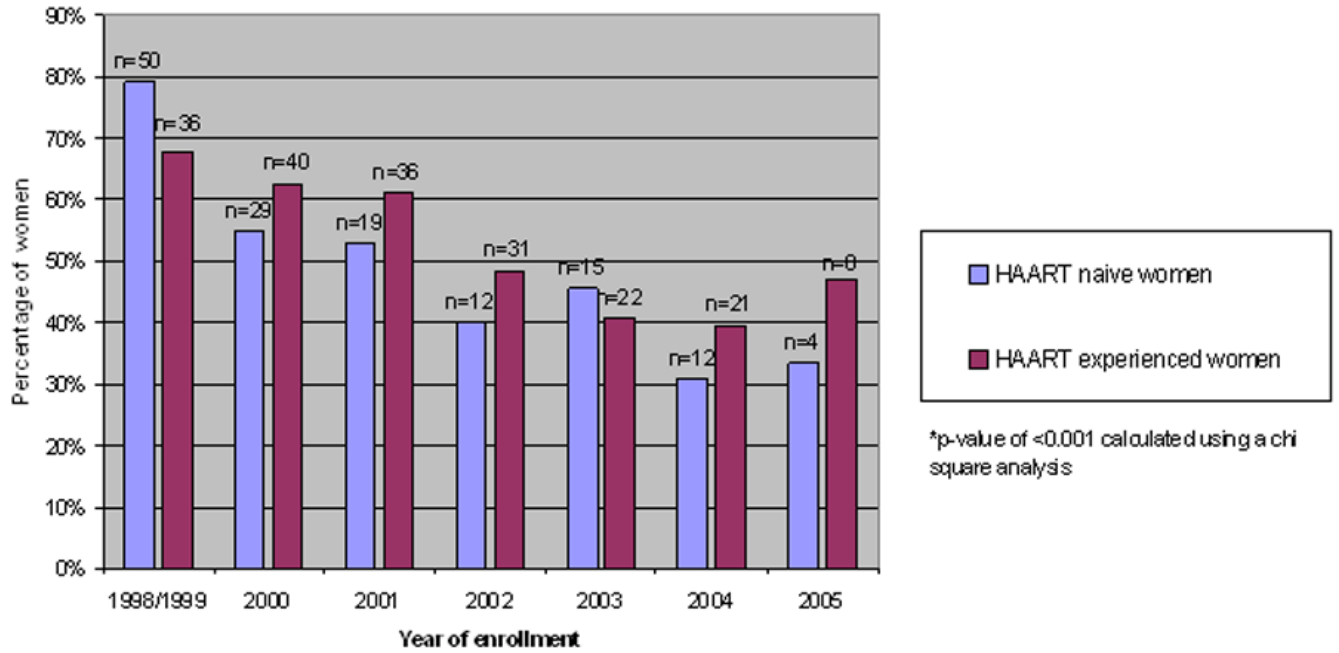
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APPENDIX

Percentage of women with detectable HIV-1 RNA at enrollment, by year*

Figure 1.

TABLE 1

Characteristics of HIV Positive Pregnant Women Meeting Inclusion Criteria by History of HAART ExposurePrior to Pregnancy

Characteristic	All women (n=630)	HAART experienced (n=364)	HAART naïve (n=266)	p-value[a]
Age at delivery				**<0.001**
<30 years	372 (59)	187 (51)	185 (70)	
≥30 years	258 (41)	177 (49)	81 (30)	
Race/Ethnicity				0.109
White	47 (7)	34 (9)	13 (5)	
Black	361 (57)	205 (56)	156 (59)	
Hispanic and Other	222 (35)	125 (35)	97 (36)	
Insurance status				**0.020**
Public Insurance(Medicaid, etc.)	507 (80)	305 (84)	202 (76)	
Private Insurance	87 (14)	45 (12)	42 (16)	
Other/unknown	36 (6)	14 (4)	22 (8)	
Parity				**<0.001**
Nulliparous	157 (25)	63 (17)	94 (36)	
Parous	469 (74)	299 (83)	170 (64)	
Number of live births (n=606)				**0.424**
Singleton	591 (98)	337 (98)	254 (97)	
Twins or +	15 (2)	7 (2)	8(3)	
Maternal illicit drug use				0.165
No illicit drug use	504 (80)	284 (78)	220 (83)	
Illicit drug use	125 (20)	79 (22)	46 (17)	
Timing of HIV diagnosis (n=622)				**<0.001**
Antenatal	168 (27)	4 (1)	164 (62)	
Prepregnancy	454 (73)	354 (99)	100 (38)	
Median duration of HIV diagnosis, Yrs	2.92	5.04	0.59	**<0.001**
CDC Class				**<0.001**
Class A	390 (62)	197 (54)	193 (73)	
Class B	193 (31)	131 (36)	62 (23)	
Class C	47 (7)	36 (10)	11 (4)	
CD4+ cell count at enrollment (n=598)				**<0.001**
<200 cells/μl	71 (12)	56 (16)	15 (6)	
200–399 cells/μl	180 (30)	97 (28)	83 (33)	
≥400 cells/μl	347 (58)	190 (55)	157 (62)	
Median CD4+ cell count at enrollment, cells/μl	435	433	447	0.525
HIV-1 RNA at enrollment				0.943
Undetectable (<400cp/ml)	295 (47)	170 (47)	125 (47)	
Detectable (≥400 cp/ml)	335 (53)	194 (53)	141 (53)	
HAART regimen (n=623)				**<0.001**
PI with ritonavir	109 (17)	81 (22)	28 (11)	

Characteristic	All women (n=630)	HAART experienced (n=364)	HAART naïve (n=266)	p-value[a]
PI without ritonavir	402 (65)	207 (57)	195 (73)	
NNRTI	87 (14)	55 (15)	32 (12)	
NRTI	25 (4)	18 (5)	7 (3)	

Note: Data are no. (column%) of patients unless otherwise indicated.

Cumulative percentage may not exactly equal 100% based upon rounding to nearest decimal.

[a] p-values were calculated with χ^2 test (for categorical variables) or non-parametric statistic for median to compare distributions of baseline characteristics

TABLE 2

Univariate Analysis of Factors Associated With HIV-1 RNA >400 cp/ml at Delivery by History of HAART Exposure Prior to Pregnancy

Characteristic	All women N (%)detectable HIV RNA*	p-value	HAART experienced N (%)detectable HIV RNA*	p-value	HAART naïve N (%)detectable HIV RNA*	p-value
Overall detection rate	201/630 (32)	N/A	136/364 (37)	N/A	65/266 (24)	N/A
HAART prior to pregnancy		0.001	------	N/A	------	N/A
Experienced	136/364 (37)					
Naïve	65/266 (24)					
Age at delivery**		0.013		0.009		0.073
<30 years	133/372 (36)		82/187 (44)		51/185 (28)	
≥30 years	68/258 (26)		54/177 (31)		14/81 (17)	
Race/Ethnicity		<0.001		0.010		0.085
White	7/47 (15)		6/34 (18)		1/13 (8)	
Black	123/361 (34)		80/205 (39)		43/156 (28)	
Hispanic	59/199 (30)		42/112 (38)		17/87 (20)	
Insurance status		0.015		0.14		0.12
Public	173/507 (34)		119/305 (39)		54/202 (27)	
Private/Other	28/123 (23)		17/59 (29)		11/64 (17)	
Parity		0.13		0.51		0.59
Nulliparous	42/157 (27)		21/63 (33)		21/94 (22)	
Parous	156/469 (33)		113/299 (38)		43/170 (25)	
Maternal illicit drug use		0.016		0.22		0.030
No illicit drug use	149/504 (30)		101/284 (36)		48/220 (22)	
Illicit drug use	51/125 (41)		34/79 (43)		17/46 (37)	
Timing of HIV diagnosis		0.001		N/A		0.045
Antenatal	35/168 (21)		***		33/164 (20)	
Prepregnancy	161/454 (35)		----		31/100 (31)	
HIV-1 RNA at enrollment**		<0.001		<0.001		<0.001
Undetectable (<400 cp/ml)	39/295 (13)		25/170 (15)		14/125 (11)	
Detectable (≥ 400 cp/ml)	162/335 (48)		111/194 (57)		51/141 (36)	
HAART regimen		0.051		0.081		0.32

Characteristic	All women N (%)detectable HIV RNA *	p-value	HAART experienced N (%)detectable HIV RNA *	p-value	HAART naïve N (%)detectable HIV RNA *	p-value
PI with ritonavir	37/109 (34)		30/81 (37)		7/28 (25)	
PI without ritonavir	137/402 (34)		86/207 (42)		51/195 (26)	
NNRTI	18/87 (21)		13/55 (24)		5/32 (16)	
NRTI	5/25 (20)		5/18 (28)		0/7 (0)	
Year of Enrollment		<0.001		<0.001		0.063
1998/1999	56/116 (48)		32/53 (60)		24/63 (38)	
2000	45/117 (38)		32/64 (50)		13/53 (25)	
2001	38/95 (40)		29/59 (49)		9/36 (25)	
2002	23/94 (24)		20/64 (31)		3/30 (10)	
2003	17/87 (20)		10/54 (19)		7/33 (21)	
2004	17/92 (18)		9/53 (17)		8/39 (21)	
2005	5/29 (17)		4/17 (24)		1/12 (8)	

*
Percentage reflects women with detectable HIV viral load within each category (e.g. black women with detectable viral load/all black women)

**
All numerical cutpoints (age, years of HIV diagnosis and enrollment) are derived from the median value

***
4 women were diagnosed during pregnancy, but were classified as HAART-experienced because they were already on medications prior to enrollment in the WITS.

TABLE 3

Gestational age at delivery and number of women with detectable HIV-1 RNA by history of HAART Exposure Prior to Pregnancy*

Characteristic	HAART experienced prior to pregnancy (n=361)*					HAART naïve prior to pregnancy (n=262)*				
	PI with ritonavir n=81	PI no ritonavir n=207	NNRTI n=55	NRTI n=18	p-value	PI with ritonavir n=28	PI no ritonavir n=195	NNRTI n=32	NRTI n=7	p-value
Gestational age at delivery**	38.0 (36.0,40.0)	38.0 (36.0, 40.0)	38.0 (35.0, 41.0)	38.5 (35.5, 41.5)	0.69	38.0 (36.0, 40.0)	38.0 (36.0, 40.0)	38.0 (35.0, 41.0)	38.0 (35.0, 41.0)	0.22
HIV-1 RNA at enrollment	n= 191 for Experienced women					n= 138 for Naïve women				
Detectable***	46 (57)	118 (57)	22 (40)	5 (28)	<0.001	13 (46)	111 (57)	12 (38)	2 (29)	<0.001
HIV-1 RNA at delivery	n=134 for Experienced women					n=63 for Naïve Women				
Detectable***	30 (37)	86 (42)	13 (24)	5 (28)	<0.001	7 (25)	51 (26)	5 (16)	0 (0)	<0.001

Note: Data are no. (column % where applicable) of patients unless otherwise indicated

p-value calculated using Chi Square or Fisher's Exact Test, as relevant

*
Total n for this table is 623 due to incomplete data on regimens for 1% of cohort

**
Values are median wks (interquartile range)

***
Detectable is ≥400 cp/ml

TABLE 4

Multivariable Analysis of Factors Associated with HIV-1 RNA >400 cp/ml at Delivery by History of HAART Exposure Prior to Pregnancy*

Characteristic	HAART experienced (n=364)		HAART naïve (n=266)	
	AOR[**]	95% CI	AOR	95% CI
CD4+ cell count at enrollment, per 100 cells/μl lower	1.20	**1.04–1.37**	1.24	**1.05–1.48**
HIV-1 RNA load at enrollment, per 1 $\log_{10}$ copies/ml higher	1.52	**1.32–1.75**	1.35	**1.12–1.63**
HAART regimen (using PI-based without ritonavir as the reference group)				
PI-based with ritonavir	1.21	0.46–3.19	0.90	0.18–4.50
NNRTI-based	2.23	0.48–10.38	1.13	0.35–3.62
NRTI-based	1.30	0.57–2.97	---	---
Age at delivery per 10 years older	0.98	0.93–1.03	0.92	**0.86–0.99**
Maternal illicit drug use	0.75	0.39–1.46	3.15	**1.34–7.41**
Year of enrollment (as compared to 2004/2005)				
1998/1999	5.56	**2.01–15.42**	0.90	0.29–2.80
2000	3.57	**1.39–9.13**	0.61	0.18–2.04
2001	2.94	**1.14–7.55**	1.03	0.31–3.46
2002	2.09	0.81–5.38	0.41	0.09–1.87
2003	0.79	0.28–2.29	0.91	0.24–3.50

The following variables were considered for inclusion in the logistic regression model, with selection using stepwise variable selection: race, SES, number of live births, gestational age, side effects, age at delivery, maternal illicit drug use, year of enrollment (as a categorical variable), enrollment CD4 count, enrollment HIV RNA, and ART regimen. A variable was retained in the model if significant at a level of $p<0.05$ in either the HAART-experienced population or the HAART-naïve population.

[**] AOR is Adjusted Odds Ratio

NB: NRTI-based regimen was removed from the analysis for HAART-naïve women due to the small sample size (n=7)