Pregnancy outcomes and birth defects from an antiretroviral drug safety study of women in South Africa and Zambia

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Objective: To evaluate the safety of combination antiretroviral therapy (ART) in conception and pregnancy in different health systems.

Design: A pilot ART registry to measure the prevalence of birth defects and adverse pregnancy outcomes in South Africa and Zambia.

Methods: HIV-infected pregnant women on ART prior to conception were enrolled until delivery, and their infants were followed until 1 year old.

Results: Between October 2010 and April 2011, 600 women were enrolled. The median $CD4^+$ cell count at study enrollment was lower in South Africa than Zambia (320 vs. 430 cells/μl; $P < 0.01$). The most common antiretroviral drugs at the time of conception included stavudine, lamivudine, and nevirapine. There were 16 abortions (2.7%), 1 ectopic pregnancy (0.2%), 12 (2.0%) stillbirths, and 571 (95.2%) live infants. Deliveries were more often preterm (29.7 vs. 18.4%; $P = 0.01$) and the infants had lower birth weights (2900 vs. 2995 g; $P = 0.11$) in Zambia compared to South Africa. Thirty-six infants had birth defects: 13 major and 23 minor. There were more major anomalies detected in South Africa and more minor ones in Zambia. No neonatal deaths were attributed to congenital birth defects.

Conclusions: An Africa-specific, multi-site antiretroviral drug safety registry for pregnant women is feasible. Different prevalence for preterm delivery, delivery mode, and birth defect types between women on preconception ART in South Africa and Zambia highlight the potential impact of health systems on pregnancy outcomes. As countries establish ART drug safety registries, documenting health facility limitations may be as essential as the specific ART details.

Keywords: antiretroviral therapy, birth defects, drug safety, HIV, pregnancy

Introduction

With the widespread availability of affordable combination antiretroviral therapy (ART)in sub-Saharan Africa, HIV-infected womenare living longer and becoming pregnant while on ART [1–3]. Furthermore, women in developing countries are often exposed to multiple risk factors for adverse pregnancy outcomes, such as poor

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nutrition, anemia, and untreated hypertension [4–6]. Whereas individual-level variables areoften considered in ART drug safety studies, very few analyses look at the influence of health systems on pregnancy outcomes in women on ART [7,8]. Population-level characteristics, clinical guidelines and policies, and health system-svarywithin sub-Saharan Africa and may impact the detection and occurrence of adverse maternal, fetal, and newborn outcomes.

Data regarding antenatal ART and risk of stillbirths, preterm delivery (PTD), and other adverse outcomes are mixed. A district-wide Zambian obstetric database comprised approximately 70% of delivery data from primary urban health centers and 30% from the tertiary hospital, andfound that antenatal ART compared to none led to decreased odds of stillbirth [9]. However, a study in Botswana based in six government hospitals, two of which were tertiary referral centers, demonstrated an increased risk of PTD, small for gestational age (SGA), and stillbirth in women on prepregnancy ART [10]. The difference in findings may be due to the possible increased proportion of complicated pregnancies in the hospital-based population andhigher skilled health care workers' ability to document clinical details. Different settings may be an unaccounted variable in analyses, looking at ART exposure and pregnancy outcomes.

The WHO recommends establishing pregnancy registries for ART surveillance when feasible [11]. Thediverse structure of health systems found in developing countries may affect the implementation of such registries and the ability to detect adverse outcomes, especially congenital anomalies. The scope of technology, human resources, and clinical expertise needs to beconsidered. The Maternal Events and Pregnancy Outcomes in a Cohort of HIV-Infected Women Receiving ART in sub-Saharan Africa (MEP) study measured the congenital anomalies and pregnancy outcomes reported in women receiving ART at conception and during pregnancy through a pilot program in two unique health systems. Sharing the baseline population characteristics and study outcomes between our distinct settings may inform patients, health care workers, and policy-makerson the limitations and strengths of drug safety monitoring in sub-Saharan Africa.

Methods

Study settings

Similar to a multicountry drug registry, the study was conducted in two different health systems:referral hospitals with specialists (South Africa) andprimary health facilities with midwives (Zambia). South Africa and Zambia rank among the top 10 countries worldwide affected by the HIV epidemic [12].

In South Africa, study activities from enrollment to exit took place at the Dr GeorgeMukhari Hospital (DGMH), a tertiary hospital affiliated with the University of Limpopo, which is located north of Pretoria. It conducts over 10 000 deliveries per year, composed of routine obstetrics from nearby communities and high-risk patients in the region [13]. Due to low numbers of enrollment, additional recruitment occurred at two affiliated primary health centers with obstetric and HIV services. In Zambia, five primary health centers in the capital city of Lusaka were selected; these sites are part of a larger public-sector network that conducts approximately 60 000 total deliveries annually [14]. Chosen for their high patient volume, the Zambian sites provide low-risk obstetric and HIV services to approximately 20 000 pregnant women annually. Most pregnant women in the public sector receive their antenatal care from nurse-midwives at primary health centers; HIVinfection is not a reason for hospital referral. There is no capacity to perform cesarean deliveries or provide advanced clinical care for mother or newborn at these centers.

Study procedures

Inclusion criteria were HIV-infected pregnant womenoncombination ARTat conception and age at least 18 years. Exclusion criteria included a history ofmentalillness; any condition that would make participation in the study unsafe; and inability to provide informed consent. Maternal participants were recruited from the antenatal or HIV care clinic. Women were followed prospectively until delivery and their infants until 1 year old.

Maternal study visits were scheduled on the same day as antenatal care visits. Gestational age at enrollment was determined by the last menstrual period in Zambia,-whereas in South Africa, most participants underwent a dating ultrasound. Laboratory values, HIV test date, and ART regimens were extracted from the antenatal card or clinical file. There were no study-specific laboratory tests and clinical studies beyond routine care in either health system. Details regarding hospitalizations and deaths were recorded by verbal report and/or medical chart extraction. Autopsies for infant participants were offered in South Africa only.

The infants born in the study were enrolled at birth or soon after. For multiple gestations, both infants were enrolled. Infant participants underwent a physical examination at every study visit (birth, 6 weeks, 3 months, 6 months and 1 year old).

In South Africa, the participants were examined by specialists and infants with suspected congenital anomalies by the clinical geneticist. The specialists also provided routine clinical care to participants. In Zambia, the study-specific midwives were specially trained on physical examinations to look for congenital anomalies. In-

country specialistsand the South African geneticist (viaelectronic consultation) were available upon request.

The study team telephoned participants who missed visits. If a participant failed to return, at least one home visit was conducted. Lost to follow-up was originally defined as no contact for 6 months from the last study visit and was revised to 6 months from the date of study restart when the study was briefly suspended due to changes in funding mechanisms. Data were included in the analysis from participants who re-enrolled on their own accordeven though they were absent for 6 or more months.

Data analysis

The outcomes of interest included abortion, stillbirth, PTD, neonatal death, and congenital anomalies. 'Abortion' was defined as a pregnancy loss at less than 28 weeks gestation and birth weight below 1000 g [15]. The only exception was an infant less than 28 weeks' gestation and who weighed 900 g, but was classified as a live birth to match the twin, who weighed 1000 g. 'Stillbirth' was a fetal death prior to delivery at least 28 weeks' gestation or birth weight of at least 1000 g. 'Term' referred to deliveries at least 37 weeks' gestation,whereas 'preterm'-comprised viable deliveries less than 37 weeks' gestation. 'Neonatal deaths' occurred within the first 28 days of life.

Physical examinations were performed at infant study visits to identify 'congenital anomalies'. Minor and major birth defects were reviewed and classified by the clinical geneticist. A major congenital anomaly has an adverse outcome on either the function or the social acceptability of the individual, and a minor congenital anomaly has no medical or cosmetic importance [16]. When a live or stillbirth infant had more than one anomaly, he/she was categorized by the anomaly with higher severity.

Analyses were conducted via SAS version 9.2 (SAS Institute, Cary, North Carolina, USA). Maternal characteristics and pregnancy and infant outcomes were analyzed for differences between countries via Pearson chi-square test, Fisher's exact test, and Wilcoxon rank-sum test.

The study was approved by the ethical review committees at the Harvard School of Public Health (Boston, Massachusetts, USA), Medical University of Southern Africa (Pretoria, South Africa), University of Zambia (Lusaka, Zambia), University of Alabama at Birmingham (Birmingham, Alabama, USA), and University of North Carolina at Chapel Hill (Chapel Hill, North Carolina, USA).

Results

From October 2010 to April 2011, 697 women were recruited and 636 were screened. Of the 600 women who were enrolled (300 in South Africa, 300 in Zambia), 3 were never pregnant and 1 had initiated ART after conception. Whereas one woman withdrew prior to delivery, 7 (1 in South Africa, 6 in Zambia) participants were lost to follow-up. Due to twin gestations, 588 women contributed 600 pregnancy outcomes (Fig. 1).

The mean number of study visits, including enrollment and exit, was 3.4 (SD 1.6) in South Africa and 2.4 (SD 1.3) in Zambia. There was one postnatal maternal deathin Zambia due to severe anemia following home delivery, complicated by bleeding. The last infants exited the study in October 2012 in Zambia and in December 2012 in South Africa.

Characteristics of the study population

Maternal characteristics at enrollment are shown in Table 1. More participants in Zambia compared to South Africa were married (87.9 vs. 19.4%; $P < 0.0001$), whereas more in South Africa compared to Zambia enrolled into the study in the first trimester (11.7 vs. 6.4%; $P = 0.017$). The median parity in Zambia was higher than those in South Africa (3 vs. 2; $P < 0.0001$). More participants in Zambia had syphilis (6.4 vs. 1.0%; $P < 0.0001$), whereas more in South Africa had anemia (27.4 vs. 10.8%; $P < 0.0001$). Overall, two (0.3%) maternal participants reported having a previous pregnancy with ananomaly, and 73 (12.2%) women had one or more prior PTD with a median gestational age of 29.5 weeks [interquartile range (IQR) 28–32]. All 31 (5.2%) women who reported recreational drug use during the index pregnancy were in Zambia, of whom 30 drank alcohol ($P < 0.0001$).

Maternal participants in Zambia were diagnosed with HIV earlier (35.6 vs. 29.3 months; $P = 0.010$) and had beenon triple-drug ART longer (27.4 vs. 17.2 months; $P < 0.0001$) than those in South Africa. Almost all participants were WHO stage 1 or 2 at study enrollment. The median $CD4^+$ cell count at study enrollment was lower in South Africa than Zambia (320 vs. 430 cells/μl; $P < 0.0001$).[1]

The most common antiretroviral drugs at the time of conception included stavudine (d4T), lamivudine (3TC), and nevirapine (NVP). Exposure to d4T was higher in South Africa than Zambia (55.9 vs. 30.3%; $P < 0.0001$), whereas TDF use in Zambia was almost double that in South Africa (44.1 vs. 24.7%; $P < 0.0001$). More women in South Africa compared to Zambia were exposed to EFV (52.5 vs. 25.6%; $P < 0.0001$) or protease inhibitor (8.4vs. 1.7%; $P = 0.0002$), but protease inhibitor use was uncommon overall.

Pregnancy outcomes and congenital anomalies

Pregnancy outcomes are shown in Table 2. There were 17 (2.9%) nonviable pregnancies: 16 abortions (6 in South

[1] At the time of the study, maternal HIV RNA PCR was not measured as part of standard of care for HIV care and treatment during pregnancy in either country.

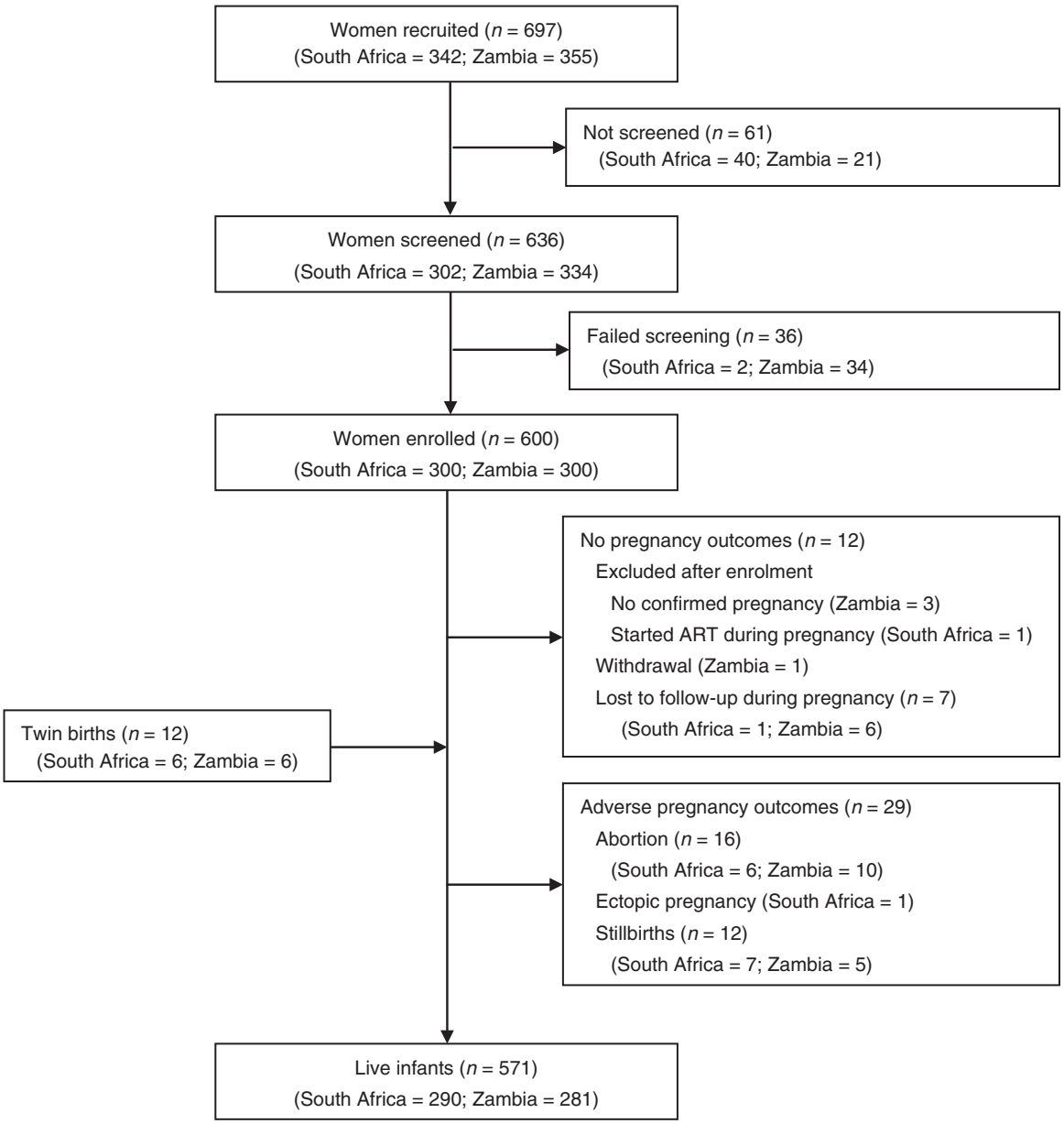

Fig. 1. Flow diagram of maternal participant recruitment, enrollment, and retention and pregnancy outcomes. Maternal Events and Pregnancy Outcomes Study, 2010–2012.

Africa, 10 in Zambia) and 1 ectopic pregnancy. Of the 12 stillbirths, 75% were preterm and 25% were term. There were more preterm births in Zambia than in South Africa (29.7 vs. 18.4%; $P = 0.010$). More infants were born by cesarean delivery in South Africa than in Zambia (18.2 vs. 7.0%; $P < 0.0001$). Infants in Zambia compared to South Africa had lower mean birth weight (2900 vs. 2995 g; $P = 0.106$) and shorter mean lengths (48 vs. 50 cm; $P < 0.0001$). In addition, there were seven neonatal deaths in Zambia and one in South Africa ($P = 0.079$).

We identified 38congenital anomalies in 36 individual infants (Fig. 2). One infant with multiple anomalies had a major birth defect, whereas the other had two minor birth defects. Thus, 23 infants had minor anomalies and 13had major anomalies, giving a major congenital anomaly prevalence of 2.2% among women who conceived on combination ART. The most common congenital anomalies were minor – umbilical hernia and polydactyly – affecting 18 infants. More major than minor congenital anomalies were detected in South Africa, whereas in Zambia, more minor than major congenital anomalies were detected. One stillbirth had a major anomaly, ambiguous genitalia; no neonatal deaths were attributed to congenital birth defects.

Table 1. Characteristics of maternal participants at study enrollment and/or during pregnancy in a cohort of HIV-infected women on combination antiretroviral therapyat the time of conception by country.

Characteristic	Overall [N = 596 (%)]	South Africa [N = 299 (%)]	Zambia [N = 297 (%)]	P value
Marital status				
Single or never married	253 (42.4)	239 (79.9)	14 (4.7)	<0.0001
Married or cohabiting[a]	319 (53.5)	58 (19.4)	261 (87.9)	
Divorced, separated, or widowed	24 (4.0)	2 (0.7)	22 (7.4)	
Education (highest level completed)				
None	67 (11.2)	32 (10.7)	35 (11.8)	0.087
Primary	306 (51.3)	169 (56.5)	137 (46.1)	
Secondary	192 (32.2)	83 (27.8)	109 (36.7)	
Tertiary	30 (5.0)	14 (4.7)	16 (5.4)	
Missing	1 (0.2)	1 (0.3)	0 (0)	
Age at study enrollment, median years (IQR)	31 (28, 35)	31 (28, 35)	31 (28, 35)	0.854**
<20	3 (0.5)	0 (0)	3 (1.0)	0.038*
20–24	49 (8.2)	17 (5.7)	32 (10.8)	
25–29	158 (26.5)	88 (29.4)	70 (23.6)	
30–34	223 (37.4)	115 (38.5)	108 (36.4)	
≥35	163 (27.3)	79 (26.4)	84 (28.3)	
Gestational age at study enrollment, median weeks (IQR)	24 (18, 31)	25 (17, 31)	24 (19, 31)	
≤12 weeks gestation	54 (9.1)	35 (11.7)	19 (6.4)	0.017
13–26 weeks gestation	294 (49.3)	133 (44.5)	161 (54.2)	
>26 weeks gestation	248 (41.6)	131 (43.8)	117 (39.4)	
Gravidity, median	3 (2, 4)	3 (2, 4)	4 (3, 5)	
1	34 (5.7)	22 (7.4)	12 (4.0)	<0.0001
2–3	313 (52.5)	188 (62.8)	125 (42.1)	
4–5	200 (33.6)	78 (26.1)	122 (41.1)	
≥6	49 (8.2)	11 (3.7)	38 (12.8)	
Parity, median	2 (1, 3)	2 (1, 3)	3 (2, 4)	
0	45 (7.6)	27 (9.0)	18 (6.1)	<0.0001
1–2	324 (54.4)	197 (65.9)	127 (42.8)	
3–4	185 (31.0)	68 (22.7)	117 (39.4)	
≥5	42 (7.0)	7 (2.3)	35 (11.8)	
Syphilis status during this pregnancy				
Nonreactive	467 (78.4)	285 (95.3)	182 (61.3)	<0.0001
Reactive	22 (3.7)	3 (1.0)	19 (6.4)	
Not done	107 (18.0)	11 (3.7)	96 (32.3)	
Hemoglobin during this pregnancy, median mg/dl (IQR)	11.3 (10.4, 12.1)	11.2 (10.3, 12.1)	11.6 (10.4, 12.1)	0.216**
≥11	167 (28.0)	107 (35.8)	60 (20.2)	<0.0001*
7–10.9	113 (19.0)	81 (27.1)	32 (10.8)	
<7	1 (0.2)	1 (0.3)	0 (0)	
Not done	315 (52.9)	110 (36.8)	205 (69.0)	
History of congenital anomaly				
No	591 (99.2)	298 (99.7)	293 (98.7)	0.341*
Yes, 1 prior pregnancy with congenital anomaly	2 (0.3)	0 (0)	2 (0.7)	
Unknown	3 (0.5)	1 (0.3)	2 (0.7)	
History of preterm delivery				
No	523 (87.8)	262 (87.6)	261 (87.9)	0.0842
Yes, 1 previous preterm delivery	61 (10.2)	30 (10.0)	31 (10.4)	
Yes, >1 previous preterm delivery	12 (2.0)	7 (2.3)	5 (1.7)	
Gestational age of last preterm delivery if applicable, median weeks (IQR)	29.5 (28, 32)	29 (26, 32)	30 (28, 32)	0.417**
Recreational drug use (including illegal substances) during this pregnancy				
No	565 (94.8)	299 (100.0)	266 (89.6)	<0.0001
Yes, alcohol	30 (5.0)	0 (0)	30 (10.1)	
Yes, traditional or herbal medicine	1 (0.2)	0 (0)	1 (0.3)	
HIV infection diagnosis, months (IQR) (timing prior to conception[b])	32.0 (16.4, 52.4)	29.3 (13.3, 52.0)	35.6 (18.6, 53.3)	0.010**
<6 months	49 (8.2)	38 (12.7)	11 (3.7)	0.002
6–12 months	55 (9.2)	31 (10.4)	24 (8.1)	
12–23 months	117 (19.6)	49 (16.4)	68 (22.9)	
2–4 years	192 (32.2)	93 (31.1)	99 (33.3)	
5–10 years	179 (30.0)	86 (28.8)	93 (31.3)	
>10 years	4 (0.7)	2 (0.7)	2 (0.7)	
HAART start date, months (IQR) (timing prior to conception[b])	22.0 (10.2, 39.3)	17.2 (7.5, 32.5)	27.4 (14.9, 45.3)	<0.0001**
<6 months	81 (13.6)	59 (19.7)	22 (7.4)	<0.0001
6–12 months	91 (15.3)	61 (20.4)	30 (10.1)	
12–23 months	141 (23.7)	63 (21.1)	78 (26.3)	
2–4 years	175 (29.4)	74 (24.7)	101 (34.0)	
5–10 years	108 (18.1)	42 (14.0)	66 (22.2)	

Characteristic	Overall [$N = 596$ (%)]	South Africa [$N = 299$ (%)]	Zambia [$N = 297$ (%)]	P value
WHO stage at enrollment				
Stage 1 or 2	590 (99.0)	297 (99.3)	293 (98.7)	0.407
Stage 3 or 4	6 (1.0)	2 (0.7)	4 (1.3)	
Last $CD4^+$ cell count prior to enrollment, median cells/μl (IQR)	385 (254, 519)	320 (205, 465)	430 (296, 604)	
0–199	90 (15.1)	68 (22.7)	22 (7.4)	<0.0001
200–349	165 (27.7)	87 (29.1)	78 (26.3)	
350–499	169 (28.4)	75 (25.1)	94 (31.6)	
≥500	161 (27.0)	59 (19.7)	102 (34.3)	
Missing	11 (1.8)	10 (3.3)	1 (0.3)	
Antiretroviral drug regimen at time of conception[b]				
Nucleoside reverse transcriptase inhibitor				
Abacavir (ABC)	9 (1.5)	1 (0.3)	8 (2.7)	0.020*
Didanosine (ddI)	2 (0.3)	2 (0.7)	0 (0)	0.499*
Emtricitabine (FTC)	87 (14.6)	0 (0)	87 (29.3)	<0.0001
Lamivudine (3TC)	505 (84.7)	295 (98.7)	210 (70.7)	<0.0001
Stavudine (d4T)	257 (43.1)	167 (55.9)	90 (30.3)	<0.0001
Tenofovir (TDF)	205 (34.4)	74 (24.7)	131 (44.1)	<0.0001
Zidovudine (AZT)	128 (21.5)	59 (19.7)	69 (23.2)	0.298
Non-nucleoside reverse transcriptase inhibitor				
Efavirenz (EFV)	233 (39.1)	157 (52.5)	76 (25.6)	<0.0001
Nevirapine (NVP)	332 (55.7)	117 (39.1)	215 (72.4)	<0.0001
Protease inhibitor				
Indinavir (IDV)	2 (0.3)	2 (0.7)	0 (0)	0.499*
Lopinavir/ritonavir (LPV/r)	25 (4.2)	20 (6.7)	5 (1.7)	<0.003*
Saquinavir (SQV)	3 (0.5)	3 (1.0)	0 (0)	0.249*

Maternal Events and Pregnancy Outcomes Study, 2010–2012 ($N = 596$). IQR, interquartile range.
[a]In Zambia most women view their main partner as their husband; 254 women considered themselves married, while 7 responded as cohabiting. In South Africa, no participants reported cohabiting as their marital status.
[b]Time of conception refers to 2 weeks after last menstrual period per verbal report, assuming a 28-day menstrual cycle.
*P value is for Fisher's exact test (others are Chi-square).
**P value is for Wilcoxon's test.

Indications for nonelective cesarean deliveries are shown in Table 3. Fetal distress, poor progress of labor, and severe preeclampsia remote from delivery were the most common indications.

Discussion

Pregnancy outcomes differed significantly betweenour prospective cohorts of women who conceived on combination ART in South Africa and Zambia: PTD, low birth weight (LBW) infants, mode of delivery, major and minor congenital anomalies, and neonatal deaths. Some baseline characteristics varied significantly between the countries, highlighting the diversityof the HIV-infected pregnant population and resource availability in sub-Saharan Africa. Whereas the higher risk of PTD in Zambia may be attributable to differences in maternal characteristics, such as higher parity [17], higher prevalence of syphilis [18], and higher rate of alcohol use [19], the disparity between the settings may also contribute. Syphilis and hemoglobin screening were often not done in Zambia. On the contrary, participants in South Africa received hospital-based antenatal care from an obstetrician and were more likely to undergo routine antenatal testing. Screening may have led to treatment of infectionsand consequently less incidence of PTD compared to Zambia. In addition, the nonsignificant mean birth weight difference of 95 g between the two countries may demonstrate the beneficial accuracy of gestational age ascertainment by ultrasound or clinical estimateover using last menstrual period [20]. The addition of dating ultrasounds in Zambian participants may have mitigated the PTD incidence [21].

The strengths of our study are numerous. The lost to follow-up rate was only 1.2% prior to delivery with an overall 2.0% of participants excluded in the analysis. Study sites spanned two countries in sub-Saharan Africa at different levels of the health system. Participants were recruited from government clinics, reflecting common drug exposures [22]. In addition, the study procedure to detect congenital anomalies was a simple, nonlabor-intensive physical examination of the infant. With adequate training and mentorship, the midwives performedinfant examinationsand confirmed findings with specialists as needed. Finally, our cohort continued preconception ART throughout pregnancy, representing a group we expect to encounter commonly in the future as combination ART eligibility criteria broaden worldwide [11].

Table 2. Pregnancy outcomes for all fetuses and viable pregnancies in a cohort of HIV-infected women on combination antiretroviral therapy at the time of conception by country.

Outcomes	Overall [$N = 600$ (%)]	South Africa [$N = 304$ (%)]	Zambia [$N = 296$ (%)]	P value
Pregnancy outcome				
Live birth, term	427 (71.2)	234 (77.0)	193 (65.2)	0.010
Live birth, preterm	144 (24.0)	56 (18.4)	88 (29.7)	
Stillbirth, term	3 (0.5)	2 (0.7)	1 (0.3)	
Stillbirth, preterm	9 (1.5)	5 (1.6)	4 (1.4)	
Abortion[a]	16 (2.7)	6 (2.0)	10 (3.4)	
Ectopic pregnancy	1 (0.2)	1 (0.3)	0 (0)	
Gestational age at delivery				
<28 weeks gestation	19 (3.2)	6 (2.0)	13 (4.4)	<0.0001
28–33 weeks gestation	42 (7.0)	6 (2.0)	36 (12.2)	
34–36 weeks gestation	107 (17.8)	54 (17.8)	53 (17.9)	
37–41 weeks gestation	403 (67.2)	234 (77.0)	169 (57.1)	
≥42 weeks gestation	26 (4.3)	1 (0.3)	25 (8.5)	
Missing specific gestational age	3 (0.5)	3 (1.0)	0 (0)	
Characteristics of viable pregnancy outcomes[b]	Overall [$N = 583$ (%)]	South Africa [$N = 297$ (%)]	Zambia [$N = 286$ (%)]	P value
Number of fetuses				
Singleton	559 (95.9)	285 (96.0)	274 (95.8)	0.925
Of a set of twins	24 (4.1)	12 (4.0)	12 (4.2)	
Gestational age at delivery, median weeks (IQR)	38 (36, 40)	38 (37, 39)	38 (36, 40)	0.552**
Sex of infant				
Male	301 (51.6)	167 (56.2)	134 (46.9)	0.023*
Female	281 (48.2)	129 (43.4)	152 (53.1)	
Not determined	1 (0.2)	1 (0.3)	0 (0)	
Birth weight, median grams (%)	2960 (2600, 3240)	2995 (2655, 3265)	2900 (2500, 3200)	0.106**
<500	1 (0.2)	1 (0.3)	0 (0)	0.866
500–1499	10 (1.7)	5 (1.7)	5 (1.7)	
1500–2499	88 (15.1)	41 (13.8)	47 (16.4)	
2500–3999	466 (79.9)	240 (80.8)	226 (79.0)	
≥4000	16 (2.7)	9 (3.0)	7 (2.4)	
Missing	2 (0.3)	1 (0.3)	1 (0.3)	
Length of newborn at delivery, median cm (IQR)	49 (47,51)	50 (48, 51)	48 (45, 50)	<0.0001**
Missing	102 (17.5)	4 (1.3)	98 (34.3)	
Characteristics of viable pregnancy outcomes	Overall [$N = 583$ (%)]	South Africa [$N = 297$ (%)]	Zambia [$N = 286$ (%)]	P value
Mode of delivery				
Vaginal delivery	509 (87.3)	243 (81.8)	266 (93.0)	<0.0001
Cesarean delivery (total)	74 (12.7)	54 (18.2)	20 (7.0)	
Nonelective cesarean delivery	41 (55.4)	28 (51.9)	13 (65.0)	0.022*
Elective cesarean delivery	31 (41.9)	26 (48.1)	5 (25.0)	
Unknown type of cesarean delivery	2 (2.7)	0 (0)	2 (10.0)	
Congenital anomaly at delivery	36 (6.2)	20 (6.4)	16 (5.6)	0.545
Infant with major congenital anomaly	13 (36.1)	11 (55.0)	2 (12.5)	
Infant with minor congenital anomaly	23 (63.9)	9 (45.0)	14 (87.5)	
Neonatal death[c]				
Term	3 (0.5)	0 (0)	3 (1.0)	0.079*
Preterm	5 (0.9)	1 (0.3)	4 (1.4)	

Maternal Events and Pregnancy Outcomes Study, 2010–2012 ($N = 600$). IQR, interquartile range.
[a]Abortion is defined as estimated gestational age (EGA)less than 28 weeks' gestation and birth weight below 1000 g. Using the alternate WHO definition of EGA less than 22 weeks' gestation and birth weight below 500 g, South Africa has eight preterm stillbirths and three abortions, and Zambia seven preterm stillbirths and seven abortions.
[b]Viable pregnancies are defined as EGA at least 28 weeks' gestation or birth weight at least 1000 g.
[c]Percentages are based on live births.
*P value is for Fisher's exact test (others are chi-square).
**P value is for Wilcoxon's test.

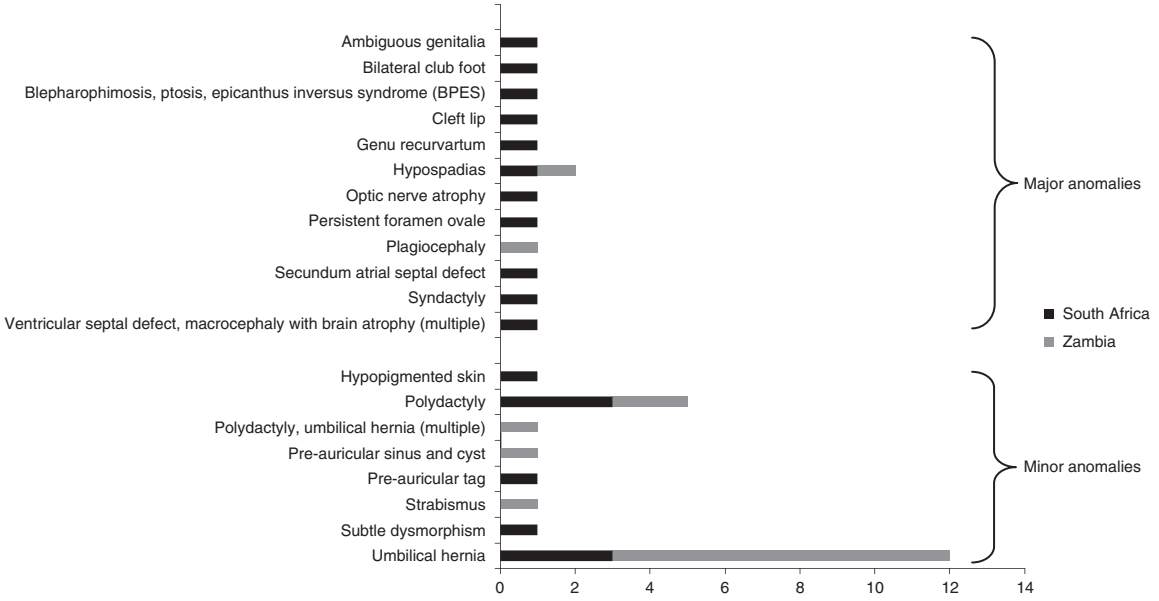

Fig. 2. Congenital anomalies in infant participants by major and minor categories in a cohort of HIV-infected women on combination antiretroviral therapy at the time of conception by country. Maternal Events and Pregnancy Outcomes Study, 2010–2012 ($N = 36$).

The higher rate of cesarean deliveries (with higher proportion of elective indications), higher detection of major congenital anomalies,and lower incidence of neonatal deaths likely reflect bolstered clinical resources in South Africa compared to those in Zambia. Lack of appropriate-sized endotracheal tubes, limited incubators, and inability to diagnose definitively the major causes of neonatal deaths result in a poor survival rate for newborns admitted to the neonatalICU in Zambia. A study in the United States showed significantly fewer in-hospital deaths among infants delivered at a hospital with a high-level neonatal ICU (NICU) than other hospitals [23]. Moreover, the study participants in South Africa were evaluated by a pediatrician and clinical geneticist as needed. The national incidences of neonatal encephalopathy and neonatal deaths decrease with increased access to skilled care at delivery [24]. As drug safety studies look at the risk of PTD, LBW, congenital anomalies, and perinatal mortality with ART exposure at conception and during pregnancy, aspects of health systemsshould be considered.

The significantly lower gestational age at study enrollment, utilization of autopsies, and higher participant retention in the study likely signify either better health-seeking behavior or more developed health care infrastructure or both in South Africa compared to Zambia. Two or more antenatal care visitscompared to fewer has been associated with decreased risk of stillbirth [25]. However, because participants generally enrolled in the study in the late second trimester, first-trimester abortions and second-trimester losses are likely underrepresented in this cohort of HIV-infected pregnant women on pre-conception ART. The Development of Antiretroviral Therapy in Africa (DART) trial in Zimbabwe found 21.5% of outcomes were spontaneous abortions and intrauterine deaths less than 22

Table 3. Indications for nonelective cesarean deliveryin a cohort of HIV-infected women on combination antiretroviral therapy at the time of conception by country.

Indication for cesarean delivery	Overall [$N = 41$ (%)]	South Africa [$N = 28$ (%)]	Zambia [$N = 13$ (%)]	P value*
Antepartum hemorrhage	1 (2.4)	1 (3.6)	0 (0)	8
Fetal distress	23 (56.1)	19 (67.9)	4 (30.8)	
Malpresentation	1 (2.4)	1 (3.6)	0 (0)	
Poor progress of labor	6 (14.6)	3 (10.7)	3 (23.1)	
Placenta previa	4 (9.8)	1 (3.6)	3 (23.1)	
Severe preeclampsia remote from delivery	5 (12.2)	2 (7.1)	3 (23.1)	
Other	1 (2.4)	1 (3.6)	0 (0)	

Maternal Events and Pregnancy Outcomes Study, 2010–2012 ($N = 41$).
*P value is for Fisher's exact test.

weeks' gestation [26], whereas nonelective abortions comprised of 36.6% of pregnancy outcomes in the Tshepo study [27].

With regard to HIV care and treatment, women in Zambia initiated ART for longer durations before the index pregnancy and had higher $CD4^+$ cell counts than women in South Africa. In addition, antiretroviral drug exposure between the two countries was significantly different, with many women in Zambia being exposed to TDF and NVP,whereas d4T and EFV were commonly used in South Africa. In 2010, the Zambian national guidelines recommended d4T for use in second-line regimens only due to its toxicity profile and $CD4^+$ cell count threshold of 350 cells/ml for ART eligibility in pregnant women [28]. The difference in national policy and guidelines may result in higher numbers of ART-exposed pregnancies in Zambia compared to South Africa among healthier HIV-infected women who are willing to initiate treatment. The capacity to provide broader combination ART coverage to the HIV-infected population may imply stronger support for HIV care and treatment programs in Zambia than South Africa. Such inequalities within health systems may also impact associations among specific ART exposures and pregnancy outcomes.

Study limitations

Several limitations are acknowledged. First, most participants enrolled in the study after 20 weeks' gestation, a common time for pregnant women to book antenatal care [14]; so abortions were likely under-represented. Second, we might have missed nonviable anomalies as autopsies for any deaths, including abortions and stillbirths, werenot offered as part of the study in Zambia and not uniformly acceptedin South Africa. Third, because we did not add resources beyond the local standards of care, there is heterogeneity in estimated gestational age (EGA). Finally, we did not validate infant examinations by midwives for proficiency to detect congenital anomalies, and so birth defects may be underestimated in Zambia. The study team in Zambia, though, did detect a number of congenital anomalies, demonstrating promise that such skills can be transferred to nonspecialists.

In conclusion, pharmacovigilance of combination ART prior to conception and during the antenatal period is a critical undertaking in sub-Saharan Africa where the burden of disease is high [2]. The potential impact of health systems on the detection of congenital anomalies and incidences of stillbirths, preterm deliveries, and neonatal deaths highlights the importance of comparing facility-level, as well as individual-level variables. Patients should be encouraged to establish antenatal care early to lessen the risk of adverse pregnancy outcomes, if any, with ART exposure. Health care workers should be trained in newborn examination and low-technology measures to not only detect congenital anomalies but also diminish the incidences of perinatal mortality. Standard definitions and high-quality data collection are currently lacking in resource-limited settings [29]. Policy-makers should strive to incorporate health system measurements in monitoring and evaluation, especially as investments improve clinical standards of care. International sentinel sites for ART surveillance may be a preferred alternative to routine registries in developing countries. Sentinel sites should be equipped with a minimum packageof resources to ascertain outcomes accurately, such as PTD. Ultrasound studies to determine EGA would require the ultrasound machine, continuous supplies, and a trained health care worker with months of mentorship [30]. Although gestational age estimation would improve, health care costs in resource-limited settings would rise with unlikely reduction of adverse pregnancy outcomes [31]. Findings from sentinel sites may not be generalizable to the wider HIV-infected pregnant population. As countries establish ART drug safety registries, documenting the limitations of health facility levels, including technology and human resources,may be as essential as the specific ART drug regimen and length of exposure.

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Conflicts of interest

Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC. Trainee support was provided by the National

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