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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

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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,

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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.

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APPENDIX

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