Title

Birth Weight and Preterm Delivery Outcomes of Perinatally vs Nonperinatally Human Immunodeficiency Virus-Infected Pregnant Women in the United States: Results From the PHACS SMARTT Study and IMPAACT P1025 Protocol.

Journal

Clinical Infectious Diseases, 65(6)

ISSN

1058-4838

Authors

Jao, Jennifer
Kacanek, Deborah
Williams, Paige L
et al.

Publication Date

2017-09-15

DOI

10.1093/cid/cix488

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

Birth Weight and Preterm Delivery Outcomes of Perinatally vs Nonperinatally Human Immunodeficiency Virus-Infected Pregnant Women in the United States: Results From the PHACS SMARTT Study and IMPAACT P1025 Protocol

Jennifer Jao,[1] Deborah Kacanek,[2] Paige L. Williams,[2] Mitchell E. Geffner,[3] Elizabeth G. Livingston,[4] Rhoda S. Sperling,[5] Kunjal Patel,[6] Arlene D. Bardeguez,[7] Sandra K. Burchett,[8] Nahida Chakhtoura,[9] Gwendolyn B. Scott,[10] Russell B. Van Dyke,[11] and Elaine J. Abrams[12]; for the Pediatric HIV/AIDS Cohort Study and the International Maternal Pediatric Adolescent AIDS Clinical Trials P1025 Protocol

[1]Departments of Medicine and Obstetrics, Gynecology, and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Department of Biostatistics, Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [3]Saban Research Institute of Children's Hospital Los Angeles, Keck School of Medicine of the University of Southern California; [4]Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina; [5]Department of Obstetrics, Gynecology, and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York; [6]Department of Epidemiology, Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [7]Department of Obstetrics, Gynecology, and Women's Health, Rutgers New Jersey Medical School, Newark; [8]Division of Infectious Diseases, Boston Children's Hospital and Harvard Medical School, Massachusetts; [9]Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; [10]Department of Pediatrics, Division of Pediatric Infectious Disease and Immunology, University of Miami Miller School of Medicine, Florida; [11]Department of Pediatrics, Section of Infectious Diseases, Tulane University School of Medicine, New Orleans, Louisiana; and [12]Mailman School of Public Health and College of Physicians & Surgeons, International Center for AIDS Care and Treatment Program, Columbia University, New York, New York

Background. Pregnancy outcomes of perinatally human immunodeficiency virus–infected women (PHIV) are poorly defined.

Methods. We compared preterm delivery and birth weight (BW) outcomes (low BW [LBW], <2500 g), small-for-gestational-age [SGA], and BW *z* scores [BWZ]) in HIV-exposed uninfected infants of PHIV vs nonperinatally HIV-infected (NPHIV) pregnant women in the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring of ART Toxicities or International Maternal Pediatric Adolescent AIDS Clinical Trials P1025 studies. Mixed effects models and log binomial models were used to assess the association of maternal PHIV status with infant outcomes. Age-stratified analyses were performed.

Results. From 1998 to 2013, 2270 HIV-infected pregnant women delivered 2692 newborns (270 born to PHIV and 2422 to NPHIV women). PHIV women were younger, (mean age 21 vs 25 years, $P < .01$) and more likely to have a pregnancy CD4 count <200 cells/mm^3 (19% vs 11%, $P = .01$). No associations between maternal PHIV status and preterm delivery, SGA, or LBW were observed. After adjustment, BWZ was 0.12 lower in infants of PHIV vs NPHIV women (adjusted mean, −0.45 vs −0.33; $P = .04$). Among women aged 23–30 years (n = 1770), maternal PHIV was associated with LBW (aRR = 1.74; 95% confidence interval, 1.18, 2.58; $P < .01$).

Conclusion. The overall lack of association between maternal PHIV status and preterm delivery or infant BW outcomes is reassuring. The higher rates of LBW observed in PHIV women aged 23–30 years warrants further mechanism-based investigations as this is a rapidly growing and aging population worldwide.

Clinical Trials Registration. PHACS SMARTT study, NCT01310023.

Clinical Trials Registration. IMPAACT 1025, NCT00028145.

Keywords. pregnancy; birth weight; preterm delivery; perinatal HIV infection.

The success of combination antiretroviral therapy (ART) has enabled an increasing number of perinatally human immunodeficiency virus (HIV)–infected (PHIV) children to reach adolescence and young adulthood [1]. Worldwide in low-middle income countries, new HIV infections in children have declined by 50% from approximately 550 000 to 250 000 per year between 2001 and 2012 [2]. However, given expanding access to potent ART globally, it is likely that the majority of these children will survive longer, resulting in an estimated 5.5 million HIV-infected children (the majority of whom may be PHIV) reaching young adulthood, with around half being females who attain child-bearing age, in the next decade in low-middle income countries alone.

Optimizing care during pregnancy for women who have lived with HIV since birth may pose unique challenges. For example,

Received 27 January 2017; editorial decision 12 May 2017; accepted 23 May 2017; published online May 30, 2017.

Correspondence: J. Jao, Icahn School of Medicine at Mount Sinai, Department of Medicine, One Gustave L. Levy Place, Box 1087, New York, NY 10029 (jennifer.jao@mssm.edu).

Clinical Infectious Diseases® 2017;65(6):982–9

DOI: 10.1093/cid/cix488

because PHIV women may have more advanced HIV disease, require more complex ART due to increased drug resistance [3, 4], and exhibit distinct immunological alterations [5, 6], choosing safe and effective ART regimens during pregnancy to both mitigate mother-to-child transmission of HIV and enhance maternal health can sometimes be difficult. In comparison to nonperinatally HIV-infected (NPHIV) women, PHIV women may also have complex psychosocial and reproductive health needs associated with growing up with HIV infection [7–9]. Although they appear to be at lower risk for acquisition of other sexually transmitted infections than NPHIV women, PHIV women are often younger due to the natural history of HIV mother-to-child transmission [10, 11].

Pregnancy and infant outcomes in PHIV women have not been well documented, the vast majority of literature in this area arising from small studies or case series [11–16]. A few small studies in the United States have demonstrated high rates of viremia at delivery [17] in PHIV women as well as high rates of preterm birth and lower birth weight (BW) in infants born to PHIV women [12, 15]. Preterm delivery and BW outcomes such as low BW (LBW; <2500 g) or small-for-gestational age (SGA) are not benign conditions, with clear evidence that both are associated with increased immediate and long-term morbidity and mortality [18, 19]. Our objective in this study was to assess the association of maternal PHIV status with preterm delivery and infant BW outcomes using data collected from 2 large prospective cohorts of pregnant women in the United States.

MATERIALS AND METHODS

Study Population

This study included women and infants enrolled in the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring of ART Toxicities (SMARTT) study or the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network P1025 study, 2 large prospective cohort studies in the United States, including Puerto Rico, designed to assess maternal and infant safety of ART prescribed for the prevention of mother-to-child transmission (PMTCT) of HIV. The PHACS SMARTT study began enrollment in 2007 across 22 sites, while IMPAACT P1025 enrolled participants between 2002 and 2013 across 67 sites. We included singleton HIV-exposed uninfected (HEU) live births of HIV-infected pregnant women ages 13–30 years at the time of delivery who were enrolled in either or both cohorts and who had infant BW, gestational age (GA) at birth, and information to classify maternal mode of HIV acquisition information available. For each study, institutional review boards at each site approved the protocol, and all participating women provided written informed consent.

Outcomes

Outcomes of interest included preterm delivery and the following BW outcomes: LBW, very LBW (VLBW), SGA, and BW *z* scores (BWZ). Preterm delivery was defined as delivery at <37 weeks GA. Our evaluation of preterm birth did not distinguish between spontaneous and indicated preterm delivery, since information necessary to make such a classification was not uniformly available. LBW was defined as <2500 g and VLBW as <1500 g at any GA. SGA was defined as a BW <10% and BWZ scores were calculated based on GA at birth and sex using United States standards [20].

Primary Exposure of Interest

The primary exposure of interest was the maternal mode of HIV acquisition: PHIV vs NPHIV. Participants were classified as PHIV if they were born in 1983 or later and either PHIV status was reported through interview or chart abstraction or the maternal date of HIV diagnosis was within 5 years of the maternal date of birth. We applied this maternal birth year criteria based on the assumption that it would be unlikely to have perinatally infected children born prior to 1983 in the United States who would have survived into young adulthood, as triple-drug ART regimens improving the morbidity and mortality of HIV-infected individuals only readily became available after 1996 [21].

Covariates

Information on potential confounders including maternal age at delivery, race, Hispanic ethnicity, calendar year of delivery (categorized as 1996–2003, 2004–2009, or 2010–2013), earliest CD4 cell count in pregnancy, HIV RNA levels at delivery, ART use during pregnancy, pre-pregnancy body mass index (BMI), and tobacco and substance use were collected at study visits as per each study's protocol. For women receiving multiple ART regimens in pregnancy, the ART regimen with the longest duration of use during pregnancy was chosen. If 2 or more ART regimens had similar durations of use during the pregnancy, the most potent regimen was included in the analysis. ART regimens were categorized in the following order of potency, from most potent to least potent: regimen with ≥3 classes of ARVs, integrase strand inhibitor (INSTI)-based ART, protease inhibitor (PI)-based ART, nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART, nucleoside reverse transcriptase inhibitor (NRTI)-based ART, noncombination ART regimen, and no ARVs/ unknown. GA was confirmed by ultrasound.

Statistical Analysis

Characteristics of women were compared by maternal PHIV status using the Student *t* test or Wilcoxon test for continuous variables and χ^2 or Fisher exact test as appropriate for discrete variables. Characteristics of infants were compared by applying univariate log binomial or linear models using generalized estimating equations (GEE). Linear mixed effects models were fit to calculate unadjusted and adjusted estimates of the association of maternal PHIV status with the BWZ outcome,

accounting for multiple pregnancies in the same woman. For binary outcomes (LBW, SGA, and preterm delivery), log binomial models using GEE with an exchangeable covariance structure were fit to estimate the unadjusted and adjusted relative risk (aRR) of each outcome for infants in the maternal PHIV vs NPHIV group. Variables considered to be potential confounders were those associated with both the outcome and exposure at $P \leq .1$. In addition, age-stratified analyses were performed to determine whether associations between maternal PHIV status and each outcome were modified by maternal age group (13–17, 18–22, or 23–30 years). For covariates with >15% missing data, a missing indicator approach was used in adjusted models. Sensitivity analyses were performed with and without participants who had any inconsistent data on the maternal mode of HIV acquisition. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Between 1996 and 2013, 2270 HIV-infected pregnant women (235 PHIV and 2035 NPHIV) gave birth to 2692 HEU infants (270 born to PHIV and 2422 born to NPHIV women) who met inclusion criteria for this analysis (Table 1). Overall, 726 (32%) women were enrolled in PHACS SMARTT, 1087 (48%) in IMPAACT 1025, and 457 (20%) in both studies. Compared to NPHIV women, PHIV women were younger (mean age 21 vs 25 years, $P < .01$) and less often black (55% vs 67%, $P < .01$). PHIV women were more likely to have a CD4 count <200 cells/mm^3 during pregnancy (19% vs 11%, $P = .01$), delivery HIV RNA level ≥400 copies/mL (28% vs 17%, $P < .01$), receipt of ≥3-class ART during pregnancy (23% vs 2%, $P < .01$), and pre-pregnancy BMI <18.5 kg/m^2 (8% vs 4%, $P < .01$). In addition, PHIV women were less likely to report tobacco use (14% vs 20%, $P = .01$) during pregnancy. In age-stratified analyses, women with PHIV were more likely to have a CD4 count <200 cells/mm^3 in pregnancy relative to NPHIV women in the 18- to 22-year-old (22% vs 10%, $P < .01$) and 23- to 30-year-old (21% vs 12%, $P = .05$) age groups. Among women in the youngest age group, PHIV women were more likely to have an HIV RNA level ≥400 copies/mL at delivery than NPHIV women (42% vs 17%, $P < .01$; data not shown).

Overall, 429 (16%) infants were born preterm, 398 (15%) were LBW, 40 (1%) were VLBW, and 297 (11%) were SGA for BW. The proportion of infants born preterm, LBW, VLBW, and SGA did not differ by maternal PHIV status (Table 1). Mean BWZ was lower in infants of PHIV vs NPHIV women (−0.44 vs. −0.33, $P = .06$). After adjustment, this difference persisted, and BWZ was 0.12 lower in infants of PHIV vs NPHIV women (adjusted mean, −0.45 vs −0.33; $P = .03$; Table 2). In addition, black race, tobacco and substance use in pregnancy, and maternal pre-pregnancy BMI <18.5 kg/m^2 were significantly associated with lower infant BWZ. In adjusted models, there remained no overall associations between maternal PHIV status and LBW, SGA, or preterm delivery. However, in age-stratified analyses, among infants of women in the oldest category (23 to 30 years old; n = 1770), PHIV women had higher proportions of LBW infants (24% vs 15%; Table 3). This association persisted even after adjustment for confounders (aRR = 1.74; 95% confidence interval [CI], 1.18, 2.58; $P < .01$). No associations were seen between PHIV status and preterm delivery or SGA outcomes in age-stratified adjusted analyses. Sensitivity analyses excluding women with inconsistent report of maternal mode of HIV acquisition based on the criteria applied (n = 42) resulted in similar findings.

DISCUSSION

Despite lifelong HIV infection and the potential for difficulties in optimizing healthcare during pregnancy, PHIV pregnant women in the United States do not appear to be at increased risk for preterm delivery or adverse infant BW outcomes compared to NPHIV pregnant women. The lack of these major outcomes is reassuring. However, among the oldest age group, maternal PHIV status was associated with LBW infant outcomes, raising some concern for distinct mechanisms among older PHIV women that may give rise to suboptimal intrauterine growth. In addition, rates of preterm delivery and LBW in HEU infants of PHIV and NPHIV women are still notably higher than reported rates in the United States among singleton newborns (7.7% preterm delivery and 6.2% LBW) [22] or in other industrialized countries [23, 24].

Our findings regarding overall preterm delivery in PHIV vs NPHIV women are largely consistent with the few smaller studies that have compared rates of these outcomes between PHIV and NPHIV women [11, 12, 14, 17, 25]. Despite 1 United States case series that reported a high rate of preterm delivery (31%) among PHIV women [15], several other studies have reported low rates of preterm delivery in PHIV women, ranging from 3% to 17% [10, 13, 14, 17, 25, 26], which were similar to those found in our cohort (16%).

The overall rate of SGA in our population was 11%, similar to the expected 10%. The lack of association observed between maternal PHIV status and SGA infant outcomes in our study is in contrast with another study evaluating pregnancy outcomes in PHIV women [12]. This smaller United States study observed an increased risk for SGA in infants born to PHIV compared to NPHIV women in adjusted analysis and had higher rates of SGA (47%) than those found in our cohort (11%) or in another small case series in the United Kingdom (12%) [10] These differences may be attributed to variability in maternal HIV immune status or standard of overall healthcare and antenatal care. For example, 19% of PHIV women in our cohort had a CD4 cell count in pregnancy <200 cells/mm^3, whereas the smaller United States study reported 64% of PHIV women with this same level of immunosuppression.

The small statistical difference in mean BWZ score that we observed between infants of PHIV and NPHIV women appears

Table 1. Characteristics of Women and Infants by Maternal Mode of Human Immunodeficiency Virus Acquisition

Characteristic				
Women at First Pregnancy	PHIV (n = 235)	NPHIV (n = 2035)	Total (n = 2270)	*P* Value
Age, y	21 (2.9)	25 (3.6)	24 (3.7)	<.01
Race				
White/Other	91 (39%)	535 (26%)	626 (28%)	<.01
Black	129 (55%)	1360 (67%)	1489 (66%)	
Unknown/ Declined	15 (6%)	140 (7%)	155 (7%)	
Hispanic ethnicity	85 (36%)	545 (27%)	630 (28%)	<.01
Achieved high school graduation	148 (63%)	1246 (61%)	1394 (61%)	.67
Year of delivery				
1996–2005	16 (7%)	670 (33%)	686 (30%)	<.01
2006–2009	80 (34%)	717 (35%)	797 (35%)	
2010–2013	138 (59%)	647 (32%)	785 (35%)	
Body mass index, kg/m^2 §				
<18.5	15 (8%)	54 (4%)	69 (4%)	<.01
18.5–24.9	86 (49%)	485 (35%)	571 (36%)	
25.0–29.9	35 (20%)	333 (24%)	368 (24%)	
≥30	40 (23%)	521 (37%)	561 (36%)	
Tobacco use in pregnancy^	32 (14%)	397 (20%)	429 (19%)	.01
Alcohol use in pregnancy*	45 (19%)	379 (19%)	424 (19%)	.99
Illicit drug use in pregnancy¶	21 (9%)	252 (12%)	273 (12%)	.10
CD4 at enrollment, cells/mm^3				
<200	44 (19%)	228 (11%)	272 (12%)	.01
200–500	107 (46%)	943 (46%)	1050 (46%)	
>500	81 (34%)	774 (38%)	855 (38%)	
Unknown	3 (1%)	90 (4%)	93 (4%)	
HIV RNA level at delivery, copies/mL				
≤400	164 (70%)	1572 (77%)	1736 (76%)	<.01
>400–1000	12 (5%)	86 (4%)	98 (4%)	
>1000–10000	34 (14%)	158 (8%)	192 (8%)	
>10000	20 (9%)	105 (5%)	125 (6%)	
Unknown	5 (2%)	114 (6%)	119 (5%)	
ART during pregnancy				
≥3 classes	54 (23%)	50 (2%)	104 (5%)	<.01
INSTI-based	3 (1%)	18 (1%)	21 (1%)	
PI-based	159 (68%)	1422 (70%)	1581 (70%)	
NNRTI-based	3 (1%)	158 (8%)	161 (7%)	
NRTI-based	11 (5%)	233 (11%)	244 (11%)	
Noncombination ART regimen	2 (1%)	82 (4%)	84 (4%)	
No ARVs/Unknown	3 (1%)	72 (4%)	75 (4%)	
Infants	PHIV (n = 270)	NPHIV (n = 2422)	TOTAL (n = 2692)	
Female	134 (50%)	1190 (49%)	1324 (49%)	.84
Gestational age (wk)	38.1 (1.9)	38.2 (2.0)	38.2 (2.0)	.56
Preterm delivery (<37 wk)	41 (15%)	388 (16%)	429 (16%)	.69
Small for gestational age	32 (12%)	265 (11%)	297 (11%)	.72
Low birth weight (<2500 g)	48 (18%)	350 (14%)	398 (15%)	.17
Very low birth weight (<1500 g)	4 (1%)	36 (1%)	40 (1%)	.96
Birth weight *z* score	-0.44 (0.75)	-0.33 (0.84)	-0.34 (0.83)	.06

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NPHIV, nonperinatally HIV-infected; PHIV, perinatally HIV-infected; PI, protease inhibitor.

All continuous variables shown as mean (standard deviation) and categorical variables as n (%); § n = 176 PHIV, n = 1393 NPHIV; ^n = 206 PHIV, n = 1712 NPHIV; *n = 222 PHIV, n = 1874 NPHIV; ¶n = 222 PHIV, n = 1873 NPHIV.

to be of little clinical significance. Overall, the BWZ of infants born to PHIV women was 0.12 lower than that of infants born to NPHIV women; in a term 40 week GA male infant, this corresponds to a difference of approximately 59 g.

Although we observed no associations between maternal PHIV status and LBW outcomes in the overall study sample, we did observe an increased risk for LBW outcomes but not SGA or preterm birth in HEU infants born to PHIV vs NPHIV

Table 2. Unadjusted and Adjusted Models for Outcomes Comparing Infants of Perinatally vs Nonperinatally Human Immunodeficiency Virus–Infected Women, Adjusting for Calendar Period of Delivery

LBW[a]		*SGA*[a]		*Preterm Delivery*[a]		*BWZ*[b]	
RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value	Difference (95% CI)	*P* value
Unadjusted							
1.22 (0.92,1.62)	.17	1.06 (0.76,1.49)	.72	0.94 (0.70,1.27)	.69	-0.11 (-0.22, -0.01)	.03
Adjusted							
1.23 (0.89,1.70)	.19	0.98 (0.66,1.44)	.89	1.01 (0.72,1.44)	.93	-0.12 (-0.24, -0.003)	.04

Models adjusted for maternal age, race, earliest CD4 count in pregnancy, maternal substance use in pregnancy, maternal tobacco use during pregnancy, maternal pre-pregnancy body mass index, most potent antiretroviral regimen in pregnancy, calendar year period of delivery.

Abbreviations: BWZ, birth weight *z* score; CI, confidence interval; LBW, low birth weight (<2500 g); RR, relative risk; SGA, small for gestational age.

[a]Log binomial models using generalized estimating equations

[b]Linear mixed effects models

women from the oldest age category (23 to 30 years old). While the proportion of infants with LBW was higher among those of PHIV vs NPHIV women in this age group, this was not observed in infants of women in the youngest age group or in the overall study population. This finding of an association between maternal PHIV status and LBW in the oldest age category should be interpreted with caution as LBW infants may include term infants with intrauterine growth restriction or preterm infants with normal BWZ scores. Nonetheless, the greater proportion of women with a CD4 count <200 cells/mm^3 in PHIV vs NPHIV women within the older aged group may point to potential hypotheses including heightened long-standing immune activation and dysfunction as well as immunosenescence, the age-associated evolution of the immune system, in these pregnant women, which may, in turn, affect the in utero inflammatory microenvironment and fetal growth. HIV infection, including that in infants, is known to be associated with chronic immune activation [6, 27]. Those with persistently poor immune reconstitution despite viral suppression exhibit not only chronic immune activation but also T-cell features similar to those found in immunosenescence [28–30]. Advanced maternal age is associated with LBW and other adverse pregnancy outcomes [31]. In fact, the oldest age group of PHIV in our study was 23–30 years old, hardly meeting current obstetrical definitions of advanced maternal age (commonly >35 years old) [32], but the chronicity of HIV infection in these oldest PHIV women may heighten their risk for sustained inflammation and immune activation as well as accelerated aging compared to NPHIV women, which in turn, adversely affect intrauterine fetal growth. Suboptimal intrauterine growth carries additional risks for the infant including fetal and neonatal death as well as increased long-term morbidity [18, 33].

Our study was limited by the heterogeneity of in utero ARV exposure due to the wide period of time over which women in the two cohorts could have delivered infants. This presents some difficulties in disentangling the actual effects of any in utero ART exposure from maternal PHIV status. In addition, we were unable to distinguish between spontaneous vs nonspontaneous preterm birth. There is also the potential for misclassification bias since the mode of maternal HIV acquisition

Table 3. Adjusted Estimates of Relative Risk for Low Birth Weight, Small-for-Gestational Age, Preterm Birth, and Birth Weight *z* Score Outcomes by Maternal Perinatally Human Immunodeficiency Virus (HIV)-Infected Status and Maternal Age Among HIV-exposed Uninfected Infants Born to 13–30 year-old Women with HIV in the SMARTT or IMPAACT P1025 Studies

Maternal		Low Birth Weight (<2500 g)			Small for Gestational Age			Preterm Birth			BWZ	
Age Group	N	%	RR (95% CI)	*P*	%	RR (95% CI)	*P*	%	RR (95% CI)	*P*	Difference (95% CI)	*P*
13–17 y												
PHIV	20	10%	0.44 (0.10,1.89)[a]	.27	15%	1.07 (0.29, 4.03)[a]	.92	10%	0.67 (0.14, 3.16)[a]	.62	-0.06 (-0.47, -0.35)[a]	.77
NPHIV	36	22%	1.00		14%	1.00		15%	1.00			
18–22 y												
PHIV	171	16%	0.84 (0.53,1.34)	.47	12%	0.94 (0.59, 1.51)	.79	14%	0.77 (0.48, 1.24)	.29	-0.08 (-0.24, 0.08)	.33
NPHIV	602	15%	1.00		14%	1.00		15%	1.00			
23–30 y												
PHIV	78	24%	1.74 (1.18, 2.58)	<.01	12%	1.24 (0.66, 2.34)	.51	19%	1.30 (0.84, 2.02)	.24	-0.13 (-0.33, 0.07)	.22
NPHIV	1692	15%	1.00		10%	1.00		17%	1.00			

Abbreviations: BWZ, birth weight *z* score; CI, confidence interval; HIV, human immunodeficiency virus; NPHIV, nonperinatally HIV-infected; PHIV, perinatally HIV-infected; RR, relative risk.

[a]The 13- to 17-year age group results are from unadjusted models due to small sample size. For age groups 18–22 and 23–30, models adjusted for race, earliest CD4 count in pregnancy, maternal substance use in pregnancy, maternal tobacco use during pregnancy, maternal prepregnancy body mass index, and most potent antiretroviral regimen in pregnancy.

was determined primarily via self-report or medical record review, and in some cases, reports were inconsistent. However, sensitivity analyses that excluded those with inconsistent PHIV status yielded similar results. Information on use of in vitro fertilization or a previous history of preterm birth, both of which may affect preterm birth, was not comprehensively collected. Lastly, there may be selection bias given that this was a research cohort in a resource-rich setting where controlled monitoring and improved antenatal care were available. Despite these limitations, a substantial strength of this study is the large sample size of PHIV pregnant women, likely the largest yet published.

In conclusion, the lack of overall association between maternal PHIV status and preterm delivery or adverse infant BW outcomes in the United States is reassuring, though observed rates of these outcomes in PHIV and NPHIV women remain higher than those for the general United States population. Further studies in resource-constrained settings will be helpful in assessing the reproducibility of these findings as well as understanding how differences in antenatal care might affect pregnancy and infant outcomes of PHIV women worldwide. As growing numbers of women with PHIV become pregnant at different stages of adulthood, future studies may also be warranted to understand mechanisms underlying the association of maternal PHIV status with LBW in older pregnant women with HIV.

Notes

Author contributions. J. J. conceptualized the study, performed major literature searches, and wrote the manuscript. D. K. performed the data analysis and helped with significant revisions. P. W., M. G., K. P., E. L., and R. V. D. reviewed and revised the manuscript. R. S. and E. A. helped to conceptualize and made significant edits to the manuscript. A. B., S. B., N. C., and G. S. gave input on revisions.

Acknowledgments. We thank the children and families for their participation in PHACS and IMPAACT and the individuals and institutions involved in the conduct of PHACS and IMPAACT. Data management services were provided by Frontier Science and Technology Research Foundation (principal investigator: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc. (principal investigator: Julie Davidson).

Disclaimer. The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the NIH or U.S. Department of Health and Human Services. The funding source played no role in this study analysis, the interpretation of data, the writing of the report, or in the decision to submit the paper for publication

Financial support. J. J. is supported by NICHD (K23HD070760). PHACS is funded under cooperative agreements (HD052104, PHACS Coordinating Center, Tulane University School of Medicine; and HD052102, PHACS Data and Operations Center, Harvard T.H. Chan School of Public Health). IMPAACT is supported by NIAID (UM1AI068632, IMPAACT LOC, UM1AI068616, IMPAACT SDMC, and UM1AI106716, IMPAACT LC) with cofunding from NICHD and NIMH.

PHACS was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases (NIAID), the Office of AIDS Research, the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) and the Tulane University School of Medicine (HD052104). Overall support for the IMPAACT Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from NICHD and NIMH.

Potential conflicts of interest. E. J. A. has participated on advisory boards of Merck and ViiV Pharmaceuticals. E. G. L. holds financial stock in Merck Pharmaceuticals. All remaining authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Abrams EJ, Weedon J, Bertolli J, et al; New York City Pediatric Surveillance of Disease Consortium. Centers for Disease Control and Prevention. Aging cohort of perinatally human immunodeficiency virus-infected children in New York City. Pediatr Infect Dis J **2001**; 20:511–7.
2. UNAIDS 2013 AIDS by the numbers. Accessed at http://www.unaids.org/sites/default/files/media_asset/JC2571_AIDS_by_the_numbers_en_1.pdf on 29 October 2016. Geneva: UNAIDS.
3. Judd A, Lodwick R, Noguera-Julian A, et al. Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe. HIV Med **2017**; 18:171–80.
4. Van Dyke RB, Patel K, Kagan RM, et al; Pediatric HIV/AIDS Cohort Study. Antiretroviral drug resistance among children and youth in the United States with perinatal HIV. Clin Infect Dis **2016**; 63:133–7.
5. Huang S, Dunkley-Thompson J, Tang Y, et al. Deficiency of HIV-Gag-specific T cells in early childhood correlates with poor viral containment. J Immunol **2008**; 181:8103–11.
6. Slyker JA, John-Stewart GC, Dong T, et al. Phenotypic characterization of HIV-specific CD8+ T cells during early and chronic infant HIV-1 infection. PLoS One **2011**; 6:e20375.
7. Koenig LJ, Nesheim S, Abramowitz S. Adolescents with perinatally acquired HIV: emerging behavioral and health needs for long-term survivors. Curr Opin Obstet Gynecol **2011**; 23:321–7.
8. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. Am J Public Health **2007**; 97:1047–52.
9. Koenig LJ, Pals SL, Chandwani S, et al. Sexual transmission risk behavior of adolescents with HIV acquired perinatally or through risky behaviors. J Acquir Immune Defic Syndr **2010**; 55:380–90.
10. Kenny J, Williams B, Prime K, Tookey P, Foster C. Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV. HIV Med **2012**; 13:304–8.
11. Agwu AL, Jang SS, Korthuis PT, Araneta MR, Gebo KA. Pregnancy incidence and outcomes in vertically and behaviorally HIV-infected youth. JAMA **2011**; 305:468–70.
12. Jao J, Sigel KM, Chen KT, et al. Small for gestational age birth outcomes in pregnant women with perinatally acquired HIV. AIDS **2012**; 26:855–9.
13. Byrne L, Thorne C, Foster C, Tookey P. Pregnancy outcomes in women growing up with perinatally acquired HIV in the United Kingdom and Ireland. J Int AIDS Soc **2014**; 17:19693.
14. Chibber R, Khurranna A. Birth outcomes in perinatally HIV-infected adolescents and young adults in Manipur, India: a new frontier. Arch Gynecol Obstet **2005**; 271:127–31.
15. Williams SF, Keane-Tarchichi MH, Bettica L, Dieudonne A, Bardeguez AD. Pregnancy outcomes in young women with perinatally acquired human immunodeficiency virus-1. Am J Obstet Gynecol **2009**; 200:149 e1–5.
16. Hleyhel MDC, Tubiana R, Rouzioux C, et al. Pregnancies in Women who Acquired HIV Perinatally. Conference on Retroviruses and Opportunistic Infections. Seattle, USA, **2017**.
17. Phillips UK, Rosenberg MG, Dobroszycki J, et al. Pregnancy in women with perinatally acquired HIV-infection: outcomes and challenges. AIDS Care **2011**; 23:1076–82.
18. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med **1985**; 312:82–90.

19. Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al. CDC grand rounds: public health strategies to prevent preterm birth. Morb Mortal Wkly Rep **2016**; 65:826–30.
20. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics **2010**; 125:e214–24.
21. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. N Engl J Med **1996**; 335:1081–90.
22. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2014. Natl Vital Stat Rep **2015**; 64:1–64.
23. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis **2012**; 54:1348–60.
24. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS **2007**; 21:1019–26.
25. Badell ML, Kachikis A, Haddad LB, Nguyen ML, Lindsay M. Comparison of pregnancies between perinatally and sexually HIV-infected women: an observational study at an urban hospital. Infect Dis Obstet Gynecol **2013**; 2013:301763.
26. Cruz ML, Cardoso CA, João EC, et al. Pregnancy in HIV vertically infected adolescents and young women: a new generation of HIV-exposed infants. AIDS **2010**; 24:2727–31.
27. Lederman MM, Calabrese L, Funderburg NT, et al. Immunologic failure despite suppressive antiretroviral therapy is related to activation and turnover of memory CD4 cells. J Infect Dis **2011**; 204:1217–26.
28. Molina-Pinelo S, Vallejo A, Díaz L, et al. Premature immunosenescence in HIV-infected patients on highly active antiretroviral therapy with low-level CD4 T cell repopulation. J Antimicrob Chemother **2009**; 64:579–88.
29. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med **2011**; 62:141–55.
30. Aberg JA. Aging, inflammation, and HIV infection. Top Antivir Med **2012**; 20:101–5.
31. Khoshnood B, Wall S, Lee KS. Risk of low birth weight associated with advanced maternal age among four ethnic groups in the United States. Matern Child Health J **2005**; 9:3–9.
32. Huang L, Sauve R, Birkett N, Fergusson D, van Walraven C. Maternal age and risk of stillbirth: a systematic review. CMAJ **2008**; 178:165–72.
33. Goldenberg RL, Culhane JF. Low birth weight in the United States. Am J Clin Nutr **2007**; 85:584–90S.

APPENDIX

The following institutions, clinical site investigators, and staff participated in conducting PHACS SMARTT in 2015, in alphabetical order: Ann & Robert H. Lurie Children's Hospital of Chicago: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; Baylor College of Medicine: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris; Bronx Lebanon Hospital Center: Murli Purswani, Emma Stuard, Anna Cintron; Children's Diagnostic & Treatment Center: Ana Puga, Dia Cooley, Patricia A. Garvie, James Blood; New York University School of Medicine: William Borkowsky, Sandra Deygoo, Marsha Vasserman; Rutgers–New Jersey Medical School: Arry Dieudonne, Linda Bettica; St. Jude Children's Research Hospital: Katherine Knapp, Kim Allison, Megan Wilkins; San Juan Hospital/Department of Pediatrics: Midnela Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; SUNY Downstate Medical Center: Stephan Kohlhoff, Ava Dennie, Susan Bewley; Tulane University School of Medicine: Russell Van Dyke, Karen Craig, Patricia Sirois; University of Alabama, Birmingham: Marilyn Crain, Paige Hickman, Dan Marullo; University of California, San Diego: Stephen A. Spector, Kim Norris, Sharon Nichols; University of Colorado, Denver: Elizabeth McFarland, Carrie Chambers, Jenna Wallace, Emily Barr; University of Florida, Center for HIV/AIDS Research, Education and Service: Mobeen Rathore, Kristi Stowers, Saniyyah Mahmoudi, Ann Usitalo; University of Illinois, Chicago: Karen Hayani, Kenneth Rich, Lourdes Richardson, Renee Smith; University of Miami: Charles Mitchell, Sady Dominguez, Claudia Florez; University of Southern California: Toni Frederick, Mariam Davtyan, Guadalupe Morales-Avendano; University of Puerto Rico School of Medicine, Medical Science Campus: Zoe M. Rodriguez, Ibet Heyer, Nydia Scalley Trifilio.

The following institutions, clinical site investigators, and staff participated in conducting the IMPAACT P1025 study: G. B. Scott, University of Miami School of Medicine; R. Tuomala, Brigham and Women's Hospital; E. Smith, National Institute of Allergy and Infectious Diseases Division of AIDS, Pediatric Medicine Branch; H. Watts, National Institute of Child Health and Human Development, Maternal and Pediatric Infectious Disease Branch; K. M. Oden, International Maternal Pediatric Adolescent AIDS Clinical Trials Group; Y. Huo, Harvard School of Public Health; K. Patel, Harvard School of Public Health; E. A. Barr, University of Colorado Denver, the Children's Hospital; A. Bardeguez, University of Medicine & Dentistry of New Jersey; S. K. Burchett, Harvard Medical School; E. Livingston, Duke University Medical Center; A. M. Stek, Keck School of Medicine, University of Southern California,; M. T. Basar, A. Hernandez, and A. Jennings, Frontier Science & Technology Research Foundation, Inc.; T. R. Cressey, Program for HIV Prevention & Treatment, Chang Mai, Thailand; and J. Bryant, Westat.

Participating sites and site personnel for IMPAACT P1025 include the following: Ruth Tuomala, Brigham and Women's Hospital; Elizabeth Smith, National Institute of Allergy and Infectious Diseases Division of AIDS, Pediatric Medicine Branch; KaSaundra M. Oden, International Maternal Pediatric Adolescent AIDS Clinical Trials Group; Deborah Kacanek, Erin Leister, and David E. Shapiro, Harvard School of Public Health; Emily A. Barr, University of Colorado Denver, the Children's Hospital; Diane W. Wara, University of California at San Francisco; Arlene Bardeguez, University of Medicine & Dentistry of New Jersey; Sandra K. Burchett, Harvard Medical School; Jenny Guiterrez, Bronx-Lebanon Hospital; Kathleen Malee, Ann and Robert H. Lurie Children's Hospital of Chicago; Alice M. Stek, Keck School of Medicine, University of Southern California; Patricia Tanjutco, Washington Hospital Center; Yvonne Bryson, David Geffen School of Medicine, University of California; Michael T. Basar, Adriane Hernandez, and Amy Jennings, Frontier Science & Technology Research Foundation, Inc.; Tim R. Cressey, Program for HIV Prevention & Treatment, Chang Mai, Thailand; Jennifer Bryant, Westat.

Obstetrics site support: 2802 NJ Medical School CRS (Arlene D. Bardeguez, Linda Bettica, Charmane Calilap-Bernardo); 3601 UCLA-Los Angeles/Brazil AIDS Consortium (LABAC) CRS; 3801 Texas Children's Hospital CRS; 4001 Chicago Children's

CRS; 4101 Columbia IMPAACT CRS (Alice Higgins, Gina Silva, Sreedhar Gaddipati); 4201 University of Miami Pediatric/Perinatal HIV/AIDS CRS; 4601 UCSD Maternal, Child, and Adolescent HIV CRS (Stephen A. Spector, Andrew Hull, Mary Caffery, Jean Manning); 4701 DUMC Pediatric CRS (Elizabeth Livingston, Margaret Donnelly, Joan Wilson, Julia Giner); 5003 Metropolitan Hospital NICHD CRS; 5009 Children's Hospital of Boston NICHD CRS (Nancy Karthas, Lisa Tucker, Arlene Buck, Catherine Kneut); 5011 Boston Medical Center Pediatric HIV Program NICHD CRS; 5012 NYU NY NICHD CRS (Sandra Deygoo, Aditya Kaul, Maryam Minter, Siham Akleh, supported in part by grant UL1 TR000038 from the National Center for the Advancement of Translational Science (NCATS), National Institutes of Health); 5013 Jacobi Medical Center Bronx NICHD CRS; 5015 Children's National Medical Center Washington DC NICHD CRS; 5017 Seattle Children's Hospital CRS (Amanda Robson, Jane Hitti, Corry Venema-Weiss, Anna Klastorin); 5018 University of South Florida, Tampa NICHD CRS (Karen L. Bruder, Gail Lewis, Denise Casey); 5023 Washington Hospital Center NICHD CRS (Sara Parker, Rachel Scott, Patricia Tanjutco, Vanessa Emmanuel); 5031 San Juan City Hospital PR NICHD CRS (Antonio Mimoso, Rodrigo Diaz, Elvia Perez, Olga Pereira); 5040 SUNY Stony Brook NICHD CRS (Jennifer Griffin, Paul Ogburn); 5041 Children's Hospital of Michigan NICHD CRS; 5044 Howard University Washington DC NICHD CRS; 5045 Harbor UCLA Medical Center NICHD CRS; 5048 University of Southern California, LA NICHD CRS (Alice Stek, Francoise Kramer, LaShonda Spencer, Andrea Kovacs); 5051 University of Florida College of Medicine, Jacksonville NICHD CRS (Mobeen Rathore, Isaac Delke, Geri Thomas, Barbara Millwood); 5052 University of Colorado, Denver NICHD CRS (Alisa Katai, Tara Kennedy, Kay Kinzie, Jenna Wallace, supported by NIH/NCATS Colorado CTSI Grant Number UL1 TR000154); 5055 South Florida CDC, Ft Lauderdale NICHD CRS; 5083 Rush University Cook County Hospital, Chicago NICHD CRS (Julie Schmidt, Helen Cejtin, Maureen McNichols, Judith Senka); 5091 University of California, San Francisco NICHD CRS (Deborah Cohan; This publication was supported by NIH/NCRR UCSF-CTSI Grant Number UL1 RR024131. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH); 5092 Johns Hopkins University, Baltimore NCHD CRS (Jean Anderson, Eileen Sheridan-Malone); 5093 Miller Children's Hospital Long Beach, CA NICHD CRS (Chritina Tolentino-Balbridge, Janielle Jackson-Alvarez, David Michalik, Jagmohan S. Batra); 5094 University of Maryland Baltimore NICHD CRS (Douglas Watson, Maria Johnson, Corinda Hilyard); 5095 Tulane University, New Orleans NICHD CRS (Robert Maupin, Chi Dola, Yvette Luster, Sheila Bradford); 5096 University of Alabama Birmingham NICHD CRS (Alan Tita, Micky Parks, Sharan Robbins); 6501 St. Jude/UTHSC CRS (Edwin Thorpe, Jr., Katherine Knapp, Pamela Finnie, Nina Sublette); 6601 University of Puerto Rico Pediatric HIV/AIDS Research Program CRS (Carmen D. Zorrilla, Vivian Tamayo-Agrait); 6701 the Children's Hospital of Philadelphia IMPAACT CRS; 6901 Bronx-Lebanon Hospital IMPAACT CRS (Rodney Wright); 7301 WNE Maternal Pediatric Adolescent AIDS CRS (Sharon Cormier, Katherine Luzuriaga, supported by CTSA Grant Number: 8UL1TR000161).