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Evaluating the association of antiretroviral therapy and immune status with hypertensive disorders of pregnancy among people with HIV

Lynn M. YEE, MD, MPH[1], **Denise L. JACOBSON, PhD MPH**[2], **Lisa B. HADDAD, MD, MPH**[3], **Jennifer JAO, MD, MPH**[4], **Kathleen M. POWIS, MD, MPH, MBA**[5],[6], **Deborah KACANEK, ScD**[2], **Rebecca ZASH, MD**[7], **Alexandria DiPERNA**[8], **Ellen G. CHADWICK, MD**[4],

Pediatric HIV/AIDS Cohort Study

[1]Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL

[2]Center for Biostatistics in AIDS Research; Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Center for Biomedical Research, Population Council, New York, NY

[4]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

[5]Departments of Internal Medicine and Pediatrics, Massachusetts General Hospital, Boston, MA

[6]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA

[7]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

[8]Frontier Science Foundation, Amherst, NY

Abstract

Objective: To examine the association of timing of ART initiation and ART class with risk of new-onset hypertensive disorders of pregnancy (HDP) among people living with HIV (PLHIV).

Design: Observational study of participants in the multisite Surveillance Monitoring for ART Toxicities (SMARTT) study.

CORRESPONDING AUTHOR: Lynn M. Yee, MD, MPH, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, 250 E. Superior Street, #5-2145, Chicago, IL 60611, Phone: 312-472-4685, Fax: 312-472-0511, lynn.yee@northwestern.edu.

AUTHOR CONTRIBUTIONS

LY, EGC, and DJ conceptualized the study, drafted the manuscript, and performed project administration/supervision. EGC contributed to funding acquisition and supervision. DJ performed data analysis. LH, JJ, KP, DK, RZ, and AP contributed to conceptualization and writing (reviewing and editing).

*See Appendix for a list of the other members of the PHACS Network.

DISCLOSURE: The authors report no conflict of interest.

PRESENTATION: This abstract was presented as a “Science Spotlight” oral presentation at the 2021 Conference on Retroviruses and Opportunistic Infections (March 2021, virtual).

Methods: Data were abstracted from medical records of pregnant PLHIV enrolled in SMARTT (1/30/15–3/25/19). New-onset HDP included gestational hypertension, preeclampsia/eclampsia, or HELLP syndrome. We examined the associations of clinical risk factors and three exposures of interest, each in a separate model, with risk of new-onset HDP. Log-binomial regression models were fit using generalized estimating equations to account for correlations within people. Exposures included: timing of ART initiation, antiretroviral class among those on therapy at conception, and antiretroviral class among those initiating treatment during pregnancy.

Results: Of 1038 pregnancies in this cohort, 973 were singletons with complete data on HDP, with ART use in 948. Overall, 9% had a new-onset HDP, 10% had chronic hypertension, and 81% had no hypertension. Diabetes (aRR 2.44, 95% CI 1.42–4.21) and first/second trimester CD4 count <200 cells/mm^3 (aRR 1.99, 95% CI 1.21–3.27) were associated with greater risk of new-onset HDP. Risk of new-onset HDP was similar by antiretroviral class, but those initiating ART after 20 weeks' gestation had greater risk (aRR 1.93, 95% CI 1.12–3.30) compared with those receiving ART at conception.

Conclusion: In this large, diverse cohort of pregnant PLHIV, worse early pregnancy immune status and later ART initiation were associated with increased risk of HDP while ART class was not.

Keywords

antiretroviral therapy; human immunodeficiency virus; hypertensive disorders of pregnancy; preeclampsia

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) complicate up to 10% of pregnancies worldwide and are among the most common causes of maternal and perinatal morbidity and mortality.[1–3] In the United States (US), there has been a 25% increase in incidence of HDP over the past two decades,[2,4] largely due to increases in maternal comorbid risk factors such as obesity and diabetes.[5–7] HDP occurs disproportionately among individuals from marginalized populations, groups who may concomitantly experience higher HIV prevalence.[2,6,7]

Despite the clinical significance of HDP, clear etiologies remain elusive. Literature has revealed some associations between immune dysregulation and HDP, including an autoimmune cascade and altered angiogenic factors.[12–13] Persons living with HIV (PLHIV) in the era prior to combination antiretroviral therapy (ART) appeared to be at lower risk for development of HDP, yet contemporary cohorts including PLHIV receiving combination ART suggest the risk is either similar to or higher than that of people without HIV, and higher than PLHIV who are not taking ART.[8–16] One potential explanation for this difference is that the process of immunologic reconstitution after initiation of ART may lead to immune and endothelial dysregulation that triggers HDP.[8,14,15] Other potential explanations include shifting epidemiology, such as increases in obesity. Therefore, the timing of ART initiation and the rapidity of immune recovery may play roles in HDP risk.

The relationship between HIV and HDP in the modern era of ART has not been fully characterized.[11,13,14] The use of ART during pregnancy represents the standard of care to improve health and reduce HIV transmission risk,[17] and more PLHIV conceive while receiving ART with better immune status. Yet it is unclear whether the etiology of the increase in HDP occurring in the setting of ART is due to direct drug effects versus a response to rapid immune reconstitution when ART is initiated during pregnancy, a factor that may be more pronounced with newer antiretroviral drug classes such as integrase strand transfer inhibitors (INSTIs), a class notable for rapid reduction of HIV viral load.[13] In addition, newer ART regimens, such as those containing dolutegravir, may be associated with greater weight gain outside of pregnancy,[18,19] a known risk factor for HDP.[2,20,21] Thus, the associations of features of contemporary ART use, including class and timing, with development of HDP have not been fully elucidated.[22]

Given the short- and long-term morbidity associated with HDP, it is critical to understand these patterns and characterize aspects of comorbid conditions or ART regimens that may exacerbate risk among pregnant PLHIV. We aimed to 1) describe the frequency of HDP and examine clinical risk factors for new-onset HDP among PLHIV, and 2) examine timing of ART initiation and ART class and new-onset HDP among PLHIV. We hypothesized that clinical factors (obesity and diabetes), poor HIV disease control, later initiation of ART, and initiation of INSTIs would be associated with risk of HDP.

METHODS

Study population

Data from the Surveillance Monitoring for ART Toxicities (SMARTT) study, a prospective cohort study of the Pediatric HIV/AIDS Cohort Study (PHACS), were used to evaluate HDP and ART use among pregnant PLHIV. SMARTT has enrolled pregnant and postpartum PLHIV at 22 US clinical sites (Appendix) since 2007. SMARTT is designed to study the health of children with perinatal exposure to HIV and antiretroviral drugs but who remain uninfected, as well as the health of their caregivers. The SMARTT Dynamic cohort enrolls mother-newborn pairs during pregnancy or within 72 hours of delivery and collects socio-behavioral, medical, and biological data at enrollment and annually.

Pregnant PLHIV who enrolled in SMARTT during pregnancy or delivery between 01/30/15 and 03/25/19 were eligible for inclusion in this analysis. This time frame was selected as it represented a period of enhanced maternal health data collection within SMARTT. Individuals with multifetal gestations or no data available on maternal outcomes were excluded. For analyses of ART timing and class, individuals with no ART use during pregnancy were excluded. Individuals with multiple pregnancies meeting inclusion criteria during the study period were included.

Definitions of HDP

The outcomes of interest were diagnoses of HDP. We applied the American College of Obstetricians and Gynecologists (ACOG) classification system for HDP to reported clinician diagnoses, and thus categories included chronic hypertension (pre-pregnancy or

diagnosed before 20 weeks' gestation), superimposed preeclampsia on chronic hypertension, gestational hypertension, preeclampsia with or without severe features, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).[2] The majority of HDP classification assignments were made via clinician diagnoses. However, when diagnoses made by the clinician were unclear, start and stop dates of diagnoses and/or information on use of antihypertensive medications were used to clarify the HDP diagnosis. For example, if no chronic hypertension diagnosis was recorded but antihypertensive medications were administered before 20 weeks of gestation, the individual was considered to have chronic hypertension.

Covariates and potential confounders

Demographic covariates considered in this analysis included characteristics that have been associated with HDP, including age at conception, self-identified race and ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White or other), household income, and highest level of educational attainment at the time of delivery. Clinical covariates included parity, tobacco use in the first trimester, pre-pregnancy body mass index (BMI; or, if not available, up to 120 days after last menstrual period), and pre-gestational or gestational diabetes. These covariates were chosen given their established relationships to HDP.[2] HIV-related covariates included first CD4 count in pregnancy and in the first or second trimester (<200 vs. ≥200 cells/mm^3) and first HIV viral load in pregnancy and in the first or second trimester (≥40 vs. <40 copies/mL). Timing of prenatal care initiation among those who initiated ART in pregnancy was evaluated but found to be collinear with timing of ART initiation and thus not included in models.

Analysis

We described the distribution of covariates by HDP categories (none, new-onset HDP, and chronic hypertension with or without superimposed preeclampsia) and by timing of ART initiation using frequency for categorical variables and median (interquartile range) for continuous variables. To evaluate HDP frequency, we estimated the frequency and 95% confidence intervals (CI) for any HDP and each HDP category using binomial tests.

To evaluate the association of demographic and clinical factors with new-onset HDP (gestational hypertension, preeclampsia, and/or HELLP syndrome), we fit log-binomial regression models using generalized estimating equations to account for correlations within people with multiple singleton pregnancies during the study period to obtain estimates of the relative risk (RR) and 95% confidence intervals (CI), unadjusted and adjusted (aRR) for other covariates. Individuals with chronic hypertension with or without superimposed preeclampsia were excluded from the definition of new-onset HDP given the clinical challenges with differentiating superimposed preeclampsia from a chronic hypertension exacerbation.[2,3] We additionally performed a *post hoc* subgroup analysis evaluating differences in risk factors for superimposed preeclampsia among the population of individuals with chronic hypertension. Inclusion of other covariates was based on *a priori* decisions regarding known risk factors. Race was included in multivariable models as a marker of structural racism in the absence of direct measures. Each factor of interest was examined in a separate model.

First, in separate models we evaluated the association of clinical risk factors associated with new-onset HDP compared to no HDP. Factors included diabetes (pre-gestational or gestational), obesity (body mass index [BMI] ≥30 kg/m^2), first CD4 count in the first/second trimester, and first HIV RNA in first/second trimester. Diabetes and obesity were evaluated as clinical factors given the known associations with HDP and the limited data on these risk factors among individuals receiving contemporary ART regimens. Second, we examined the association of three exposures, each in a separate model, with risk of new-onset HDP compared to no HDP. In this analysis, individuals with no ART use in pregnancy (or only intrapartum antiretroviral use) were excluded. Models were fit for 1) timing of ART initiation, which was categorized as preconception (referent), between last menstrual period and 20 weeks of gestation, and 20 weeks of gestation or greater), 2) among individuals taking ART at conception, by class of ART (INSTI-based, protease inhibitor [PI]-based, or non-nucleoside reverse transcriptase inhibitor [NNRTI]-based), and 3) among individuals who initiated ART during pregnancy, by class of ART. Twenty weeks was chosen as the gestational age for evaluation of ART initiation as it aligned with the definition of when new-onset HDP may occur. Analyses were performed using a complete case analysis without imputation.

Analysis was performed in SAS version 9.4 (SAS Institute, Cary, NC). Each participant provided written informed consent for SMARTT participation, and the institutional review boards at the Harvard T.H. Chan School of Public Health and each site approved the study. STROBE guidelines were followed.

RESULTS

Of 1038 pregnancies of PLHIV in this cohort during the study period, 973 were singleton gestations available for analysis (Figure 1). The majority of individuals were under age 35 years (81%), identified as non-Hispanic Black (66%) or Hispanic (27%), and had at least a high school education (74%) (Table 1). The majority had a pre- or early-pregnancy BMI of 25 kg/m^2 or greater (44% with BMI 25–34.9 and 25% with BMI ≥35.0 kg/m^2) and 8% had diagnosis of gestational or pregestational diabetes. The majority (90%) had a first CD4 count ≥200 cells/mm^3 and 51% had a first viral load in pregnancy <40 copies/ml. In this cohort, half of individuals (50%) were taking ART at conception, whereas 37% initiated before and 13% initiated after 20 weeks' gestation (Table 2).

Of the pregnant PLHIV eligible for inclusion, including those with and without ART use in pregnancy, 19.22% (95% CI 16.74–21.69%) had any HDP: 9.46% (95% CI 7.62–11.29%) had gestational hypertension, preeclampsia, or HELLP (i.e., new-onset HDP), 2.77% (95% CI 1.74–3.81%) had superimposed preeclampsia on chronic hypertension, and 6.99% (95% CI 5.39–8.59%) had chronic hypertension without superimposed preeclampsia (Supplemental Figure 1). When excluding pregnancies with chronic hypertension (N=95), among the 878 pregnancies at risk for new-onset HDP, the estimated incidence of new-onset HDP was 10.5% (95% CI 8.5–12.5%).

PLHIV who started ART after conception were more likely to be younger, have a lower first CD4 count, and have a detectable first viral load. Demographic and clinical factors were

similar across timing of ART initiation (Table 2). ART core drug was similar by timing of ART initiation (Supplemental Figure 2). In this cohort, 44% of those taking ART at conception and 42% of those who initiated ART in pregnancy took an INSTI-based regimen.

Diabetes was associated with higher risk for new-onset HDP (aRR 2.44, 95% CI 1.42–4.21), after controlling for maternal age and race (Table 3). In contrast, the aRR of new-onset HDP in those with obesity (BMI ≥30 kg/m2 versus <30 kg/m^2) compared to those without was 1.37 (95% CI 0.91–2.06). Findings were unchanged when comparing BMI ≥35 kg/m2 versus <35 kg/m^2 (aRR 1.18, 95% CI 0.73–1.89). First/second trimester CD4 count <200 cells/mm^3 was associated with a nearly 2-fold greater risk of new-onset HDP (aRR 1.99, 95% CI 1.21–3.27) compared to ≥200 cells/mm^3, whereas there was no association between first/second trimester viral load and new-onset HDP.

Regarding timing and class of ART (Supplemental Figure 2), among individuals who received ART during pregnancy and who did not have chronic hypertension, the risk of new-onset HDP was 1.93-times (95% CI 1.12–3.30) higher in PLHIV who initiated ART on or after 20 weeks of gestation compared to those taking ART before conception (Table 4). Among those who initiated ART <20 weeks, the aRR was smaller (1.30, 95% CI 0.83–2.04). The risk of new-onset HDP in those receiving an NNRTI-based regimen compared to an INSTI-based regimen was 0.69 (95% CI 0.30–1.60) among those receiving ART at conception and 0.77 (95% CI 0.37–1.62) among those who initiated ART during pregnancy. Receiving a PI-based regimen compared to an INSTI-based regimen was also not associated with new-onset HDP (Table 4).

In a subgroup analysis of individuals with chronic hypertension, we identified that diabetes was more common among those who developed superimposed preeclampsia than those who did not (33% versus 19%). In addition, a detectable first or second trimester viral load and initiation of ART on or after 20 weeks were both more frequent among those who developed superimposed preeclampsia (Supplemental Table 1). Findings also suggest potentially more frequent superimposed preeclampsia among those on an INSTI-based regimen, although the sample size was small.

DISCUSSION

In this large cohort study of a diverse US-based population of pregnant PLHIV, nearly 1 in 5 individuals experienced HDP, of whom half experienced new-onset HDP. As in the general population,[2] diabetes was a risk factor for new-onset HDP. In addition, an early pregnancy CD4 cell count of <200 cells/mm^3 was associated with a 2-fold greater relative risk of new-onset HDP. Importantly, among individuals who received antenatal ART, initiation of ART in the second half of pregnancy was associated with a nearly 2-fold greater risk of new-onset HDP, compared to those who entered pregnancy taking ART. However, ART class was not associated with risk of HDP, regardless of timing of initiation.

The prevalence of both chronic and new-onset HDP in this cohort were slightly higher than that found in population-based cohorts of pregnant individuals without HIV, which have demonstrated a gradual rise in the occurrence of both conditions.[23–26] Despite changes

in contemporary management of HIV, few studies have examined HDP in a US-based population of PLHIV.[13,22] As INSTIs such as dolutegravir are now globally recommended as part of first-line ART, understanding the risk of HDP among people taking INSTIs compared with other ART is a research imperative.[17,27] INSTIs have been associated with excess weight gain and rapid immune reconstitution, two factors that may increase the risk of HDP.[2,18–21] Premkumar et al reported that PI use may be associated with HDP compared to other regimens, although most studies occurred before INSTI use was common.[14] Contrasting US data have suggested, as we hypothesized, that INSTI use may be associated with an elevated risk of HDP compared to PI-based regimens.[13] In Southern Africa, findings from the Botswana-based Tsepamo study found the prevalence of maternal hypertension to be higher with dolutegravir- versus efavirenz-based regimens, with the ART regimen acting as an effect modifier of the relationship between weight and hypertension.[28] Recent findings from a cohort of 794 pregnant PLHIV in Italy demonstrated no difference in hypertension by ART category.[29] Although only 6.2% of the Italian cohort participants were taking an INSTI-based regimen, in contrast to nearly half in our study, findings were similar to those herein. Our study provides the first data on HDP and INSTIs in the US and supports current US guidelines for the use of INSTIs in pregnancy.

Our findings provide insight and raise additional questions regarding mechanisms underlying HDP. It has been hypothesized that HIV may play a role in endothelial dysfunction and that some markers of dysregulated vascular endothelium are noted in individuals with HIV.[30] The associations of later initiation of ART with HDP supports the hypothesis that rapid immune activation later in pregnancy may exacerbate endothelial dysfunction and lead to the clinical manifestation of HDP. Immune activation may be particularly problematic in later pregnancy, if the hyperimmune response coincides with the natural rise in blood pressure. Alternatively, early pregnancy immunosuppression may be associated with greater inflammation, thus predisposing to greater risk of HDP. However, our findings contrast with data from a single-center study in France, in which there were no differences in risk of vasculoplacental complications (including HDP as well as fetal growth restriction) by maternal immune status at the beginning of pregnancy.[31] Other international data have similarly differed from our work and suggested no association between early pregnancy immune status and HDP, although findings largely predate the current era of HIV treatment.[15] It remains unclear if the elevated HDP risk can be attributed to immune reconstitution, the effects of immunosuppression, or alternative pathways. Further, as chronic hypertension is more common among nonpregnant PLHIV taking ART, it is possible that there is an undefined common mechanism linking ART use to hypertension before and during pregnancy. Individuals who initiate ART late may also differ in their HDP risk due to unmeasured factors related to late presentation to care, which may compound the effects of immune status changes. Furthermore, the extent to which other characteristics of persons with delayed initiation of antenatal care contribute to risk of HDP has not been quantified.

Our study is one of the first to include a large population of PLHIV taking INSTI-based regimens. Future work should investigate newer ART regimens; for example, many PLHIV now enter pregnancy taking regimens such as tenofovir alafenamide as an ART core drug, which may have differential effects on maternal health.[27,32] Others enter pregnancy on

newer INSTIs, such as bictegravir, which needs further study to determine if it has the same class effects. While we investigated the role of maternal CD4 and viral load with HDP risk as crude proxies for the maternal inflammatory state and immune status, future work should address other markers of immune status[33–36] that may better predict HDP and thus allow for the development of targeted interventions. Further work is also required to better understand risk factors for superimposed preeclampsia among individuals who enter pregnancy with chronic hypertension.

These findings highlight important lessons about caring for PLHIV. First, the relationships of both non-HIV (diabetes) and HIV-related morbidity (low CD4 count) with new-onset HDP demonstrate the importance of preconception health. Achievement of optimal health before pregnancy should be a fundamental goal of HIV and reproductive health clinicians. The significance of integrating reproductive life planning into HIV health care must be emphasized. Second, these findings highlight the importance of preconception ART or early adoption of ART once pregnancy is recognized. Even among individuals who present to obstetric care without optimal control of HIV, early initiation of ART presents an opportunity for improved health outcomes not only related to HIV, but potentially related to pregnancy-specific morbidity such as HDP. Access to healthcare remains vitally important to the optimization of maternal and neonatal health for many reasons, including the role of antenatal healthcare access in initiating and optimizing ART. Finally, our findings underscore that initiation of any type of suppressive ART prior to or very early in pregnancy – with the known maternal-fetal benefits of viral suppression – likely outweighs selecting a particular class for the purpose of mitigating HDP risk.

Strengths of this analysis include the large and well-characterized cohort for whom SMARTT data allowed detailed medical record abstraction and arbitration of unclear records. In addition, participants were enrolled from geographically and clinically diverse sites across the US, thus enhancing generalizability, and were recruited without regard to HDP status, which limits selection bias. However, several limitations warrant consideration. Participants may enroll in SMARTT either during or immediately after pregnancy; those who enrolled postpartum were required to have a live birth, which may limit the full breadth of obstetric outcomes experienced by this cohort. Second, data on prior HDP and aspirin use were unavailable. Our PLHIV participants were engaged in longitudinal research, thus limiting wide generalizability to other pregnant PLHIV. Similarly, due to the nature of SMARTT, which enrolls PLHIV who give birth to infants without HIV, we may be underestimating the frequency of HDP if individuals with HDP are more likely to experience perinatal transmission of HIV. Finally, there may be unmeasured confounders which restricts suggestion of causality, and power may have been limited for some analyses, as reflected in wide confidence intervals. Despite these limitations, the large and diverse sample and detailed data on ART regimens and HDP status are major study strengths.

Hypertensive disorders of pregnancy are a major source of short- and long-term maternal and neonatal morbidity.[2,37–39] With nearly 1 in 5 PLHIV in this cohort experiencing HDP, addressing its risk factors and mechanisms is a public health imperative. In this cohort, poorer immune status in early pregnancy or later initiation of ART were associated with greater risk of new-onset HDP, and although specific ART class was not associated,

validation in larger cohorts is warranted. The mechanisms underlying these associations represent important areas for future work. These findings underscore the importance of HIV control prior to pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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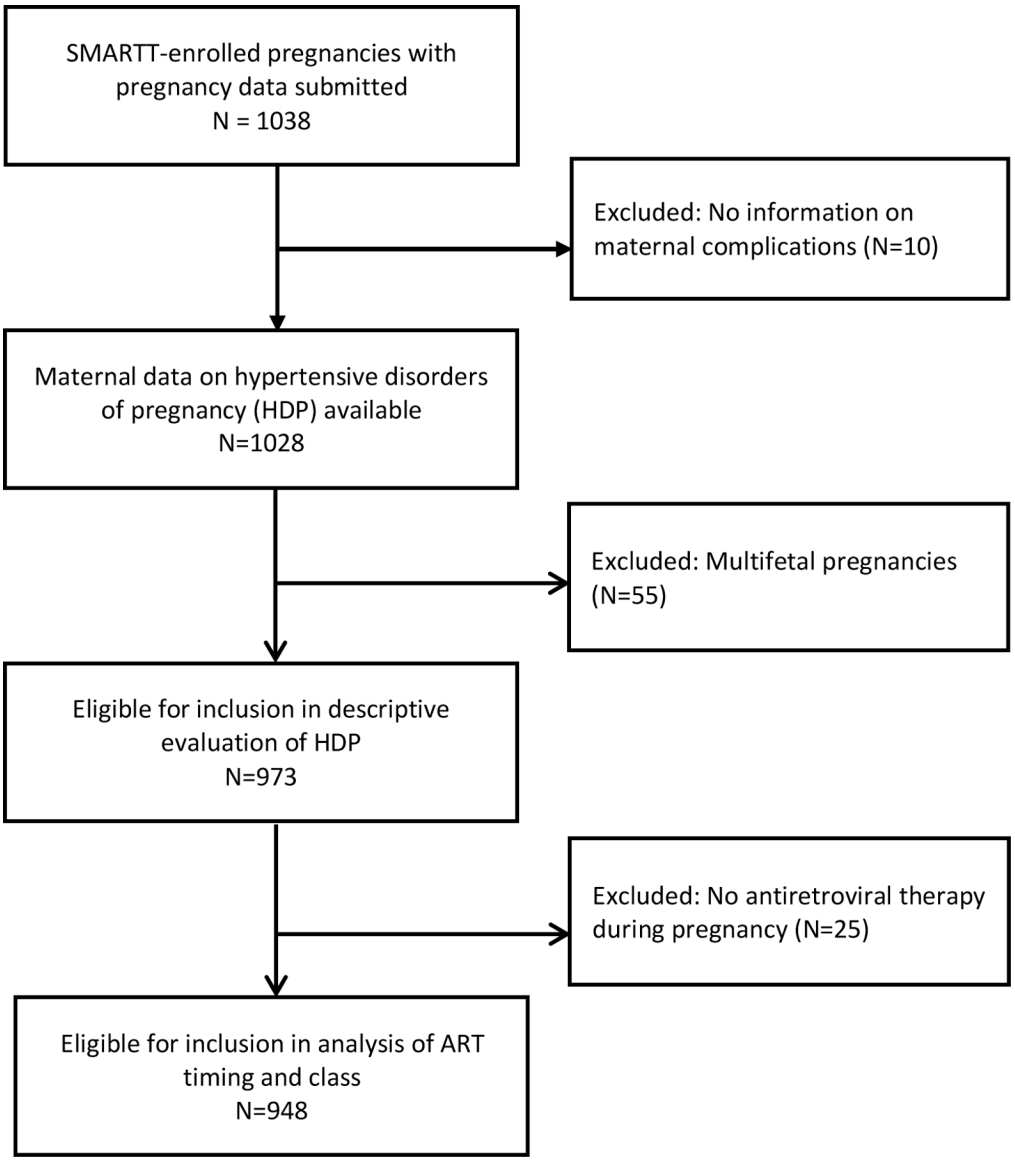

Figure 1.
Cohort flow chart

Table 1.

Demographic and clinical characteristics of pregnancies among people living with HIV by hypertensive disorder of pregnancy diagnosis

Characteristic	Category	Total[1] (N=973)	Hypertensive disorder of pregnancy		
			No HDP (N=786)	New-Onset HDP (N=92)	Chronic hypertension (with or without preeclampsia) (N=95)
Maternal age at conception ≤35 years		789 (81%)	651 (83%)	74 (80%)	64 (67%)
Maternal race/ethnicity[2]	Hispanic	258 (27%)	219 (28%)	20 (22%)	19 (20%)
	Non-Hispanic Black	636 (66%)	500 (64%)	64 (70%)	72 (76%)
	Non-Hispanic White or Other	73 (8%)	61 (8%)	8 (9%)	4 (4%)
Annual household income ≥$10,000/year[3]		457 (52%)	370 (52%)	45 (54%)	42 (48%)
High school education or greater[4]		707 (74%)	572 (75%)	67 (73%)	46 (52%)
Tobacco use in first trimester	Yes	134 (14%)	106 (13%)	14 (15%)	14 (15%)
	No	815 (84%)	659 (84%)	76 (83%)	80 (84%)
	Unknown	24 (2%)	21 (3%)	2 (2%)	1 (1%)
Parity	0	236 (24%)	182 (23%)	30 (33%)	24 (25%)
	1–3	630 (65%)	516 (66%)	54 (59%)	60 (63%)
≥4	107 (11%)	88 (11%)	8 (9%)	11 (12%)	
First CD4 in 1st/2nd trimester of pregnancy ≥200 cells/mm^3		751 (89%)	606 (90%)	63 (80%)	82 (91%)
First HIV RNA in 1st/2nd trimester of pregnancy <40 copies/mL		411 (46%)	337 (47%)	35 (44%)	39 (43%)
Gestational or pregestational diabetes		78 (8%)	43 (5%)	13 (14%)	22 (23%)
Body mass index (pre-pregnancy or within first four months),[5] kg/m^2	≥35.0 kg/m^2	218 (25%)	154 (22%)	21 (25%)	43 (48%)
	25.0–34.9 kg/m^2	382 (44%)	309 (44%)	37 (45%)	36 (40%)
	<25.0 kg/m^2	277 (32%)	241 (34%)	25 (30%)	11 (12%)

Abbreviations: HIV, human immunodeficiency virus; HDP, hypertensive disorders of pregnancy

1. Including all individuals, with and without ART during pregnancy

2. Missing race/ethnicity on N=6 (all with no HDP)

3. Missing income data on N=90 (19 no HDP, 8 new-onset HDP, 7 chronic hypertension)

4. Missing education data on N=21 (19 no HDP, 2 chronic hypertension)

5. Missing body mass index for N=96 (82 no HDP, 9 new-onset HDP, 5 chronic hypertension)

Table 2.

Demographic and clinical characteristics of pregnancies of people living with HIV by timing of antiretroviral therapy initiation, among pregnancies of individuals who were taking antiretroviral therapy during pregnancy

Characteristic		Timing of antiretroviral initiation[1]		
		Taking ART at conception (N=475)	Start < 20 weeks (N=353)	Start ≥20 weeks (N=120)
Maternal age at conception ≤35 years		362 (76%)	302 (86%)	106 (88%)
Maternal race/ethnicity[2]	Hispanic	137 (29%)	88 (25%)	24 (20%)
	Non-Hispanic Black	298 (63%)	239 (68%)	85 (71%)
	Non-Hispanic White or Other	37 (8%)	24 (7%)	10 (8%)
Annual household income ≥$10,000/year[3]		241 (56%)	161 (50%)	45 (43%)
High school education or greater[4]		338 (73%)	272 (79%)	80 (69%)
Tobacco use in first trimester	Yes	52 (11%)	52 (15%)	25 (21%)
	No	412 (87%)	292 (83%)	91 (76%)
	Unknown	11 (2%)	9 (3%)	4 (3%)
Parity	0	108 (23%)	87 (25%)	34 (28%)
	1–3	316 (67%)	228 (65%)	74 (62%)
	≥4	51 (11%)	38 (11%)	12 (10%)
First CD4 in 1st/2nd trimester of pregnancy ≥200 cells/mm[3]		405 (92%)	274 (85%)	59 (84%)
First HIV RNA in 1st/2nd trimester of pregnancy <40 copies/mL		288 (64%)	99 (29%)	15 (19%)
Gestational or pregestational diabetes		42 (9%)	27 (8%)	6 (5%)
Body mass index (pre-pregnancy or within first four months),[5] kg/m^2	≥35.0 kg/m^2	111 (25%)	81 (25%)	19 (22%)
	25.0–34.9 kg/m^2	196 (44%)	144 (44%)	34 (40%)
	<25.0 kg/m^2	138 (31%)	101 (31%)	32 (38%)
Chronic hypertension		43 (9%)	42 (12%)	10 (8%)

Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy

1. Excluding individuals who were ever on antiretroviral therapy during pregnancy.

2. Missing race and ethnicity data on N=6 (1 starting ≥20 weeks, 2 starting <20 weeks, 3 taking ART at conception).

3. Missing income data on N=89 (16 starting ≥20 weeks, 31 starting <20 weeks, 42 taking ART at conception).

4. Missing education data on N=21 (4 starting ≥20 weeks, 8 starting <20 weeks, 9 taking ART at conception).

5. Missing BMI for N=92 (35 starting ≥20 weeks, 27 starting <20 weeks, 30 taking ART at conception).

Table 3.

Association of selected clinical factors with new-onset hypertensive disorders of pregnancy among people living with HIV

Exposure of interest	Category Level of Exposure	OUTCOME: New-onset HDP[1] Number in group	Risk of outcome	UNADJUSTED Risk Ratio (95% CI)	ADJUSTED[2] Risk Ratio (95% CI)
Diabetes[3]	No diabetes	816	9.68%	(Ref)	(Ref)
	Diabetes	56	23.21%	2.40 (1.43, 4.03)	2.44 (1.42, 4.21)
Pre-pregnancy BMI	BMI ≤ 30 kg/m^2	467	9.21%	(Ref)	(Ref)
	BMI > 30 kg/m^2	314	12.74%	1.39 (0.92, 2.08)	1.37 (0.91, 2.06)
First CD4 count in 1st/2nd trimester of pregnancy[4]	≥200 cells/mm^3	662	9.37%	(Ref)	(Ref)
	<200 cells/mm^3	85	18.82%	1.99 (1.21, 3.28)	1.99 (1.21, 3.27)
First RNA in 1st/2nd trimester of pregnancy[4]	<40 copies/mL	369	9.49%	(Ref)	(Ref)
	≥40 copies/mL	420	10.48%	1.11 (0.73, 1.69)	1.13 (0.73, 1.73)

Abbreviations: HIV, human immunodeficiency virus; HDP-hypertensive disorders of pregnancy; BMI, body mass index

1. New-onset HDP is defined as gestational hypertension, pre-eclampsia/eclampsia with or without severe features of HELLP, or HELLP alone. New onset HDP does not include the 27 individuals with superimposed preeclampsia. Those with chronic hypertension only (N=68) are not included in those without new onset HDP.

2. Models for new-onset HDP were adjusted for maternal age and Black race; Includes individuals taking and not taking ART during pregnancy.

3. Includes pre-gestational and gestational diabetes

4. The first CD4 and RNA in the first or second trimester were chosen in order to ensure these markers of HIV status occurred before the diagnosis of HDP.

5. The number in the unadjusted and adjusted models for each exposure are: 878 and 872 for diabetes, 787 and 781 for pre-pregnancy BMI, 752 and 747 for CD4 count in 1st/2nd trimester, and 794 and 789 for RNA in the 1st/2nd trimester, respectively.

Table 4.

Models for association of timing and class of antiretroviral therapy on risk of new-onset hypertensive disorder of pregnancy among people living with HIV

		OUTCOME: New-onset HDP[1]		UNADJUSTED	ADJUSTED[2]
Exposure of interest	**Category Level of Exposure**	**Number in group**	**Risk of outcome**	**Risk Ratio (95% CI)**	**Risk Ratio (95% CI)**
Timing of ART initiation	Start ≥20 weeks	109	16.51%	1.91 (1.12, 3.26)	1.93 (1.12, 3.30)
	Start <20 weeks	310	10.97%	1.27 (0.82, 1.98)	1.30 (0.83, 2.04)
	Taking ART at conception	429	8.62%	(Ref)	(Ref)
At conception – ART core drug class[3]	NNRTI-based	114	6.14%	0.69 (0.30, 1.62)	0.69 (0.30, 1.60)
	PI-based	130	10.00%	1.13 (0.56, 2.26)	1.13 (0.57, 2.24)
	INSTI-based	178	8.99%	(Ref)	(Ref)
Initiating in pregnancy – ART core drug class	NNRTI-based	77	10.39%	0.79 (0.37, 1.67)	0.77 (0.37, 1.62)
	PI-based	158	13.29%	0.99 (0.57, 1.70)	0.99 (0.58, 1.71)
	INSTI-based	169	13.61%	(Ref)	(Ref)

Abbreviation: HIV, human immunodeficiency virus; HDP, hypertensive disorders of pregnancy; ART, antiretroviral therapy; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor

1. Population excludes individuals who were never taking ART during pregnancy. New-onset hypertension of pregnancy is defined as gestational hypertension, pre-eclampsia/eclampsia with or without severe features of HELLP, or HELLP alone. New onset HTN does not include 27 individuals with superimposed preeclampsia or chronic hypertension only.

2. Models for the new onset HDP outcome were adjusted for maternal age and Black race.

3. "Core drug class" refers to the highest potency antiretroviral drug in the ART regimen

4. The number in the unadjusted and adjusted models for each exposure are: 854 and 848 for timing of ART initiation, 425 and 422 for ART at conception, and 407 and 404 for ART at initiating in pregnancy, respectively.