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## HYPERTENSION, PREECLAMPSIA AND ECLAMPSIA AMONG HIV-INFECTED PREGNANT WOMEN FROM LATIN AMERICA AND CARIBBEAN COUNTRIES

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### Abstract

**Objectives**—To evaluate the incidence of and risk factors for hypertensive disorders in a cohort of HIV-infected pregnant women.

**Methods**—Hypertensive disorders (HD) including preeclampsia/eclampsia (PE/E) and pregnancy-induced hypertension, and risk factors were evaluated in a cohort of HIV-infected pregnant women from Latin America and the Caribbean enrolled between 2002–2009. Only pregnant women enrolled for the first time in the study and delivered at ≥ 20 weeks gestation were analyzed.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US National Institutes of Health or the Department of Health and Human Services.

**Results**—HD were diagnosed in 73 (4.8%, 95% CI: 3.8%-6.0%) of 1513 patients; 35(47.9%) had PE/E. HD was significantly increased among women with a gestational age-adjusted body mass index (gBMI)  $\geq 25$  kg/m<sup>2</sup> (OR=3.1; 95% CI: 1.9-5.0), hemoglobin (Hg)  $\geq 11$  g/dL at delivery (OR=2.1; 95% CI: 1.2-3.6) and age  $\geq 35$  years (OR=1.8; 95% CI: 1.1-3.2). PE/E was increased among women with a gBMI  $\geq 25$  kg/m<sup>2</sup> (OR=3.0; 95% CI: 1.5-6.0) and Hg  $\geq 11$  g/dL at delivery (OR=2.8; 95% CI: 1.2-6.5). A previous history of PE/E increased the risk of PE/E 6.7 fold (95% CI: 1.8-25.5). HAART before conception was associated with PE/E (OR=2.3; 95% CI: 1.1-4.9)

**Conclusions**—HIV-infected women, with a previous history of PE/E, a gBMI  $\geq 25$  kg/m<sup>2</sup>, Hg at delivery  $\geq 11$  g/dL and in use of HAART before conception are at an increased risk of developing PE/E during pregnancy.

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## INTRODUCTION

The prevention of maternal to child transmission (PMTCT) of HIV has progressed from recommending caesarean section, formula feeding, and treatment with Zidovudine monotherapy<sup>1</sup>, to additionally, implementing the use of highly active antiretroviral therapy (HAART), which led to transmission rates as low as 1-2%<sup>2</sup>. In spite of this impressive result, the use of HAART during pregnancy has been related to adverse outcomes such as low birth weight, prematurity<sup>3</sup>, and an increased rate of gestational diabetes was observed comparing data before and after the introduction of HAART<sup>4</sup>.

Hypertensive disorders during pregnancy are a major cause of morbidity and mortality for both mother and child worldwide, and are the number one cause of maternal mortality in some regions in Brazil<sup>5,6</sup>.

However, prevalence data on preeclampsia and eclampsia (PE/E) among HIV-infected women are discrepant. In PACTG 185, where pregnant women were treated predominantly with ZDV during pregnancy, PE was reported to be as low as 2% among 497 women studied<sup>7</sup>. In the USA, the rate of PE has remained stable, regardless of the use of HAART during pregnancy<sup>4</sup>. Other studies have suggested that HIV-infected pregnant women treated with HAART have an increased risk for PE and fetal death<sup>8,9</sup>. Wimalasundera *et al* (2002) showed that the rate of PE in HIV-infected women was not different from that in uninfected pregnant women (4.2% vs. 5.6%, respectively), but within the HIV-infected women, the rate of PE in those treated with mono or dual therapy was 0-1% compared to 11% among those treated with triple therapy<sup>8</sup>. A probable role of immune reconstitution was implicated in the pathogenesis of PE in women treated with HAART. Suy *et al* (2006)<sup>9</sup> found higher rates of PE among HIV-infected women (11/100 deliveries) when compared to HIV-uninfected women (2.9/100 deliveries). They also demonstrated that the rate of PE among HIV-infected women increased from 0% to 11% in two periods studied, and that this increment was related to use of HAART, especially in those treated with HAART prior to pregnancy.

In Latin America, the prevalence of PE among HIV-infected women has been rarely studied. In one report from Brazil, the rate of PE was 0.8% in HIV-infected women (1/123) and 10% among 1708 HIV-negative women, where 78% of the first group was treated with HAART<sup>10</sup>.

As more HIV infected women are being put on HAART earlier in pregnancy it is important to understand the impact of HAART on hypertensive disorders during pregnancy. Our objectives were to determine the prevalence of and risk factors for hypertensive disorders and PE/E among HIV-infected pregnant women in Latin America and to evaluate the impact of HAART in the development of these complications.

## METHODS

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) and the Perinatal Longitudinal Study in Latin American Countries (LILAC) are two consecutive observational, prospective cohorts of HIV-infected pregnant women enrolled from 2002-2009. The main objectives of the NISDI Perinatal and LILAC Studies are to describe utilization of interventions for PMTCT of HIV, rates of mother-to-child infection, and to characterize adverse events associated with receipt of and exposure to ARVs<sup>11</sup>. The protocols were approved by the ethics committee review board in each clinical site enrolling subjects, the sponsoring institution (NICHD), and the data management and statistical center (Westat). Clinical, immunologic, and virologic characteristics of the women were assessed at enrollment, during pregnancy, at the time of hospital discharge after delivery, and at the 6–12 week postpartum visit. Maternal history of substance use during the index pregnancy was ascertained through patient interview at enrollment. Maternal clinical disease staging<sup>12</sup> was performed at each study visit. Gestational age-adjusted maternal BMI (gBMI), an approach to correcting for the weight gain expected to occur during pregnancy, was calculated using a program produced by the Argentinean Ministry of Health<sup>13</sup>. Women who enrolled with a gBMI > 25 were considered overweight.

Our study population was restricted to women enrolled in the NISDI Perinatal or LILAC protocols for the first time (second pregnancies on-study excluded), prior to labor and delivery (L&D), and whose infant were born at ≥ 20 weeks gestation. Women with pre-existing nephropathy were also excluded. HAART was defined as the use of at least three drugs in two different classes. Other non-HAART regimens (mono, dual, triple NRTI) therapy was categorized as “other ARV”.

The primary outcome measure of interest was the diagnosis of any hypertensive disorder (HD) after 20 weeks of gestation. This included all cases of pregnancy induced hypertension (PIH) [defined as blood pressure persistently ≥ 140/90 mmHg without proteinuria and onset after first 20 weeks gestation with no hypertension prior to pregnancy], PE [defined as blood pressure persistently ≥ 140/90 with: proteinuria of ≥ 1+ by dipstick, on two occasions, and/or ≥ 300 mg protein in 24 hour urine collection], and eclampsia [defined as seizure during pregnancy in the absence of any underlying known etiology or without any known reason for seizure and no suspicion of epilepsy or trauma]. Previous history of hypertension (not associated with pregnancy), PIH, preeclampsia or eclampsia was obtained at enrollment. Gestational age at enrollment was estimated based on the date of the last menstrual period or any earlier ultrasound dating, if available. Analyses were also done in the subset of participants who experienced PE/E.

## Statistical analysis

Descriptive statistics (frequencies) were used to describe the study population. Bivariate analyses (Fisher's exact test) examined the association of hypertensive disorders (HD) and the subset of PE/E with variables assessed at the time of eligibility for the study.

All co-variates with alpha level of 0.2 or lower in bivariate analyses were considered candidates for inclusion in the adjusted models. Logistic regression modeling used forward stepwise, backward elimination. All analyses were conducted using the SAS statistical software, version 9.0 (SAS Institute Inc. Cary, NC).

## RESULTS

Of 1548 women experiencing their first pregnancy on study, thirty-five were excluded; three were lost to follow-up, twenty-one enrolled at the time of L&D, six delivered at <20 weeks gestation, and five for pre-existing nephropathy, leaving 1513 women in the final study population (Figure 1).

The majority of women were from Brazil (62.5%). Maternal age ranged from 20 to 34 years old for 77.7% of the participants, 72.9% were married or living with a partner, 56.2% enrolled in the cohort during the third trimester of pregnancy and 86.1% reported at least one previous pregnancy prior to study enrollment (Table 1).

There were 73 cases of HD: 38 (52.1%) diagnosed with PIH and 35 (47.9%) diagnosed with PE/E for a cumulative prevalence for HD of 4.8% (95% CI: 3.8% - 6.0%) and 2.3% (95% CI: 1.7%-3.2%) for PE/E. Three women developed eclampsia, but none died. Among those diagnosed with PIH, 81.6% (31/38) had documented normal blood pressures at the time of enrollment prior to their diagnosis of hypertension.

On bivariate analyses, HD was significantly more frequent among women who were gainfully employed, married or living with a partner, gBMI  $\geq 25$  at enrollment, and with a higher hemoglobin value ( $\geq 11$  g/dL) at enrollment and following delivery. While use of any antiretroviral therapy (ARV) at conception was not significantly associated with HD, being on HAART or any PI regimen at conception was associated with HD ( $p=.04$ ) (Table 2).

On bivariate analyses, the association of PE/E with risk factors was similar to HD; hemoglobin at delivery ( $\geq 11$  g/dL), gBMI  $\geq 25$  kg/m<sup>2</sup> at enrollment and a previous history of PE/E were all statistically significant factors for PE/E. We did not observe an association with employment or maternal age (Table 2). Being on any HAART or any PI at conception or during the 1<sup>st</sup> or 2<sup>nd</sup> trimester were all associated with increased risk of PE/E.

Logistic regression models were run using all variables with p values  $\leq 0.2$  which included: maternal age, employment, marital status, previous history of PE/E, gBMI, trimester of enrollment, ARV at conception, type of ART at conception, ART during 1<sup>st</sup> and 2<sup>nd</sup> trimesters (different models for each time period of ART use), and hemoglobin at delivery. Additional models were run forcing CD4 and viral load (to adjust for disease severity) to remain in the model. In the final logistic regression model, HD was significantly associated with women enrolled with a gestational age adjusted (gBMI)  $\geq 25$  kg/m<sup>2</sup> (OR= 3.1; 95% CI:

1.9-5.0), maternal age  $\geq 35$  years (OR=1.8; 95% CI: 1.1-3.2), and Hg  $\geq 11$  g/dl at delivery (OR=2.1; 95% CI: 1.2-3.6). Similarly, PE/E was significantly increased among women enrolled with a gBMI  $\geq 25$  kg/m<sup>2</sup> (OR=3.0; 95% CI: 1.5-6.0) and Hg  $\geq 11$  g/dl at delivery (OR=2.8; 95% CI: 1.2-6.5). A history of PE/E in previous pregnancies was an independent risk factor increasing the risk of PE/E 6.7 times (95% CI: 1.8-25.5) compared to those without a history of PE/E (Table 3). Being on HAART at conception was associated with a PE/E in adjusted models (OR=2.3; 95% CI: 1.1-4.9). Forcing CD4 and viral load (at enrollment or at the time of delivery) into the model had no impact on the final models.

## DISCUSSION

In this study of HIV-infected pregnant women, we found the prevalence of HD and PE/E was 4.8% and 2.3%, respectively. These percentages are similar to the prevalence of HD and PE/E found among pregnant women described in some Latin America countries<sup>14,15</sup>. Data from the World Health Organization (WHO) Antenatal Care Trial, which included more than 39,000 pregnant women (with unknown HIV status) from Argentina, Cuba, Saudi Arabia and Thailand described PIH in 7.0% and PE/E in 2.2%<sup>14</sup>. In Brazil, a study with almost 5000 pregnant women with unknown HIV status, enrolled between 1991-1995, showed that 3.5% develop PIH and 2.3% develop PE/E<sup>15</sup>.

In this cohort, some risk factors for PE and HD were the same described for HIV uninfected population such as older maternal age<sup>16,17</sup>, a previous history of PE/E<sup>18,19</sup>, and being overweight<sup>20,21</sup>. Several abnormalities associated with the development of PE such as lower plasma volume, activation of complement system, hyperferritinemia, insulin resistance and metabolic syndrome are also more prevalent among overweight or obese uninfected patients<sup>22-26</sup>. Furthermore, overweight has been associated with oxidative stress consisting of an imbalance of lipid metabolism and an inflammatory state that is also associated with PE<sup>27</sup>. As almost 50% of the patients in this study were enrolled during the 3<sup>rd</sup> trimester of pregnancy we cannot disregard the fact that the increased weight can also be related to fluid retention. In general, reduction of weight in an overweight or obese women prior to conception has been shown to reduce PE and improve other health outcomes<sup>28,29</sup> and should be also emphasized to HIV-infected women.

Higher hemoglobin among patients with PE/E and HD is expected and explained by the hemoconcentration caused by failure to increase the plasma volume during pregnancy, which is characteristic of PE. Usually, pregnant women start the expansion of plasma volume around the 7<sup>th</sup> week of gestation and this reaches a plateau around 32 weeks<sup>30</sup>. During pregnancy, uninfected women increase their plasma volume by almost 45% but this increase is 50% lower for those with PE/E<sup>31,32</sup>. Failure to increase the plasma volume during pregnancy leads to hemoconcentration, a higher vascular resistance with a consequently decrease in utero placental flow and higher odds for perinatal complications<sup>33</sup>.

The role of HIV infection in the development of preeclampsia is controversial. Wimalasundera et al. found a lower rate of PE among untreated HIV-infected women<sup>8</sup> when compared to uninfected women or HIV-infected on treatment. More recently, Kalumba et al<sup>34</sup> described a lower rate of HIV-infection among women with pre-eclampsia

when compared with women without pre-eclampsia. Several studies show no difference in the rates of PE between HIV-uninfected and HIV-infected women treated with HAART<sup>35,36</sup> or even a lower rate of PE among HIV-infected treated when compared to uninfected women<sup>10</sup>.

We observed that the use of HAART at conception was a risk factor for PE/E. This is in agreement with two other studies which showed that the use of HAART prior to pregnancy increase the odds for hypertension and PE<sup>9,37</sup>. Lack of stratification with the use of HAART in relation to pregnancy could explain the discrepancy among studies. Some authors suggest that immune restoration, secondary to the use of HAART could be involved in the development of PE<sup>8</sup>. It has been shown that low levels of retinol are correlated with PE and it was suggested that a mechanisms of HAART-induced PE could be a reduction of serum retinol concentrations due to hepatotoxicity<sup>38,39</sup>. HIV-infected pregnant women using HAART present a shift towards a Th1 cytokine production while, in a healthy pregnancy, a Th2 response is predominantly observed<sup>40-41</sup>. Also a Th1 immune response is observed in PE<sup>42</sup>. It is possible that HIV-infected pregnant women on HAART, especially those with long exposure to therapy, would have a blunted shift of Th2 cytokines increasing the predisposition to eclampsia.

The current pathophysiological mechanism of preeclampsia involves poor placental perfusion and the excessive release of inflammatory factors that damage the mother's vascular endothelial cells, resulting in systemic hypertension and endothelial dysfunction<sup>43</sup>. In addition, regarding HIV-infected patients, some ART has been associated with endothelial dysfunction and CVD<sup>44</sup>. Nevertheless, Torriani et al (2008)<sup>45</sup>, comparing three different randomized ARV regimens among HIV-infected naïve individuals, in order to evaluate the effect of these ARV on endothelial function, noticed rapid improvement of endothelial function after ARV administration. Savvidou et al (2011) evaluated the uteroplacental circulation by Doppler ultrasound of HIV-infected and non-infected pregnant women in the first trimester of gestation – a probable early biomarker to predict PE –, with the aim to assess the degree of placental invasion. They found normal placental perfusion among HIV-infected women, with uncomplicated pregnancies, receiving and not receiving ARV regimen. Although, these authors state that the majority of women presented CD4 cell count > 250cells/mm<sup>3</sup> and, therefore, they could not exclude problems of uteroplacental perfusion in women with a compromised immune system<sup>46</sup>.

Among the strengths of this study are the large size of the cohort, enrollment of study participants across several countries in Latin America and the Caribbean and the prospective collection of data with a very low rate of loss to follow-up. One of the limitations of this study is that we did not have information regarding adherence to ART and, also, we did not collect data on the duration of ART prior to the current pregnancy.

Strategies to prevent HD among HIV-infected women should include preconception counseling to high risk women who are planning a pregnancy. It would also be interesting to compare risk of HD between women on treatment longer before pregnancy with normalization of CD4+T-cell counts with those who started HAART during pregnancy but have already a lower CD4+ T-cell count.

The findings of this study showing a significant association of BMI  $\geq 25$ , a history of PE/E in previous pregnancies and hemoconcentration with PE are consistent with the literature regarding risk factors for PE and HD in uninfected pregnant women. Being on HAART at conception was associated with a 2.3 times risk of developing PE/E during pregnancy.

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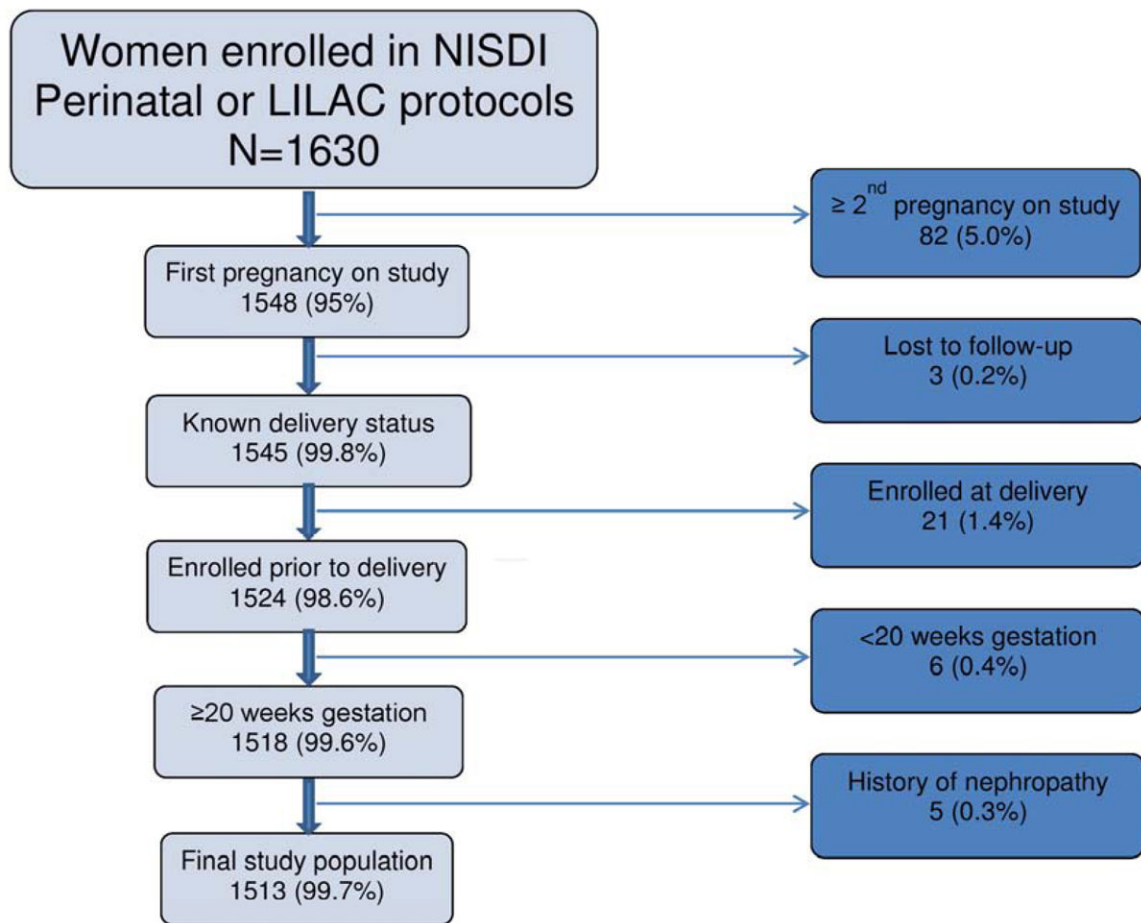
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**Figure 1.**  
Derivation of Study Population

**Table 1**

## Demographic and Clinical Characteristics of the Study Population

Variable	Stratification	Total N (%) <sup>a</sup>	HD <sup>b</sup> by row stratification N (%)	P <sup>c</sup>
Country of residence	Argentina	377 (24.9)	14 (3.7)	0.04
	Brazil	945 (62.5)	49 (5.2)	
	Peru	69 (4.5)	2 (2.9)	
	Mexico	42 (2.8)	0	
	Jamaica	37 (2.4)	2 (5.4)	
	Bahamas	43 (2.8)	6 (14.0)	
Maternal Age at enrollment (yrs)	<20	99 (6.6)	2 (2.0)	0.04
	20-34	1176 (77.7)	52 (4.4)	
	35	238 (15.7)	19 (8.0)	
Race	White	703 (57.8)	27 (3.8)	0.21
	Black	316 (26.0)	20 (6.3)	
	Mestizo/other	196 (13.7)	13 (6.6)	
	Missing	298	13	
Maternal education	0-6	473 (31.1)	24 (5.1)	0.49
	7-12	958 (63.3)	43 (4.5)	
	>12	82 (5.4)	6 (7.3)	
Gainfully employed	Yes	399 (26.4)	27 (6.8)	0.04
	No	1114 (73.6)	46 (4.1)	
Marital status	Married / partner	1103 (72.9)	61 (5.5)	0.05
	Single/prev married	410 (27.1)	12 (2.9)	
Previous hx of PE / E <sup>d</sup>	Yes	20 (1.3)	3 (15.0)	0.07
	No	1493 (98.7)	70 (4.7)	
Gravida	1	211 (13.9)	12 (5.7)	0.32
	>1	1302 (86.1)	61 (4.7)	
Multiple gestation	Yes	23 (1.5)	2 (8.7)	0.30
	No	1478 (98.5)	71 (4.8)	
	Missing	12	0	
Tobacco use during pregnancy	Yes	372 (24.9)	13 (3.5)	0.20
	No	1123 (75.1)	58 (5.2)	
	Missing	18	2	
Alcohol use during pregnancy	Yes	104 (9.1)	5 (4.8)	0.80
	No	1041 (90.9)	58 (5.2)	
	Missing	368	10	
gBMI <sup>e</sup> at enrollment	<20	245 (16.4)	4 (1.6)	<0.01

Variable	Stratification	Total N (%) <sup>a</sup>	HD <sup>b</sup> by row stratification N (%)	P <sup>c</sup>
	20-24	761 (51.0)	25 (3.3)	
	25	487 (32.6)	43 (8.8)	
	Missing	20	1	
Trimester at enrollment	1 <sup>st</sup> (1-12 wk)	71 (4.7)	7 (9.9)	0.10
	2 <sup>nd</sup> (13-26 wk)	591 (39.1)	30 (5.1)	
	3 <sup>rd</sup> (27+ wk)	851 (56.2)	36 (4.2)	
Maternal Diabetes	Yes	35 (2.3)	0	0.41
	No	1478 (97.7)	73 (4.8)	
Creatinine at enrollment	1	1466 (99.0)	69 (4.7)	0.14
	>1	14 (1.0)	2 (14.3)	
	Missing	33	2	
Hemoglobin at enrollment	< 11	708 (47.7)	26 (3.7)	0.04
	11	777 (52.3)	47 (6.0)	
	Missing	28	0	
Hemoglobin at delivery	< 11	676 (45.4)	21 (3.1)	<0.01
	11	814 (54.6)	52 (6.4)	
	Missing	23	0	
CD4 at enrollment	<200	210 (14.1)	13 (6.2)	0.64
	200-499	762 (51.0)	36 (4.7)	
	500	520 (34.9)	24 (4.6)	
	Missing	21	0	
CD4 prior to delivery	<200	180 (12.0)	12 (6.7)	0.21
	200-499	693 (46.3)	27 (3.9)	
	500	625 (41.7)	34 (5.4)	
	Missing	15	0	
VL <sup>f</sup> at enrollment	<1000	951 (63.7)	48 (5.0)	0.93
	1,000 to 10,000	277 (18.6)	13 (4.7)	
	10,000	265 (17.7)	12 (4.5)	
	Missing	20	0	
VL <sup>f</sup> at delivery	<1000	1192 (79.4)	62 (5.2)	0.34
	1,000 to 10,000	184 (12.3)	5 (2.7)	
	10,000	126 (8.3)	6 (4.8)	
	Missing	11	0	
ARV <sup>g</sup> at conception	Yes	310 (20.5)	21 (6.8)	0.08
	No	1199 (79.5)	52 (4.3)	
	Missing	4		

Variable	Stratification	Total N (%) <sup>a</sup>	HD <sup>b</sup> by row stratification N (%)	P <sup>c</sup>
Type ARV at conception	Any PI/ HAART	294 (19.5)	21 (7.1)	0.04
	Some ARV <sup>d</sup> or None	1251 (80.5)	52 (4.3)	
	Missing	4	0	
ARV during 1 <sup>st</sup> trimester	Any PI/ HAART	362 (23.9)	24 (6.6)	0.07
	Some ARV <sup>e</sup> or None	1151 (76.1)	49 (4.2)	
ARV during 2 <sup>nd</sup> trimester	Any PI/HAART	1072 (70.8)	57 (5.3)	0.18
	Some ARV <sup>f</sup> or None	441 (29.2)	16 (3.6)	
ARV during 3 <sup>rd</sup> trimester	Any PI/HAART	1367 (90.4)	69 (5.0)	0.21
	Some ARV or None <sup>g</sup>	146 (9.6)	4 (2.7)	
Delivery outcome	Stillbirth	30 (2.0)	2 (6.7)	0.65
	Live birth	1483 (98.0)	71 (4.8)	

<sup>a</sup>Subjects missing values are not included in percentages.

<sup>b</sup>Hypertensive disorders (HD),

<sup>c</sup>p value by Fisher's exact testing.

<sup>d</sup>pre-eclampsia/eclampsia (PE/E),

<sup>e</sup>gestational age adjusted body mass index (gBMI),

<sup>f</sup>Viral load (VL),

<sup>g</sup>antiretroviral (ARV)

<sup>h</sup>16 subjects on other ARV regimen

<sup>i</sup>29 subjects on other ARV regimen

<sup>j</sup>121 subjects on other ARV regimen

<sup>k</sup>15 subjects not on any ARV

**Table 2**  
Bivariate Analyses of all Hypertensive disorders (HD) and Preeclampsia and Eclampsia (PE/E) by covariates of interest

Covariates	Strata	HD N=73 (%)	No HD N=1440 (%)	P <sup>1</sup>	PE/E N=35 (%)	No PE/E N=1478 (%)	P <sup>1</sup>
Maternal age	<20	2 (2.0)	97 (98.0)	0.04	1 (1.0)	98 (99.0)	0.09
	20-34	52 (4.4)	1124 (95.6)		24 (2.0)	1152 (98.0)	
	35	19 (8.0)	219 (92.0)		10 (4.2)	228 (95.8)	
Gainfully employed	Yes	27 (6.8)	372 (93.2)	0.04	13 (3.2)	386 (96.7)	0.17
	No	46 (4.1)	1068 (95.9)		22 (2.0)	1092 (98.0)	
Marital status <sup>2</sup>	Married	61 (5.5)	1042 (94.5)	0.05	27 (2.5)	1076 (97.5)	0.57
	Single	12 (2.9)	398 (97.1)		8 (2.0)	402 (98.0)	
Previous history of PE/E	Yes	3 (15.0)	17 (85.0)	0.07	3 (15.0)	17 (85.0)	0.01
	No	70 (4.7)	1423 (95.3)		32 (2.1)	1461 (97.9)	
Gestational age adjusted BMI at enrollment (gBMD)	<20	4 (1.6)	241 (98.4)	<0.01	2 (0.8)	243 (99.2)	<0.01
	20-24	25 (3.3)	736 (96.7)		12 (1.6)	749 (98.4)	
	25	43 (8.8)	444 (91.2)		20 (4.1)	467 (95.9)	
Trimester <sup>3</sup> at enrollment	1st	7 (9.9)	64 (90.1)	0.10	4 (5.6)	67 (94.4)	0.12
	2nd	30 (5.1)	561 (94.9)		15 (2.5)	576 (97.5)	
	3rd	36 (4.2)	815 (95.8)		16 (1.9)	835 (98.1)	
Creatinine at Enrollment	1	69 (4.7)	1397 (95.3)	0.14	33 (2.2)	1433 (97.8)	0.28
	>1	2 (14.3)	12 (85.7)		1 (7.1)	13 (92.9)	
Hemoglobin at enrollment (g/dL)	<11	26 (3.7)	682 (96.3)	0.04	10 (1.4)	698 (98.6)	0.03
	11	47 (6.1)	730 (93.9)		25 (3.2)	752 (96.8)	
Hemoglobin after delivery (g/dL)	<11	21 (3.1)	655 (96.9)	<0.01	8 (1.2)	668 (98.8)	0.01
	11	52 (6.4)	762 (93.6)		27 (3.3)	787 (96.7)	
Type of ART <sup>4</sup> at conception	HAART	21 (7.1)	273 (92.9)	0.04	13 (4.4)	281 (95.6)	<0.01
	No HAART	52 (4.3)	1167 (95.7)		22 (1.8)	1197 (98.2)	

Covariates	Strata	HD N=73 (%)	No HD N=1440 (%)	P <sup>1</sup>	PE/E N=35 (%)	No PE/E N=1478 (%)	P <sup>1</sup>
ART: 1 <sup>st</sup> trimester	HAART	24 (6.6)	338 (93.4)	0.07	13 (3.6)	349 (96.4)	0.07
	No HAART	49 (4.2)	1102 (95.7)		22 (1.9)	1129 (98.1)	

<sup>1</sup> P value obtained using Fisher's exact testing.

<sup>2</sup> Marital status divided into Married (includes living with partner) and Single (includes divorced and widowed).

<sup>3</sup> Trimester of pregnancy defined as follows: 1<sup>st</sup> (1-12 weeks gestation), 2<sup>nd</sup> (13-26 weeks gestation), 3<sup>rd</sup> (27+ weeks gestation).

<sup>4</sup> Type of antiretroviral therapy (ART) divided into: HAART (including use of any PD) and no HAART (includes any mono, dual, triple therapy and no therapy)

All covariates with p < .2 considered in logistic regression modeling



**Table 3**

Final Logistic Regression Model\*

Co-variates	Final model-HD OR (95%CI)	Final Model-PE/E OR (95%CI)
<u>gBMI:</u> 25 kg/m <sup>2</sup> vs. < 25 kg/m <sup>2</sup>	3.1 (1.9-5.0)	3.0 (1.5-6.0)
<u>Hg at L&amp;D:</u> 11 g/dl vs. < 11 g/dl	2.1 (1.2-3.6)	2.8 (1.2-6.5)
<u>Maternal age:</u> 35 yr. vs. < 35 yr.	1.8 (1.1-3.2)	NA
<u>ARV type at conception:</u> <u>HAART vs non HAART</u>	NA	2.3 (1.1-4.9)
<u>Previous history of PE/E:</u> Yes vs. No	NA	6.7 (1.8-25.5)

HD – Hypertensive Disorders; PE/E – Preeclampsia/Eclampsia; NA – Not applicable

\* Forcing CD4 and viral load at enrollment or at L&amp;D had no impact on the final models