MAJOR ARTICLE

Highly Active Antiretroviral Therapy and Adverse Birth Outcomes Among HIV-Infected Women in Botswana

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Background. It is unknown whether adverse birth outcomes are associated with maternal highly active antiretroviral therapy (HAART) in pregnancy, particularly in resource-limited settings.

Methods. We abstracted obstetrical records at 6 sites in Botswana for 24 months. Outcomes included stillbirths (SBs), preterm delivery (PTD), small for gestational age (SGA), and neonatal death (NND). Among human immunodeficiency virus (HIV)–infected women, comparisons were limited to HAART exposure status at conception, and those with similar opportunities for outcomes. Comparisons were adjusted for $CD4^+$ lymphocyte cell count.

Results. Of 33 148 women, 32 113 (97%) were tested for HIV, of whom 9504 (30%) were HIV infected. Maternal HIV was significantly associated with SB, PTD, SGA, and NND. Compared with all other HIV-infected women, those continuing HAART from before pregnancy had higher odds of PTD (adjusted odds ratio [AOR], 1.2; 95% confidence interval [CI], 1.1, 1.4), SGA (AOR, 1.8; 95% CI, 1.6, 2.1) and SB (AOR, 1.5; 95% CI, 1.2, 1.8). Among women initiating antiretroviral therapy in pregnancy, HAART use (vs zidovudine) was associated with higher odds of PTD (AOR, 1.4; 95% CI, 1.2, 1.8), SGA (AOR, 1.5; 95% CI, 1.2, 1.9), and SB (AOR, 2.5; 95% CI, 1.6, 3.9). Low $CD4^+$ was independently associated with SB and SGA, and maternal hypertension during pregnancy with PTD, SGA, and SB.

Conclusions. HAART receipt during pregnancy was associated with increased PTD, SGA, and SB.

Maternal human immunodeficiency virus (HIV) infection has been associated with adverse birth outcomes [1–10], but it remains unclear whether the use of highly active antiretroviral therapy (HAART) contributes to this risk. Observational studies in both developed and developing countries have reported conflicting evidence on the association between HAART exposure and preterm delivery (PTD), low birth weight, and stillbirth (SB) [10–22] and on the association between protease inhibitors and PTD [11, 13, 14, 16, 17, 23, 24].

Conflicting data from past studies may be related to differential handling of noncomparable exposure groups and lack of power to detect modest effect sizes. In an attempt to overcome these limitations, we performed the largest surveillance study to date among HIV-infected women in the HAART era and restricted analyses to comparable exposure groups.

METHODS

Study Population

Approval was granted by human subjects committees in Botswana and at the Harvard School of Public

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Health. We included all women who delivered live births or stillbirths at a gestational age ≥20 weeks at 6 government facilities in Botswana. Surveillance occurred at Princess Marina Hospital (PMH) in Gaborone, Scottish Livingstone Hospital (SLH) in Molepolole, Deborah Retief Memorial Hospital (DRM) in Mochudi, Nyangabgwe Hospital (NH) in Francistown, Letsholathebe Memorial Hospital (LMH) in Maun, and Gantsi Primary Hospital (GPH) in Gantsi. These public hospitals were selected for geographic diversity and inclusion of primary and tertiary levels of obstetrical care (PMH and NH are referral hospitals for obstetric complications in southern and northern Botswana, respectively). Surveillance began on 1 May 2009 at PMH in Gaborone and between 1 October and 1 November 2009 at the remaining 5 sites, and continued through 30 April 2011. We reviewed obstetric records upon discharge from each maternity ward. In the event of multiple gestations, the outcome of the first-born infant was recorded.

The Botswana Ministry of Health recommends routine ("opt-out") HIV testing in pregnancy and prioritization of $CD4^+$ lymphocyte cell count testing for HIV-infected pregnant women not yet on HAART [25]. During the study period, HIV-infected women with $CD4^+$ counts<250 cells/μL or World Health Organization clinical stage 3 or 4 conditions were eligible to initiate HAART during pregnancy for maternal treatment. Women already receiving HAART at conception were advised to continue during pregnancy. In most cases, HAART consisted of nevirapine (NVP) plus zidovudine (ZDV) and lamivudine (3TC). Women not receiving HAART were eligible for ZDV monotherapy for the prevention of mother-to-child HIV transmission (PMTCT). Beginning in October 2009, a limited number of HIV-infected women with $CD4^+$ counts >250 cells/μL had access to HAART for PMTCT through a pilot Botswana government program. During the study period, this program was initiated at SLH, with 89 (24.8%) of 359 eligible women enrolled. The program also had a minor impact at other sites, with <5% of eligible women receiving HAART for PMTCT. The regimen provided through this program was usually lopinavir/ritonavir (LPV/r) plus ZDV/3TC.

Data Extraction

The information abstracted from obstetric records included maternal demographics, medical history, laboratory values measured in pregnancy (hemoglobin and rapid plasma reagin, a test to detect syphilis infection), vital signs, HIV status and antiretroviral (ARV) history, and birth outcomes. We defined anemia during pregnancy as a recorded hemoglobin ≤10 g/dL. Maternal hypertension in pregnancy was defined as a systolic blood pressure measurement >140 mmHg or a diastolic measurement >90 mmHg at any visit before labor, admission to hospital for hypertension, delivery complicated by hypertension, or induction for preeclampsia. We extracted estimated gestational age at delivery from obstetric records. For most pregnancies in Botswana, estimated date of delivery is based on date of last menstrual period alone. However, if the date is uncertain or discordant with fundal measurements, gestational age is estimated using ultrasonography.

For HIV-infected women, the date of HIV diagnosis, up to 2 $CD4^+$ cell counts in pregnancy, and details of antiretroviral therapy were extracted from the records. A hospital database was searched to locate unrecorded $CD4^+$ results. We used the most recent $CD4^+$ cell count in all analyses. Antiretroviral use during pregnancy was classified as HAART continued from before the current pregnancy, HAART initiated during pregnancy, ZDV monotherapy, or no antiretroviral drugs received prior to delivery. HAART was defined as 3 or more antiretroviral drugs. In the event that an antiretroviral regimen changed during pregnancy, the last regimen was utilized in the analyses. We excluded interventions given during labor, such as zidovudine or single-dose nevirapine, in analyses.

Outcome Definitions and Statistical Analysis

The primary birth outcomes were SB, PTD, and small for gestational age (SGA). SB was defined as fetal death with an Apgar score of 0; preterm delivery as delivery <37 weeks gestation; and SGA as below the 10th percentile of birth weight by gestational age using norms created from infants born to HIV-uninfected women in Botswana [26]. Because accurate norms were not available for deliveries before 26 weeks and after 40 weeks gestation, these deliveries were excluded from the outcome SGA. We also evaluated neonatal death (NND), defined as death during the same hospitalization and within 28 days of a live delivery.

Statistical analyses were performed using SAS, version 9.3 software (SAS Institute, Cary, NC). All reported *P* values are based on 2-sided tests. Unadjusted and adjusted logistic regression analyses of HIV-infected versus HIV-uninfected women were performed for SB, PTD, SGA, and NND. Adjusted analyses were performed using stepwise selection for logistic regression analyses, and covariates with a significance level ≤0.05 were included in the model.

Among HIV-infected women, we also used stepwise selection for logistic regression modeling. We included $CD4^+$ cell count (categorized as presence of $CD4^+$ count in pregnancy ≤200 cells/μL, >200 cells/μL, or unknown) in all models, in an attempt to account for confounding by indication. We first compared women who continued HAART from before pregnancy with all other HIV-infected women, to allow for evaluation of early events (beginning at first antenatal visit) for all women. We next compared women who initiated HAART or ZDV monotherapy during pregnancy by 34 weeks gestation, restricting comparisons to events ≥34 weeks gestation to allow for similar ARV exposure times for each group. Finally, we compared rates of SGA infants among women who

Table 1. Risks of Adverse Birth Outcomes Among HIV-Infected Women As Compared With HIV-Uninfected Women

Adverse Birth Outcome	Total (%) (N = 33 148)	HIV+ (%) (N = 9504)	HIV– (%) (N = 22 609)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Stillbirth	1080 (3.3)	437 (4.6)	564 (2.5)	1.9 (1.7–2.1)	1.5 (1.3–1.7)
Preterm delivery	6285 (19.6)	2144 (23.7)	3797 (17.2)	1.5 (1.4–1.6)	1.3 (1.3–1.4)
Small for gestational age[b]	4404 (13.5)	1721 (18.4)	2565 (11.5)	1.7 (1.6–1.9)	1.8 (1.7–1.9)
Neonatal death[b]	613 (1.9)	205 (2.3)	339 (1.5)	1.5 (1.2–1.8)	1.4 (1.2–1.7)
Congenital anomalies	826 (2.5)	215 (2.3)	568 (2.5)	.9 (.8–1.1)	0.9 (0.8–1.1)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a] Stepwise selection was utilized for the logistic regression analyses, and covariates with a significance level ≤0.05 were included in the model. Additional risk factors for stillbirth and small for gestational age in multivariate analysis were advanced maternal age, nulliparity, maternal hypertension in pregnancy, and anemia. Maternal hypertension and anemia were significantly associated with preterm delivery; and maternal hypertension, highest level of education received (primary or no education compared to secondary or tertiary level), and positive rapid plasma reagin during pregnancy were significantly associated with neonatal death.

[b] Maximum sample size available illustrated in each column; for the birth outcome small for gestational age, missing values were recorded for up to 1% of the total sample size. For the outcome neonatal death, missing values were recorded for up to 3% of the total sample size.

continued HAART from before pregnancy with those who initiated HAART during pregnancy. We directly compared rates of SGA between these groups (but not other birth outcomes) because women in each group had similar opportunity to experience the outcome SGA. Because of the limited number of events and the potential for multiple interactions between SGA, PTD, and NND, logistic regression modeling was not performed for the outcome NND.

RESULTS

From 1 May 2009 through 30 April 2011, 33 148 birth outcomes occurred at the 6 study sites: 13 181 (40%) at PMH, 4103 (12%) at SLH, 2967 (9%) at DRM, 7293 (22%) at NH, 4221 (13%) at LMH, and 1383 (4%) at GPH. These deliveries comprised at least one-third of all births in Botswana during the study period [25].

Data on HIV status and birth outcomes are shown in Table 1. Of the 33 148 women included, 32 113 women (96.9%) had a known HIV status, of whom 9504 (29.6%) were HIV infected. Some differences were noted by maternity site, with HIV prevalence ranging from a high of 34% at NH to a low of 23% at GPH. HIV-infected women experienced significantly higher rates of all adverse birth outcomes, including SB, PTD, SGA, and NND. In adjusted analysis, maternal HIV infection remained significantly associated with an increased risk for SB (adjusted odds ratio [AOR], 1.5; 95% confidence interval [CI], 1.3, 1.7); PTD (AOR, 1.3; 95% CI, 1.3, 1.4), SGA infants (AOR, 1.8; 95% CI, 1.7, 1.9), and NND (AOR, 1.4; 95% CI, 1.2, 1.7) among HIV-infected women compared with HIV-uninfected women. We did not detect an association between maternal HIV infection and congenital anomalies.

Of 9504 HIV-infected women, 9149 (96%) had a known initiation date for antiretroviral drugs received during pregnancy; 2189 (24%) continued HAART from before pregnancy, 1101 (12%) initiated HAART during pregnancy, 4625 (51%) initiated ZDV monotherapy during pregnancy, and 1234 (13%) received no antiretroviral drugs. Maternal characteristics are shown according to antiretroviral drugs received in pregnancy in Table 2.

$CD4^+$ cell count in pregnancy was available for 4492 (49%) women, and rates of $CD4^+$ cell count testing varied significantly according to antiretroviral drugs received in pregnancy (24% among those who continued HAART, 70% among those who initiated HAART, 62% among those starting ZDV, and 20% among those who received no antiretroviral drugs). The overall median $CD4^+$ cell count was 388 cells/μL, and differed by antiretroviral drugs received in pregnancy (Table 2). Among women receiving HAART during pregnancy, 2851 (87%) were noted to have received NVP/ZDV/3TC or did not have a regimen specified (and considered likely to have received NVP/ZDV/3TC), and 312 (9%) were noted to have received LPV/r/ZDV/3TC (34 from conception, and 278 started in pregnancy). Median $CD4^+$ cell count for those receiving LPV/r/ZDV/3TC was 458 cells/μL. Among the women initiating antiretroviral drugs during pregnancy, the median gestational age of HAART initiation was 25 weeks; first–third quartile (Q1–Q3) 20–29 weeks. The median age of ZDV initiation was 29 weeks (Q1–Q3, 28–31).

Among HIV-infected women, the overall rate of PTD was 24% and the median gestational age for PTD was 34 weeks (Q1–Q3, 32–36). Compared with all other HIV-infected pregnant women, HAART exposure from before pregnancy was significantly associated with PTD (AOR, 1.2; 95% CI, 1.1, 1.4) (Table 3). Compared with women initiating ZDV in pregnancy, initiating HAART in pregnancy was also significantly associated with increased odds of PTD (AOR, 1.4; 95% CI, 1.2, 1.8). Additional risk factors for PTD among HIV-infected women

Table 2. Characteristics of HIV-Infected Women by Antiretroviral Therapy Received During Pregnancy

Variable	Continued HAART (N = 2189)	Initiated HAART (N = 1101)	Initiated ZDV (N = 4625)	No ART Received (N = 1234)	Continued HAART vs Others[a] *P* Value	Initiated HAART vs Initiated ZDV[b] *P* Value
Median age (Q1–Q3)	32 (29–36)	29 (25–33)	27 (23–31)	27 (24–32)	<.0001[c]	<.0001[c]
Marital status						
Single/widowed/ divorced	1803 (82.4)	959 (87.3)	4171 (90.4)	959 (77.8)	<.0001	.0004
Married	320 (14.6)	113 (10.3)	329 (7.1)	203 (16.5)		
Unknown	66 (3.0)	28 (2.6)	125 (2.7)	72 (5.8)		
Nationality						
Botswana	2159 (98.6)	1078 (97.9)	4478 (96.8)	793 (64.3)	<.0001	.09
Other	28 (1.3)	23 (2.1)	140 (3.0)	429 (34.8)		
Unknown	2 (0.1)	0 (0)	7 (0.2)	12 (1.0)		
Educational status[d]						
None/primary	503 (23)	156 (14.1)	677 (14.6)	204 (16.5)	<.0001	.64
Secondary/tertiary	1569 (71.7)	899 (81.7)	3728 (80.6)	883 (71.5)		
Unknown	117 (5.3)	46 (4.2)	220 (4.8)	147 (11.9)		
Occupation						
Unemployed	1093 (50)	552 (50.1)	2649 (57.3)	706 (57.2)	<.0001	<.0001
Employed	914 (41.8)	455 (41.3)	1576 (34.1)	327 (26.5)		
Unknown	181 (8.3)	94 (8.5)	399 (8.6)	201 (16.3)		
Parity[e]						
0	33 (1.5)	33 (3.0)	157 (3.4)	41 (3.3)	<.0001	.41
1	552 (25.2)	324 (29.4)	1397 (30.2)	396 (32.1)		
>1	1475 (67.4)	521 (47.3)	2030 (43.9)	570 (46.2)		
Unknown	129 (5.9)	223 (20.3)	1041 (22.5)	227 (18.4)		
History of past adverse outcome[f]						
Yes	393 (18.0)	148 (13.4)	474 (10.2)	142 (11.5)	<.0001	.03
No	1084 (49.5)	520 (47.2)	2102 (45.4)	505 (40.9)		
Unknown	679 (31.0)	400 (36.3)	1892 (40.9)	546 (44.3)		
Not applicable	33 (1.5)	33 (3.0)	157 (3.4)	41 (3.3)		
Received antenatal care						
Yes	2130 (97.3)	1094 (99.4)	4571 (98.8)	946 (76.7)	<.0001	.12
No	59 (2.7)	7 (0.6)	54 (1.2)	288 (23.3)		
Positive RPR[g]						
Yes	36 (1.6)	21 (1.9)	76 (1.6)	18 (1.5)	.98	.54
No or unknown	2153 (98.3)	1080 (98.1)	4549 (98.4)	1216 (98.5)	348 (98.0)	
Alcohol use[h]						
Yes	77 (3.5)	76 (6.9)	289 (6.2)	42 (3.4)	<.0001	.42
No or unknown	2112 (95.6)	1025 (93.1)	4336 (93.8)	1192 (96.6)		
Smoking[h]						
Yes	44 (2.0)	20 (1.8)	85 (1.8)	12 (1.0)	.31	.96
No or unknown	2145 (98.0)	1081 (98.2)	4540 (98.2)	1222 (99.0)		
Median $CD4^+$ count (cells/μL) (Q1–Q3)	384 (275–512)	225 (163–359)	428 (319–572)	341 (209–539)	.33[c]	<.0001[c]
$CD4^+$ count ≤200 cells/μL						
Yes	51 (2.3)	304 (27.6)	143 (3.1)	55 (4.5)	.04	<.0001
No	468 (21.4)	471 (42.8)	2712 (58.6)	187 (15.2)		

Table 2 continued.

Variable	Continued HAART (N = 2189)	Initiated HAART (N = 1101)	Initiated ZDV (N = 4625)	No ART Received (N = 1234)	Continued HAART vs Others[a]	Initiated HAART vs Initiated ZDV[b]
					P Value	*P* Value
Unknown	1670 (76%)	326 (30%)	1770 (38%)	992 (80%)		

P value from χ^2 test unless otherwise specified.

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; Q1–Q3, first–third quartile; RPR, rapid plasma reagin; ZDV, zidovudine.

[a] Continued HAART versus others: Women who continued HAART from before pregnancy were compared with all other HIV-infected women, including those who initiated ZDV, HAART, or no antiretroviral drugs during pregnancy.

[b] HAART initiation versus ZDV Initiation: *P* values are for all women in each exposure category, regardless of timing of initiation of antiretroviral drugs or gestational age at delivery. When restricting comparisons to those who initiated antiretroviral drugs by 34 weeks gestation and delivered at ≥34 weeks gestation, we did not observe significant changes in *P* values from those listed.

[c] *P* value from Wilcoxon rank sum test.

[d] Highest level of education received was recorded, and included none, primary, secondary, or tertiary school.

[e] Parity defined as number of prior deliveries, and was categorized as 0, 1, and >1. When we compared women who continued HAART from before pregnancy with all other HIV-infected women, and women who initiated HAART with those who initiated ZDV, the variable parity was further categorized as 0 versus ≥1.

[f] Past adverse pregnancy outcome defined as past stillbirth, preterm delivery, very preterm delivery, or low birth weight infant. The category "Not applicable" refers to women who were nulliparous (defined as parity = 0).

[g] Positive RPR, a test to detect syphilis infection. Of note, 89% of women received at least 1 RPR test during pregnancy.

[h] Alcohol use and smoking during pregnancy were self-reported. Quantity, duration, and frequency of use were not recorded.

in multivariate analysis are shown in Table 3, and include maternal hypertension during pregnancy and anemia.

The rate of SGA among HIV-infected pregnant women was 18%, and the median gestational age of women with an SGA infant was 39 weeks (Q1–Q3, 36–40). Compared with all other HIV-infected women, continuing HAART from before pregnancy was associated with increased odds of having an SGA infant (AOR, 1.8; 95% CI, 1.6, 2.1) (Table 4). Compared with ZDV initiation, HAART initiation during pregnancy was also associated with an increased rate of delivering SGA infants (AOR, 1.5; 95% CI, 1.2, 1.9). When we compared women who continued HAART with those who initiated HAART, the former experienced a higher percentage of SGA infants (AOR, 1.3; 95% CI, 1.0, 1.5). Among all HIV-infected women, $CD4^+$ count ≤200 cells/μL and maternal hypertension were significantly associated with SGA infants.

We observed an SB rate of 5% among HIV-infected pregnant women at a median gestational age of 32 weeks (Q1–Q3, 28–37). Compared with all other HIV-infected pregnant women, continuing HAART from before pregnancy was associated with higher odds of SB (AOR, 1.5; 95% CI, 1.2, 1.8) (Table 5). Compared with women who initiated ZDV, initiating HAART was also associated with an increased risk of SB (AOR, 2.5; 95% CI, 1.6, 3.9). Additional risk factors were $CD4^+$ count ≤200 cells/μL and maternal hypertension.

Neonatal death occurred among 2.3% of infants born to HIV-infected women, and the median gestational age was 30 weeks (Q1–Q3, 26–37). Preterm babies experienced a significantly higher rate of NND compared with those born at term (7% vs 0.8%; $P < .0001$), as did SGA infants compared with those appropriate for gestational age (3.5% vs 1.5%; $P < .0001$). However, we did not observe significant differences in NND when we compared women who continued HAART from before pregnancy with all other HIV-infected women (2.0% vs 2.3%; $P = .41$) in univariate analysis. Women who initiated HAART experienced a higher rate of NND compared with those who initiated ZDV during pregnancy (1.9% vs. 0.8%; $P = .002$). In univariate analysis, additional risk factors for NND included maternal hypertension (3.2% vs 1.7%; $P = .0002$), but not maternal $CD4^+$ count ≤200 cells/μL (2.0% vs 1.8%; $P = .71$).

Additional Analyses

Sensitivity analyses were performed for multiple gestation and for $CD4^+$ cell count. There were 489 (1.5%) women with multiple gestation, and they were significantly more likely to experience PTD, SGA, and SB. When they were excluded from the analyses, we did not observe changes in the study findings. We also performed sensitivity analyses among only HIV-infected women with a recorded $CD4^+$ cell count (included as a continuous variable) in all logistic regression models; this limited the number included in the models but did not significantly change the magnitude or direction of associations (data not shown). In addition, we stratified analyses by women with $CD4^+$ cell count above and below 200 cells/μL. There were no differences in the direction of each association in these analyses, and we found the greatest magnitude of association between adverse outcomes and either continuing HAART or

Table 3. Univariate and Multivariate Odds Ratios for Preterm Delivery Among HIV-Infected Women

Risk Factor	Number of PTD (%)	Unadjusted OR (95% CI)[a]	Continued HAART vs Others (N = 8725) Adjusted OR (95% CI)[b]	HAART Initiation vs ZDV Initiation (N = 4653) Adjusted OR (95% CI)[c]
Marital status				
Single/widowed/divorced	1861/7813 (23.8)	1.4 (1.2–1.6)	1.4 (1.2–1.7)	1.3 (.9–1.9)
Married	176/955 (18.4)			
Educational status[d]				
None or primary	412/1540 (26.8)	1.2 (1.1–1.4)	1.2 (1.0–1.3)	.8 (.7–1.1)
Secondary or tertiary	1583/6992 (22.6)			
History of past adverse outcome[e]				
Yes	359/1125 (31.9)	1.7 (1.5–2.0)	1.6 (1.4–1.9)	1.4 (1.1–1.8)
No	901/4167 (21.6)			
Smoking				
Yes	52/158 (32.9)	1.6 (1.1–2.2)	1.4 (1.0–2.1)	1.8 (1.0–3.0)
No or unknown	2092/8907 (23.5)			
Maternal hypertension in pregnancy[f]				
Yes	405/1516 (26.7)	1.3 (1.2–1.5)	1.4 (1.2–1.5)	1.2 (.9–1.4)
No	1512/7087 (21.3)			
Anemia in pregnancy[g]				
Yes	682/3004 (22.7)	5.8 (4.7–7.2)	…	4.1 (3.0–5.7)
No	102/2128 (4.8)			
$CD4^+$ cell count ≤200 μL				
Yes	110/549 (20.0)	1.1 (.9–1.3)	1.1 (.9–1.4)	1.0 (.7–1.3)
No	714/3768 (18.9)			
Unknown	1320/4748 (27.8)			
Continued HAART in pregnancy[b]				
Continued HAART	543/2050 (26.5)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	…
All others	1515/6676 (22.7)			
Initiated HAART in pregnancy[c]				
Initiated HAART	177/892 (19.8)	1.5 (1.2–1.8)	…	1.4 (1.2–1.8)
Initiated ZDV	533/3762 (14.2)			

Stepwise selection was utilized for the logistic regression analyses, and covariates with a significance level ≤0.05 and $CD4^+$ cell count were included in the model. Anemia was excluded from analyses that included women who continued HAART from before pregnancy, because hemoglobin was measured after women started HAART.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTD, preterm delivery; RPR, rapid plasma regain; ZDV, zidovudine.

[a] Unadjusted ORs were estimated among all HIV-infected women whom had a known initiation date for antiretroviral drugs received during pregnancy and whom had information recorded for the variable of interest.

[b] Continued HAART versus all others: Women who continued HAART from before pregnancy were compared with all other HIV-infected women, including those who initiated ZDV, HAART, or no antiretroviral drugs during pregnancy.

[c] HAART initiation versus ZDV initiation: Women who initiated HAART were compared with women who initiated ZDV, including only those who initiated antiretroviral drugs by 34 weeks gestation and had birth outcomes ≥34 weeks gestation. Unadjusted ORs were estimated among this subset, but are not shown.

[d] Highest level of education received was recorded, and included none, primary, secondary, or tertiary school.

[e] Past adverse pregnancy outcome defined as past stillbirth, preterm delivery, very preterm delivery, or low birth weight infant.

[f] Maternal hypertension defined as a blood pressure measurement of more than 140/90 mmHg at any visit before labor, admission to the hospital for hypertension, delivery complicated by hypertension, or induction for preeclampsia.

[g] Anemia during pregnancy was defined as presence of recorded hemoglobin value of 10 g/dL or less, and was measured at the first antenatal visit.

starting HAART in pregnancy among women with $CD4^+$ count >200 cells/μL (data not shown).

We also evaluated associations between PI-based HAART and PTD, and the duration of HAART exposure and all outcomes. Of 48 women who continued PI-based HAART from before pregnancy, 20 (42%) experienced PTD compared with 522 (26%) of 1998 women who continued a non-PI-based HAART regimen (OR, 2.0; 95% CI, 1.1, 3.6). Of 178 women initiating PI-based HAART, 44 (25%) experienced PTD compared with 131 (20%) of 654 initiating a non-PI-based

Table 4. Univariate and Multivariate Odds Ratios for Small for Gestational Age Infants Among HIV-Infected Women

Risk Factor	Number of SGA (%)	Unadjusted OR[a] (95% CI)	Continued HAART vs Others (N = 8991) Adjusted OR (95% CI)[b]	HAART Initiation vs ZDV Initiation (N = 4740) Adjusted OR (95% CI)[c]	Continued HAART vs Initiated HAART (N = 3246) Adjusted OR (95% CI)[d]
History of past adverse outcome[e]					
Yes	284/1175 (24.2)	1.6 (1.4–1.9)	1.5 (1.3–1.7)	1.5 (1.1–1.9)	1.3 (1.0–1.6)
No	708/4297 (16.5)				
History of TB[f]					
Yes	67/267 (25.1)	1.5 (1.1–2.0)	1.2 (.9–1.7)	1.9 (1.2–3.1)	1.4 (.9–2.0)
No	1585/8711 (18.2)				
Alcohol use					
Yes	108/494 (21.9)	1.3 (1.0–1.6)	1.4 (1.1–1.7)	1.4 (1.0–1.8)	1.4 (1.0–2.1)
No or unknown	1613/8847 (18.2)				
Maternal hypertension in pregnancy[g]					
Yes	422/1638 (25.8)	1.7 (1.5–1.9)	1.7 (1.5–1.9)	1.4 (1.1–1.7)	1.9 (1.6–2.3)
No	1228/7252 (16.9)				
Anemia in pregnancy[h]					
Yes	572/3085 (18.5)	1.1 (1.0–1.3)	…	1.3 (1.1–1.6)	…
No	365/2168 (16.8)				
$CD4^+$ cell count ≤200 μL					
Yes	134/573 (23.4)	1.6 (1.3–2.0)	1.7 (1.4–2.1)	1.6 (1.2–2.1)	1.2 (.9–1.6)
No	615/3864 (15.9)				
Unknown	972/4904 (19.8)				
Continued HAART in pregnancy[b]					
Continued HAART	562/2151 (26.1)	1.9 (1.7–2.1)	1.8 (1.6–2.1)	…	…
All others	1067/6840 (15.6)				
Initiated HAART in pregnancy[c]	200/930 (21.5)	1.7 (1.4–2.0)	…	1.5 (1.2–1.9)	…
Initiated HAART					
Initiated ZDV	542/3811 (14.2)				
Continued HAART in pregnancy[d]					
Continued HAART	562/2151 (26.1)	1.3 (1.1–1.5)	…	…	1.3 (1.0–1.5)
Initiated HAART	237/1095 (21.6)				

Stepwise selection was utilized for the logistic regression analyses, and covariates with a significance level ≤0.05 and $CD4^+$ cell count were included in the model. Anemia was excluded from analyses that included women who continued HAART from before pregnancy, because hemoglobin was measured after women started HAART.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age; TB, tuberculosis; ZDV, zidovudine.

[a] Unadjusted ORs were estimated among all HIV-infected women whom had a known initiation date for antiretroviral drugs received during pregnancy and whom had information recorded for the variable of interest.

[b] Continued HAART versus all others: Women who continued HAART from before pregnancy were compared with all other HIV-infected women, including those who initiated ZDV, HAART, or no antiretroviral drugs during pregnancy.

[c] HAART initiation versus ZDV initiation: Women who initiated HAART were compared to women who initiated ZDV, including only those who initiated antiretroviral drugs by 34 weeks gestation and had birth outcomes ≥34 weeks gestation. Unadjusted ORs were estimated among this subset, but are not shown.

[d] Continued HAART versus HAART initiation: Women who continued HAART from before pregnancy were compared with women who initiated HAART. Unadjusted ORs were estimated among this subset, but are not shown.

[e] Past adverse pregnancy outcome defined as past stillbirth, preterm delivery, very preterm delivery, or low birth weight infant.

[f] Medical history of tuberculosis was self-reported.

[g] Maternal hypertension defined as a blood pressure measurement of more than 140/90 mmHg at any visit before labor, admission to the hospital for hypertension, delivery complicated by hypertension, or induction for preeclampsia.

[h] Anemia during pregnancy was defined as presence of recorded hemoglobin value of 10 g/dL or less, and was measured at the first antenatal visit.

Table 5. Univariate and Multivariate Odds Ratios for Stillbirth Among HIV-Infected Women

Risk Factor	Number of Stillbirths (%)	Unadjusted OR (95% CI)[a]	Continued HAART vs Others (N = 9146)	HAART Initiation vs ZDV Initiation (N = 4763)
			Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
Initiated antenatal care ≤20 wk				
Yes	212/4272 (5.0)	1.3 (1.1–1.6)	1.3 (1.1–1.7)	1.1 (.8–1.7)
No	178/4645 (3.8)			
Positive RPR				
Yes	12/158 (7.6)	1.7 (1.0–3.1)	1.9 (1.0–3.4)	3.3 (.9–11.7)
No or unknown	425/9346 (4.6)			
Maternal hypertension in pregnancy[d]				
Yes	170/1686 (10.1)	3.3 (2.7–4.1)	3.1 (2.5–3.9)	2.5 (1.7–3.8)
No	238/7327 (3.3)			
Anemia in pregnancy[e]				
Yes	126/3131 (4.0)	1.8 (1.3–2.5)	…	1.3 (.7–2.2)
No	49/2177 (2.3)			
$CD4^+$ cell count ≤200 μL				
Yes	34/583 (5.8)	1.7 (1.1–2.5)	1.7 (1.2–2.6)	1.7 (.9–3.1)
No	139/3909 (3.6)			
Unknown	264/5012 (5.3)			
Continued HAART in pregnancy[b]				
Continued HAART	138/2189 (6.3)	1.6 (1.3–2.0)	1.5 (1.2–1.8)	…
All others	283/6960 (4.1)			
Initiated HAART in pregnancy[c]				
Initiated HAART	44/936 (4.7)	2.9 (2.0–4.3)	…	2.5 (1.6–3.9)
Initiated ZDV	64/3827 (1.7)			

Stepwise selection was utilized for the logistic regression analyses, and covariates with a significance level ≤0.05 and $CD4^+$ cell count were included in the model. Anemia was excluded from analyses that included women who continued HAART from before pregnancy, because hemoglobin was measured after women started HAART.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; RPR, rapid plasma reagin; ZDV, zidovudine.

[a] Unadjusted ORs were estimated among all HIV-infected women with known initiation date for antiretroviral drugs received during pregnancy and information recorded for the variable of interest.

[b] Continued HAART versus all others: Women who continued HAART from before pregnancy were compared with all other HIV-infected women, including those who initiated ZDV, HAART, or no antiretroviral drugs during pregnancy.

[c] HAART initiation versus ZDV initiation: Women who initiated HAART were compared to women who initiated ZDV, including only those who initiated antiretroviral drugs by 34 weeks gestation and had outcomes ≥34 weeks gestation. Unadjusted ORs were estimated among this subset, but are not shown.

[d] Maternal hypertension defined as a blood pressure measurement of more than 140/90 mmHg at any visit before labor, admission to the hospital for hypertension, delivery complicated by hypertension, or induction for preeclampsia.

[e] Anemia during pregnancy was defined as presence of recorded hemoglobin value of 10 g/dL or less, and was measured at the first antenatal visit.

HAART regimen (OR, 1.3; 95% CI, .9, 1.9). We did not observe significant differences in rates of PTD, SGA infants, or SB according to timing of HAART initiation during pregnancy (before or after 32 weeks gestation; data not shown).

DISCUSSION

We performed the largest study of birth outcomes to date among HIV-infected women with access to HAART in pregnancy. In this study from Botswana, adverse birth outcomes such as preterm delivery, SGA infants, and SB were more common among HIV-infected women compared with HIV-uninfected women. In addition, HAART exposure during pregnancy (continued from before pregnancy and initiated during pregnancy) was associated with adverse birth outcomes when compared with all other HIV-infected women and with ZDV monotherapy during pregnancy, respectively. We also identified maternal hypertension during pregnancy as an independent risk factor for each adverse outcome.

Previous data for adverse birth outcomes related to HAART use are mixed, and largely from cohorts in the developed world [10–19]. We believe the conflicting results may be related to limited power, differences among the populations studied and the availability of obstetrical care, and

confounding by indication for HAART use in pregnancy. The selection of exposure categories has varied widely in previous studies, in particular with respect to the inclusion of HIV-infected women who did not receive antiretroviral drugs in pregnancy. However, the importance of selecting appropriate exposure categories must be underscored, since bias is introduced by many factors, including differences in opportunity to start treatment prior to delivery [27]. We were cautious in our interpretation of results among women who were untreated in pregnancy, since these women had less access to antenatal care and may have delivered before having had the opportunity to receive antiretroviral drugs. We limited most of our comparisons to either those categorized as HAART exposed versus unexposed at conception, or to a time-limited comparison of HAART versus ZDV initiation in pregnancy, and attempted to control for $CD4^+$ cell count differences (including sensitivity analyses with $CD4^+$ cell count as a continuous variable and additional analyses stratified by CD4 categories) to reduce confounding by indication. Through these comparisons, we found in all analyses that HAART exposure was significantly associated with adverse birth outcomes. Our findings agree with several previous associations between HAART exposure and preterm delivery [10, 11, 19, 23, 27, 28], SBs [28], and SGA infants [28], including a study comparing historical cohorts from West Africa [21] and a previous study in Botswana [29].

NND is an important birth outcome that in part reflects the severity of PTD and SGA, and may also differ by the level of obstetrical and neonatal care. Our evaluation of NND was limited by the smaller number of outcomes, and only captured deaths that occurred before leaving the hospital. We were reassured by the lack of association between NND and women who continued HAART from conception, when compared with all other women. This was not the case for women starting HAART in pregnancy, which may reflect the more targeted comparison with those receiving ZDV in pregnancy that excluded women not receiving any ARVs (who may have had higher risks for other reasons). Additional studies are needed to determine the relationship between HAART exposure in pregnancy and neonatal mortality in different settings, particularly those lacking skilled obstetrical and neonatal care.

Several mechanisms have been proposed to account for associations between HAART and adverse birth outcomes. These include modulation of the immune system by a cytokine-mediated effect from HAART [30, 31], and increased risk for hypertension and preeclampsia in pregnancy [32]. Studies in Spain and the United Kingdom identified significantly higher rates of preeclampsia among HIV-infected women in the HAART era compared with the pre-HAART era [32, 33]. A study of placental pathology among HIV-infected women delivering stillbirths in Botswana identified chronic placental hypertensive damage to be significantly more common in HAART-treated women compared with those not receiving HAART [34]. We found maternal hypertension to be significantly associated with an increased risk for PTD, SGA, and SB (which is consistent with prior studies [35–40]) and believe further clarification of the relationship between HAART and hypertension is needed. Overall, these findings highlight the need for additional research to study potential causal mechanisms between HAART use during pregnancy and adverse birth outcomes. Because hypertension itself was a strong predictor for all adverse outcomes, we believe the management of hypertension in pregnancy should be prioritized for all high-risk women, including those receiving HAART.

Our study was limited by missing $CD4^+$ cell count data, with a recorded $CD4^+$ cell count available in pregnancy for only 49% of all women. However, women initiating either HAART or ZDV in pregnancy had higher rates available (70% initiating HAART and 62% initiating ZDV). We believe a sufficient number of $CD4^+$ results were available from the various treatment groups to reduce bias by indication (in addition to the fact that many of those receiving HAART from conception were already immune reconstituted), and that associations with HAART were not merely residual confounding by maternal disease status. We evaluated all birth outcomes for confounding by maternal $CD4^+$ cell count, and found that the associations between HAART use and adverse birth outcomes were independent of maternal $CD4^+$ cell count. When we restricted our analyses to HIV-infected women with a recorded $CD4^+$ cell count, the associations between HAART and adverse birth outcomes remained significant. Furthermore, when we stratified our data and analyzed only women with $CD4^+$ counts >200 cells/μL, the strength of the associations increased; this suggests the associations with HAART were unlikely to be a marker for low $CD4^+$ cell count or maternal illness. A randomized study comparing HAART with ZDV monotherapy at higher $CD4^+$ cell counts would reduce the possibility of confounding and provide a clearer understanding of this association. However, at lower $CD4^+$ cell counts, the established benefits of HAART make such a trial unethical to perform.

Our study had several additional limitations. Several variables in the obstetric records were self-reported, and some information was missing. The calculation of the gestational age by the use of the last-normal-menstrual-period method (with fundal height and ultrasound confirmation) is less precise than the use of ultrasound, but we would not expect significant differences in gestational age calculations by antiretroviral exposure category. Although we utilized logistic regression modeling, there may have been unmeasured confounding by maternal clinical factors, and women receiving HAART were sicker than other women in the cohort. We did not have access to HIV RNA level data during pregnancy or nadir $CD4^+$ cell counts for women who were receiving HAART

from conception, and we acknowledge that the reconstituted $CD4^+$ cell count may be an imperfect marker for a woman's immune status or her risk for adverse events in pregnancy. Although 62% of births occurred at PMH and NH (the 2 referral hospitals), and there were minor differences in rates of adverse outcomes according to site (with higher rates of PTD observed at PMH, Francistown, and Maun, and a higher rate of SB at PMH), the magnitude and direction of the findings were consistent at all sites.

This study highlights the complexity of issues regarding the use of HAART and adverse birth outcomes. The benefits of HAART for the health of immunocompromised HIV-infected persons [41–44] and for PMTCT [45–47] have been well documented. In this study, we observed an increased risk for preterm delivery, SGA infants, SBs, and neonatal death among pregnant women exposed to HAART. Although these data are observational, they serve to underscore the need for further research into potential mechanisms by which HAART may affect birth outcomes as well as investigation of the safest antiretroviral regimens for use during pregnancy. These data also demonstrate the high number of adverse birth outcomes in this population. As more women gain access to HAART during pregnancy, additional efforts are needed to identify those at high risk for adverse outcomes, and to provide intensified support systems that address modifiable risk factors such as hypertension in pregnancy. Public health efforts should focus on supporting high-risk obstetrical and neonatal care services in countries like Botswana to maximize the benefits of HAART use during pregnancy for mothers and their infants.

Notes

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