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Hypertension, preeclampsia and eclampsia among HIV-infected pregnant women from Latin America and Caribbean countries☆

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Summary *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

☆ 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.

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Preeclampsia;
Eclampsia

women from Latin America and the Caribbean enrolled between 2002 and 2009. Only pregnant women enrolled for the first time in the study and delivered at ≥20 weeks gestation were analyzed.

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) ≥25 kg/m^2 (OR = 3.1; 95% CI: 1.9—5.0), hemoglobin (Hg) ≥11 g/dL at delivery (OR = 2.1; 95% CI: 1.2—3.6) and age ≥35 years (OR = 1.8; 95% CI: 1.1—3.2). PE/E was increased among women with a gBMI ≥25 kg/m^2 (OR = 3.0; 95% CI: 1.5—6.0) and Hg ≥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 ≥25 kg/m^2, Hg at delivery ≥11 g/dL and in use of HAART before conception are at an increased risk of developing PE/E during pregnancy.

Introduction

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

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.[5,6]

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.[7] In the USA, the rate of PE has remained stable, regardless of the use of HAART during pregnancy.[4] Other studies have suggested that HIV-infected pregnant women treated with HAART have an increased risk for PE and fetal death.[8,9] 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.[8] A probable role of immune reconstitution was implicated in the pathogenesis of PE in women treated with HAART. Suy et al. (2006)[9] 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 were treated with HAART.[10]

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 to 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.[11]

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[12] 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.[13] 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 h 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 covariates 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 (Fig. 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% (31/3) 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 ≥25 at enrollment, and with a higher hemoglobin value (≥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).

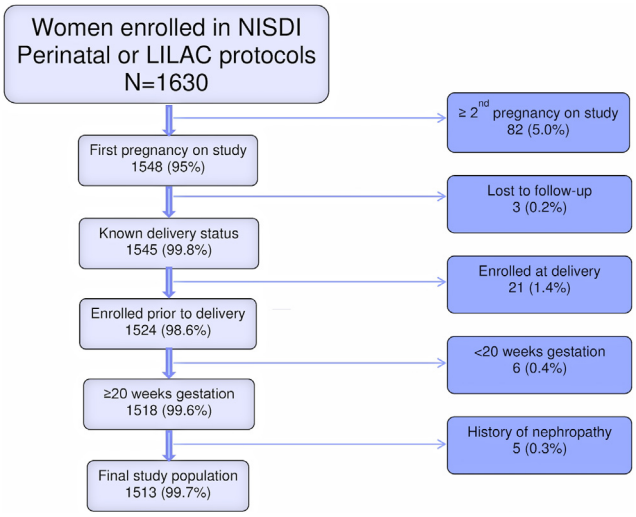

Figure 1 Derivation of study population.

On bivariate analyses, the association of PE/E with risk factors was similar to HD; hemoglobin at delivery (≥11 g/dL), gBMI ≥25 kg/m^2 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 1st or 2nd trimester were all associated with increased risk of PE/E.

Logistic regression models were run using all variables with p values ≤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 1st and 2nd 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) ≥25 kg/m^2 (OR = 3.1; 95% CI: 1.9–5.0), maternal age ≥35 years (OR = 1.8; 95% CI: 1.1–3.2), and Hg ≥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 ≥25 kg/m^2 (OR = 3.0; 95% CI: 1.5–6.0) and Hg ≥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.

Table 1 Demographic and clinical characteristics of the study population.

Variable	Stratification	Total *N* (%)[a]	HD[b] by row stratification *N* (%)	*p*[c]
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[d]	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[e] at enrollment	<20	245 (16.4)	4 (1.6)	<0.01
	20–24	761 (51.0)	25 (3.3)	
	≥25	487 (32.6)	43 (8.8)	
	Missing	20	1	
Trimester at enrollment	1st (1–12 wk)	71 (4.7)	7 (9.9)	0.10
	2nd (13–26 wk)	591 (39.1)	30 (5.1)	
	3rd (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	

(*continued on next page*)

Table 1 (*continued*)

Variable	Stratification	Total *N* (%)[a]	HD[b] by row stratification *N* (%)	*p*[c]
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[f] at enrollment	<1000	951 (63.7)	48 (5.0)	0.93
	1000–10,000	277 (18.6)	13 (4.7)	
	≥10,000	265 (17.7)	12 (4.5)	
	Missing	20	0	
VL[f] at delivery	<1000	1192 (79.4)	62 (5.2)	0.34
	1000–10,000	184 (12.3)	5 (2.7)	
	≥10,000	126 (8.3)	6 (4.8)	
	Missing	11	0	
ARV[g] at conception	Yes	310 (20.5)	21 (6.8)	0.08
	No	1199 (79.5)	52 (4.3)	
	Missing	4		
Type ARV at conception	Any PI/HAART	294 (19.5)	21 (7.1)	0.04
	Some ARV[h] or None	1251 (80.5)	52 (4.3)	
	Missing	4	0	
ARV during 1st trimester	Any PI/HAART	362 (23.9)	24 (6.6)	0.07
	Some ARV[i] or None	1151 (76.1)	49 (4.2)	
ARV during 2nd trimester	Any PI/HAART	1072 (70.8)	57 (5.3)	0.18
	Some ARV[j] or None	441 (29.2)	16 (3.6)	
ARV during 3rd trimester	Any PI/HAART	1367 (90.4)	69 (5.0)	0.21
	Some ARV or None[k]	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)	

[a] Subjects missing values are not included in percentages.
[b] Hypertensive disorders (HD).
[c] *p* Value by Fisher's exact testing.
[d] Pre-eclampsia/eclampsia (PE/E).
[e] Gestational age-adjusted body mass index (gBMI).
[f] Viral load (VL).
[g] Antiretroviral (ARV).
[h] 16 subjects on other ARV regimen.
[i] 29 subjects on other ARV regimen.
[j] 121 subjects on other ARV regimen.
[k] 15 subjects not on any ARV.

These percentages are similar to the prevalence of HD and PE/E found among pregnant women described in some Latin America countries.[14,15] 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%.[14] In Brazil, a study with almost 5000 pregnant women with unknown HIV status, enrolled between 1991 and 1995, showed that 3.5% develop PIH and 2.3% develop PE/E.[15]

In this cohort, some risk factors for PE and HD were the same described for HIV-uninfected population such as older maternal age,[16,17] a previous history of PE/E,[18,19] and being overweight.[20,21] 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.[22–26] Futhermore, overweight has been associated with oxidative stress consisting of an imbalance of lipid metabolism and an inflammatory state that is also associated with PE.[27] As almost 50% of the patients in this study were enrolled during the 3rd 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[28,29] 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 7th week of gestation and this reaches a plateau around 32 weeks.[30] During pregnancy, uninfected women increase their plasma volume by almost 45% but this increase is 50% lower for those with PE/E.[31,32] Failure to increase the plasma volume during pregnancy leads to hemoconcentration, a higher vascular resistance with a consequently decrease in uteroplacental flow and higher odds for perinatal complications.[33]

The role of HIV-infection in the development of pre-eclampsia is controversial. Wimalasundera et al. found a

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[a]	PE/E $N = 35$ (%)	No PE/E $N = 1478$ (%)	p[a]
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[b]	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 (gBMI)	<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[c] 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[d] 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)	
ART: 1st 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)	

All covariates with $p < .2$ considered in logistic regression modeling.
[a] p Value obtained using Fisher's exact testing.
[b] Marital status divided into Married (includes living with partner) and Single (includes divorced and widowed).
[c] Trimester of pregnancy defined as follows: 1st (1–12 weeks gestation), 2nd (13–26 weeks gestation), 3rd (27+ weeks gestation).
[d] Type of antiretroviral therapy (ART) divided into: HAART (including use of any PI) and no HAART (includes any mono, dual, triple therapy and no therapy).

lower rate of PE among untreated HIV-infected women[8] when compared to uninfected women or HIV-infected on treatment. More recently, Kalumba et al.[34] described a lower rate of HIV-infection among women with preeclampsia when compared with women without preeclampsia. Several studies show no difference in the rates of PE between HIV-uninfected and HIV-infected women treated with HAART[35,36] or even a lower rate of PE among HIV-infected treated when compared to uninfected women.[10]

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.[9,37] 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.[8] It has been shown that low levels of retinol are correlated with PE and it was suggested that a mechanism of HAART-induced PE could be a reduction of serum retinol concentrations due to hepatotoxicity.[38,39] HIV-infected pregnant women using HAART present a shift towards a

Table 3 Final logistic regression model.[a]

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

HD – hypertensive disorders; PE/E – preeclampsia/eclampsia; NA – not applicable.
[a] Forcing CD4 and viral load at enrollment or at L&D had no impact on the final models.

Th1 cytokine production while, in a healthy pregnancy, a Th2 response is predominantly observed.[40,41] Also a Th1 immune response is observed in PE.[42] 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 pre-eclampsia 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.[43] In addition, regarding HIV-infected patients, some ART has been associated with endothelial dysfunction and CVD.[44] Nevertheless, Torriani et al. (2008),[45] 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 >250 cells/mm^3 and, therefore, they could not exclude problems of uteroplacental perfusion in women with a compromised immune system.[46]

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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NICHD International Site Development Initiative: Perinatal/LILAC Protocol

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References

1. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal—infant transmission of human immunodeficiency virus type 1 with zidovudine

treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;**331**:1173—80.
2. Coovadia H. Antiretroviral agents — how best to protect infants from HIV and save their mothers from AIDS. *N Engl J Med* 2004; **351**:289—92.
3. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS* 2004;**18**:2337—9.
4. Kourtis AP, Bansil P, McPheeters M, Meikle SF, Posner SF, Jamieson DJ. Hospitalizations of pregnant HIV-infected women in the USA prior to and during the era of HAART, 1994—2003. *AIDS* 2006;**20**:1823—31.
5. Kale PL, Costa AJL. Maternal deaths in the city of Rio de Janeiro, Brazil, 2000—2003. *J Health Popul Nutr* 2009;**27**: 794—801.
6. Vega CEP, Kahhale S, Zugaib M. Maternal mortality due to arterial hypertension in São Paulo City (1995—1999). *Clinics* 2007; **62**:679—84.
7. Lambert JS, Watts DH, Mofenson L, Stiehm ER, Harris DR, Bethel J, et al. Risk factors for preterm birth, low birth weight, and intrauterine growth retardation in infants born to HIV-infected pregnant women receiving zidovudine. Pediatric AIDS Clinical Trials Group 185 Team. *AIDS* 2000;**14**:1389—99.
8. Wimalasundera RC, Larbalestier N, Smith JH, de Ruiter A, McG Thom SA, Hughes AD, et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. *Lancet* 2002;**360**:1152—4.
9. Suy A, Martínez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *AIDS* 2006;**20**:59—66.
10. Mattar R, Amed AM, Lindsey PC, Sass N, Daher S. Preeclampsia and HIV infection. *Eur J Obstet Gynecol Reprod Biol* 2004;**117**: 240—1.
11. Read JS, Cahn P, Losso M, Pinto J, Joao E, Duarte G, et al. Management of human immunodeficiency virus-infected pregnant women at Latin American and Caribbean sites. *Obstet Gynecol* 2007;**109**:1358—67.
12. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;**41**(RR-17):1—19.
13. Calvo EB, Durán P, Longo EN, Mazza C, Gilardon EOA. *Evaluación del estado nutricional de ninas, ninos y embarazadas mediante antropometría*. 1a ed. Ministerio de Salud de la Nación; 2009. pp. 87—92 http://www.msal.gov.ar/promin/publications/pdf/manual-nutricion-press.pdf.
14. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Pre-eclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol* 2006;**194**:921—31.
15. Gaio DS, Schmidt MI, Duncan BB, Nucci LB, Matos MC, Branchtein L. Hypertensive disorders in pregnancy: frequency and associated factors in a cohort of Brazilian women. *Hypertens Pregnancy* 2001;**20**:269—81.
16. Sultana R, Chen XK, Lee C, Hader J. Outcomes in multiple gestation pregnancies among Canadian women age 35 years and older. *Healthc Q* 2011;**14**:22—4.
17. Lamminpaa R, Vehvilainen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primaparous women in Finland 1997—2008. *BMC Pregnancy Childbirth* 2012;**12**:47.
18. Ganesh KS, Unnikrishnan B, Nagaraj K, Jayaram S. Determinants of pre-eclampsia: a case-control study in a District Hospital in South India. *Indian J Community Med* 2010;**35**:502—5.
19. Guzman-Juarez W, Avila-Esparza M, Contretas-Solia RE, Levario-Carrillo M. Factors associated with gestational hypertension and preeclampsia. *Ginecol Obstet Mex* 2012;**80**:461—6.
20. Dennedy MC, Avalos G, O'Reilly MW, O'Sullivan EP, Dunne FP. The impact of maternal obesity on gestational outcomes. *Ir Med J* 2012;**105**:23—5.
21. Mandal D, Manda S, Rakshi A, Dey RP, Biswas SC, Banerjee A. Maternal obesity and pregnancy outcome: a prospective analysis. *J Assoc Physicians India* 2011;**59**:486—9.
22. Aardenburg R, Spaanderman ME, Ekhart TH, van Eijndhoven HW, van der Heijden OW, Peeters LL. Low plasma volume following pregnancy complicated by pre-eclampsia predisposes for hypertensive disease in a next pregnancy. *BJOG* 2003;**110**:1001—6.
23. Lynch AM, Eckel RH, Murphy JR, Gibbs RS, West NA, Giclas PC, et al. Prepregnancy obesity and complement system activation in early pregnancy and the subsequent development of preeclampsia. *Am J Obstet Gynecol* 2012;**206**. 428.e1—428.e8.
24. Raman L, Pawashe AB, Yasodhara P. Hyperferritinemia in pregnancy induced hypertension and eclampsia. *J Postgrad Med* 1992;**38**:65—7.
25. Lu J, Zhao YY, Qiao J, Zhang HJ, Ge L, Wei Y. A follow-up study of women with a history of severe preeclampsia: relationship between metabolic syndrome and PE. *Chin Med J (Engl)* 2011;**124**:775—9.
26. Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, et al. Maternal insulin resistance and preeclampsia. *Am J Obstet Gynecol* 2011;**204**. 327.e1—327.e6.
27. Zavalza-Gomez AB. Obesity and oxidative stress: a direct link to preeclampsia? *Arch Gynecol Obstet* 2011;**283**:415—22.
28. Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012;**344**: e2088.
29. Mostello D, Jen Chang J, Allen J, Luehr L, Shyken J, Leet T. Recurrent preeclampsia: the effect of weight change between pregnancies. *Obstet Gynecol* 2012;**116**:667—72.
30. Bridges EJ, Womble S, Wallace M, McCartney J. Hemodynamic monitoring in high-risk obstetrics patients, I: expected hemodynamic changes in pregnancy. *Crit Care Nurse* 2003;**23**: 53—62.
31. Hytten F. Blood volume changes in normal pregnancy. *Clin Haematol* 1985;**14**:601—12.
32. Silver HM, Seebeck M, Carlson R. Comparison of total blood volume in normal, preeclamptic, and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. *Am J Obstet Gynecol* 1998; **179**:87—93.
33. Yang JM, Yang YC, Wang KG. Central and peripheral hemodynamics in severe preeclampsia. *Acta Obstet Gynecol Scand* 1996;**75**:120—6.
34. Kalumba VMS, Moodley J, Naidoo TD. Is the prevalence of preeclampsia affected by HIV/AIDS? A retrospective case—control study. *Cardiovasc J Afr* 2013;**24**:24—7.
35. Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2008;**198**:7—22.
36. Boyajian T, Shah PS, Murphy KE. Pregnant women receiving HAART: a matched cohort study. *J Obstet Gynaecol Can* 2012;**34**:136—41.
37. Parekh N, Ribaudo H, Souda S, Chen J, Mmalane M, Powis K, et al. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. *Int J Gynaecol Obstet* 2011;**115**:20—5.
38. Zhang C, Williams MA, Sanchez SE, King IB, Ware-Jauregui S, Larrabure G, et al. Plasma concentrations of carotenoids, retinol, and tocopherols in preeclamptic and normotensive pregnant women. *Am J Epidemiol* 2001;**153**:572—80.

39. Mawson AR. Effects of antiretroviral therapy on occurrence of pre-eclampsia. *Lancet* 2003;**361**:347—8.
40. Fiore S, Newell ML, Trabattoni D, Thorne C, Gray L, Savasi V, et al. Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women. *J Reprod Immunol* 2006;**70**:143—50.
41. Jonsson Y, Matthiesen L, Berg G, Emerudh J, Nieminen K, Ekerfelt C. Indications of an altered immune balance in pre-eclampsia: a decrease in in vitro secretion of IL-5 and IL-10 from blood mononuclear cells an in blood basophil counts compared with normal pregnancy. *J Reprod Immunol* 2005; **66**:69—84.
42. Laresgoiti-Servitje E, Gomez-Lopez N, Olson DM. An immunological insight into the origins of pre-eclampsia. *Hum Reprod Update* 2010;**16**:510—24.
43. Fei X, Hongxiang Z, Qi C, Daozhen C. Maternal plasma levels of endothelial dysfunction mediators including AM, CGRP, sICAM-1 and tHcy in pre-eclampsia. *Adv Clin Exp Med* 2012;**21**:573—9.
44. Gupta SK, Shen C, Moe SM, Kamendulis LM, Goldman M, Dubé MP. Worsening endothelial function with efavirenz compared to protease inhibitors: a 12-month prospective study. *PLoS One* 2012;**7**:e45716.
45. Savvidou MD, Samuel MI, Akolekar R, Poulton M, Nicolaides KH. First trimester maternal uterine artery Doppler examination in HIV-positive women. *HIV Med* 2011;**12**:632—6.
46. Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, et al. Endothelial function in HIV-infected antiretroviral naïve subjects before and after starting potent antiretroviral therapy: AIDS Clinical Trials Group Study 5152s. *J Am Coll Cardiol* 2008;**52**:569—76.