OPEN

Risk of Adverse Birth Outcomes and Birth Defects Among Women Living With HIV on Antiretroviral Therapy and HIV-Negative Women in Uganda, 2015–2021

Robert Serunjogi, BSTAT,[a] Daniel Mumpe-Mwanja, MBChB, MPH,[a] Dhelia M. Williamson, PhD,[b] Diana Valencia, MSc, MS,[c] Joyce Namale-Matovu, BCP, MA,[a] Ronald Kusolo, BSTAT, MSc,[a] Cynthia A. Moore, MD, PhD,[c,d] Natalia Nyombi, MBChB in Paediatrics,[e] Vincent Kayina, MBChB, M.MED-Paediatrics, LAM,[f,g] Faridah Nansubuga, MBChB, MMed Obs/Gyn,[h] Joanita Nampija, MBChB, MMED(PAED),[i] Victoria Nakibuuka, MBCHB, MMED(PAED), MPHIL (Neonatology),[j] Lisa J. Nelson, MD, MPH, MSc,[k] Emilio Dirlikov, PhD, MA,[k] Phoebe Namukanja, MBChB, MPH,[k] Kenneth Mwambi, BA (SS), DGC, MPH,[k] Jennifer L. Williams, PhD, MSN, MPH, FNP-BC, FAANP,[c] Cara T. Mai, DrPH, MPH,[c] Yan Ping Qi, QI,[c] and Philippa Musoke, MBChB, PhD[a,l]

Introduction: We assessed the risk of adverse pregnancy and birth outcomes and birth defects among women living with HIV (WLHIV) on antiretroviral therapy (ART) and HIV-negative women.

Methods: We analyzed data on live births, stillbirths, and spontaneous abortions during 2015–2021 from a hospital-based birth defects surveillance system in Kampala, Uganda. ART regimens were recorded from hospital records and maternal self-reports. Using a log-binomial regression model, we compared the prevalence of 16 major external birth defects and other adverse birth outcomes among WLHIV on ART and HIV-negative women.

Results: A total of 203,092 births were included from 196,373 women of whom 15,020 (7.6%) were WLHIV on ART. During pregnancy, 15,566 infants were primarily exposed to non-nucleoside reverse transcriptase inhibitor-based ART (n = 13,614; 87.5%). After adjusting for maternal age, parity, and number of antenatal care visits, WLHIV on non-nucleoside reverse transcriptase inhibitor were more likely than HIV-negative women to deliver preterm (adjusted prevalence ratio [aPR] = 1.27, 95% confidence interval: 1.21 to 1.32), post-term (aPR = 1.23, 95% CI: 1.16 to 1.32), or small for gestational age infants (aPR = 1.35, 95% CI: 1.30 to 1.40). Spina bifida was more prevalent among infants born to WLHIV on ART periconceptionally compared with HIV-negative women (aPR = 2.45, 95% CI: 1.27 to 4.33). The prevalence of the other selected birth defects was similar between infants from WLHIV on ART and HIV-negative women.

Conclusions: In Uganda, WLHIV on ART were more likely than HIV-negative women to experience selected adverse birth outcomes. Further surveillance of maternal ART exposure, including by drug class and ART regimen, is needed to monitor and prevent adverse birth outcomes in WLHIV.

Key Words: antiretrovirals, birth defects, HIV, Uganda, adverse birth outcomes

(*J Acquir Immune Defic Syndr* 2025;98:434–443)

INTRODUCTION

Antiretroviral therapy (ART) has led to the reduction of vertical transmission (VT) of HIV from >20% in 2010 to <5% in 2019, in many sub-Saharan African countries.[1,2]

Received for publication April 29, 2024; accepted November 15, 2024.

From the [a]Makerere University, Johns Hopkins University Research Collaboration, Kampala, Uganda; [b]Division of Global HIV and TB, US Centers for Disease Control and Prevention (CDC), Atlanta, GA; [c]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA; [d]Goldbelt Professional Services, LLC, Chesapeake, VA; [e]Department of Paediatrics, Kawempe National Referral Hospital, Kampala, Uganda; [f]Department of Paediatrics, Mengo Hospital, Kampala, Uganda; [g]Department of Paediatrics and Child Health, Gulu University, Uganda; [h]Department of Obstetrician/Gynecologist, St. Francis' Hospital Nsambya, Kampala, Uganda; [i]Department of Paediatrics, Uganda Martyrs Hospital, Lubaga, Kampala, Uganda; [j]Department of Paediatrics, St. Francis Hospital Nsambya, Kampala, Uganda; [k]Division of Global HIV and TB, CDC, Kampala, Uganda; and [l]Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Kampala, Uganda.

Supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under the terms of a Cooperative Agreement numbers GH0000487, GH002171, and GH002359.

The authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

The findings and conclusions are those of the authors and do not necessarily represent the official position of the funding agencies.

Correspondence to: Robert Serunjogi, Makerere University, Johns Hopkins University Research Collaboration, Kampala, Uganda 25601 (e-mail: rserunjogi@mujhu.org).

The World Health Organization (WHO) currently recommends all people living with HIV, including pregnant and breastfeeding women, initiate ART on the same day they receive an HIV diagnosis.[1] Initiating ART early before a pregnancy is important for maternal health—including the prevention of VT. However, among women of reproductive age, antiretroviral (ARV) exposure during the time of conception and during pregnancy can occur. As a result, concerns have been raised about the potential effects of ARVs on a developing fetus, including risk of birth defects.[3]

In 2013, WHO recommended an EFV-based ART for pregnant women including during the first trimester,[4] and continued after pregnancy, leading to periconceptional exposure for subsequent pregnancies. Some studies have reported higher rates of birth defects among infants exposed to EFV during the first trimester.[5,6] The systematic reviews and multicohort analysis did show an association between neural tube defects (NTDs) and EFV exposure during pregnancy.[7,8] Initial animal studies suggested efavirenz might pose a risk for NTDs, but subsequent human studies published in 2010 and updated in 2014 found no significant increase in NTD cases, with only 1 reported instance, indicating no strong association between efavirenz and NTDs in humans.[8] In July 2019, the WHO recommended dolutegravir (DTG) as the preferred HIV treatment option for all populations, including pregnant and breastfeeding women.[1] Dolutegravir-based regimens have been scaled up among pregnant WLHIV in Uganda and globally.[9] Initial surveillance data from Botswana suggested a higher prevalence of NTDs among deliveries from women living with HIV (WLHIV) on DTG-based regimens at the time of conception compared with deliveries among HIV-negative women, but the prevalence declined over time.[10–12] However, the risk of NTDs and other adverse outcomes among WLHIV on DTG regimens remains uncertain. More safety information is needed to compare the prevalence of adverse birth outcomes, including birth defects among WLHIV on ART compared with HIV-negative women and by drug class and ART regimen.[13]

This analysis uses data from Uganda to examine the risk of major external birth defects and other adverse birth outcomes (spontaneous abortions, stillbirth, preterm birth, low birth weight [LBW], small for gestational age [SGA], and early neonatal death [ENND]) among WLHIV on ART, including those on EFV-based, DTG-based, and other regimens, compared with HIV-negative women.

METHODS

This analysis includes data on births or pregnancies from August 2015 through December 2021 from an ongoing birth defects surveillance system at 4 major hospitals (Kawempe National Referral Hospital, Lubaga Hospital, St. Francis Nsambya Hospital, and Mengo Hospital) in Kampala, Uganda. Details of the surveillance methodology have been described elsewhere.[14] In brief, all informative live births, stillbirths, and spontaneous abortions regardless of gestational age were recorded through the surveillance system. Informative births are those in which the presence or absence of an external birth defect can be reliably ascertained. Infants born at home, or at nonparticipating health centers and referred to the surveillance hospitals for follow-up, were not included in the surveillance system. In this study, HIV status was determined through self-reported cards for those with prior diagnoses. Pregnant women without prior HIV testing or documentation of HIV results had on-site testing at the hospital, following national HIV testing guidelines. All WLHIV on ART and HIV-negative women were included in this analysis. To the best of our knowledge, none of the women who received oral PrEP were included in this surveillance project. The birth defect surveillance protocol was reviewed and approved by US Centers for Diseases Control, Joint Clinical Research Center Institutional Review Board (JCRC IRB), and the Uganda National Council for Science and Technology.

Data Collection

Birth defects surveillance data included maternal demographic and reproductive characteristics (eg, obstetric history, HIV status, ART regimen, chronic diseases) and infant characteristics (eg, birth outcomes, infant anthropometric measurements, detailed narrative descriptions of the birth defect, and photographs/drawings of the birth defect). Data were collected by midwives trained in surveillance who examined all births including stillbirths for the presence of external birth defects. ART regimens used during pregnancy were recorded from hospital records and maternal self-reports. ART classes included non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors (INT), and protease inhibitors (PI). ART regimens included efavirenz (EFV), nevirapine (NVP), DTG, atazanavir/ritonavir (ATV/r), and lopinavir/ritonavir (LPV/r) with 2 nucleoside/nucleotide (NRTI) backbone. Nucleoside reverse transcriptases were the backbone of each regimen and all classes were included for review. ART exposure during the periconceptional period was defined as ART use 1 month before conception through the first trimester. ART exposure during pregnancy refers to the use of ART by WLHIV at any time during pregnancy, except those who received single dose nevirapine for prevention of VT identified during labor and delivery.

Informed consent for photographs of the identified birth defects during newborn examination was obtained from mothers/caretakers and photographs were used for birth defects coding and classification. If photograph consent was not obtained, then the examining midwife made a drawing of the birth defect. In addition, all births with identified birth defects had narrative descriptions, which together with the photographs and/or drawings were reviewed by a local birth defects case verification team (2 pediatricians and 1 program manager) and subject matter experts (SMEs) at the US Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD).

Adverse Birth Outcomes

Gestational age was defined as the interval between the date of delivery and the last normal menstrual period (LNMP)

in complete weeks. If the LNMP was unknown or missing, a clinical estimate of gestational age was used, such as estimates from fundal height or abdominal ultrasound. The last menstrual period method was used over ultrasound-based gestational age estimation because of the unavailability of the ultrasound scan timing, which is crucial for accurate dating. We defined preterm delivery as live births occurring at a gestation of <37 weeks. LBW was defined as an infant weighing <2500 grams measured ≤24 hours after birth using digital scales among term (≥37 weeks) live births. SGA was defined as an infant's birth weight more than 2 SDs below the mean weight for infants of the same gestational age, according to Fenton 2013 preterm growth chart reference values.[15] The Fenton growth chart was selected because its extensive data set covers a wide range of gestational ages, making it suitable for both preterm and term populations[15] aligning well with the demographics of the study. Early neonatal death was defined as death among term live births ≤48 hours after delivery or before the mother was discharged from the hospital. Stillbirth was defined as a baby born with no signs of life ≥28 weeks gestation, while a spontaneous abortion was defined as fetal death at <28 weeks gestation. We included the following 16 major external birth defects in the analysis: anencephaly, encephalocele, spina bifida, craniorachischisis, iniencephaly as the different types of NTDs, microcephaly, anophthalmia/microphthalmia, anotia/microtia, cleft palate only, cleft lip with or without cleft palate, imperforate anus, hypospadias (males only), talipes equinovarus, limb deficiencies, gastroschisis, and omphalocele.

Exclusions From Analyses

Women of unknown HIV status and WLHIV not on ART were excluded from all analyses. WLHIV with unknown or incomplete ART regimen information, or women who reported implausible dates of the timing of ART, were also excluded. Owing to challenges in accurately determining birth defects in small fetuses, only births with a birth weight >227 grams were included in the analyses.[16]

Statistical Analysis

Descriptive statistics of maternal and infant characteristics by maternal age group were calculated as frequencies and percentages, and the differences between proportions were tested with Pearson χ^2 test. The prevalence of major external birth defects was assessed by maternal HIV status (ie, WLHIV on ART and HIV-negative women). Prevalence was expressed per 10,000 births and calculated by dividing the number of specific birth defects by the total number of live births, stillbirths, and spontaneous abortions in the participating hospitals. Wilson 95% confidence intervals (CIs) were reported for each birth defect. Birth defects with fewer than 3 cases were not shown because of the instability of the estimate. An infant or fetus with more than 1 major external birth defect was counted as a separate case for each birth defect. An infant or fetus with multiple birth defects in the same category was counted separately for the specific types of birth defects within a category but counted only once for the overall birth defects category. For example, infants with both encephalocele and spina bifida were counted once in tabulations for encephalocele and once in tabulations for spina bifida but only once in the tabulation for the overall category of NTDs. We also assessed the association between ART exposure during the periconceptional period and birth defects, and the association between ART exposure throughout pregnancy and the other adverse birth outcomes. Differences among WLHIV by ARV drug class and individual ARV regimen were assessed by calculating the crude (cPR) and adjusted prevalence ratios (aPR) with 95% CIs using a log-binomial regression model. We identified potential covariates based on the literature and excluded possible collider variables. These potential covariates included maternal age (<20 years, 20–34 years, ≥35 years), parity (P0, P1–3, ≥P4), and number of antenatal care (ANC) visits (none, 1–3, ≥4). Data were analyzed using R Statistical Software[17] (R version 4.2.0) using packages "gtsummary"[18] for tables and "tidyverse" for logistic regression modeling.[19]

RESULTS

Maternal and Infant Characteristics of the Study Population

A total of 203,092 births from 196,373 mothers were included in this analysis. We excluded 1213 women who had unknown HIV status (n = 217), were not on ART (n = 658), had unknown or incomplete ART regimen information (n = 42), reported implausible dates of the timing of ART (n = 51), or gave birth to a live born infant weighing ≤227 grams (n = 245; n = 11 WLHIV on ART and n = 234 HIV-negative women).

The overall birth prevalence of selected major external birth defects was 0.5% in both infants born to women living with HIV (WLHIV) on ART and those born to HIV-negative women (Table 1).

Most of those included in the analysis (92.4%; n = 181,353) were HIV-negative women, and 7.6% (n = 15,020) were WLHIV on ART (Table 2). WLHIV on ART were older than HIV-negative women, with a median age of 28 years (interquartile range [IQR]: 24–32) compared with 26 years (IQR: 22–30), respectively ($P < 0.001$; Table 2). The proportion of WLHIV on ART aged <20 years was significantly lower (n = 700; 4.7%) than HIV-negative women (n = 17,322; 9.6%) ($P < 0.001$), while a significantly higher proportion of WLHIV on ART (n = 2238; 14.9%) were aged ≥35 years compared with HIV-negative women (n = 18,086; 10.0%) ($P < 0.001$). Approximately half of the WLHIV on ART (n = 7905; 52.6%) and HIV-negative women (n = 90,150, 49.7%) attended 1–3 ANC visits. However, fewer WLHIV on ART attended their first ANC visit within the first trimester (n = 999, 9.3%) compared with HIV-negative women (n = 12,975, 9.8%) ($P < 0.012$).

Overall, infants of WLHIV on ART had a lower median birth weight (3020 grams; IQR: 2650–3400) than infants of

TABLE 1. Characteristics Among Infants in Kampala, Uganda, by Maternal HIV Serostatus, August 2015–December 2021

Characteristic	Infants of WLHIV on ART N = 15,566 (7.7%)*	Infants of HIV-negative women N = 187,526 (92.3%)*	Overall N = 203,092*	*P*
Infant sex, n (%)				0.090†
Male	7965 (51.2)	97,083 (51.8)	105,048 (51.7)	
Female	7595 (48.8)	90,408 (48.2)	98,003 (48.3)	
Indeterminate	6 (0.0)	35 (0.0)	41 (0.0)	
Birth outcome, n (%)				0.030†
Live births	14,941 (96.0)	180,194 (96.1)	195,135 (96.1)	
Stillbirths	507 (3.3)	5622 (3.0)	6129 (3.0)	
Spontaneous abortion	118 (0.8)	1710 (0.9)	1828 (0.9)	
Delivery type, n (%)				<0.001†
Vaginal	10,275 (66.0)	118,838 (63.4)	129,113 (63.6)	
Cesarean section	5291 (34.0)	68,688 (36.6)	73,979 (36.4)	
Gestational age				<0.001‡
Median (IQR)	38 (37–40)	38 (37–40)	38 (37–40)	
Range	12–51	8–50	8–51	
Gestational age, wk n (%)				<0.001†
Preterm (<37)	2953 (19.8)	28,957 (16.1)	31,910 (16.4)	
Term (37–<42)	11,018 (73.7)	140,843 (78.2)	151,861 (77.8)	
Post-term (42+)	970 (6.5)	10,394 (5.8)	11,364 (5.8)	
Early neonatal death, n (%)§				0.334†
No	11,926 (99.5)	150,554 (99.5)	162,935 (99.5)	
Yes	62 (0.5)	682 (0.5)	748 (0.5)	
Birth weight				<0.001‡
Median (IQR)	3020 (2,650–3400)	3150 (2,785–3500)	3130 (2,770–3490)	
Range	241–5540	228–7000	228–7000	
Size for gestational age, n (%)				<0.001†
Appropriate-for-gestation age	13,156 (84.9)	164,160 (88.0)	177,316 (87.8)	
Small-for-gestation age	1777 (11.5)	15,624 (8.4)	17,401 (8.6)	
Large-for-gestational age	564 (3.6)	6683 (3.6)	7247 (3.6)	
Implausible values‖	69	1059	1128	
Length for gestational age, n (%)				<0.0012†
Normal	10,145 (89.6)	136,716 (91.9)	146,861 (91.8)	
Stunted	884 (7.8)	8568 (5.8)	9452 (5.9)	
Severely stunted	294 (2.6)	3420 (2.3)	3714 (2.3)	
Implausible values‖	4243	38,822	43,065	
Birth weight, n (%)				<0.001†
Less than 2500	1043 (8.7)	8945 (5.9)	9988 (6.1)	
2500 or more	10,945 (91.3)	142,292 (94.1)	153,236 (93.9)	
Major external birth defects, n (%)¶				0.688†
No defect	15,493 (99.5)	186,596 (99.5)	202,089 (99.5)	
Defect	73 (0.5)	930 (0.5)	1003 (0.5)	

*Median (IQR—interquartile range) for continuous; n (%) for categorical.
†Pearson χ^2 test.
‡Kruskal–Wallis rank sum test.
§Early neonatal death (ENND) was defined as death among live neonates born at term during the first 48 hours or before mother was discharged from the hospital.
‖Implausible values based on the Fenton 2013 preterm growth chart reference z-score values.
¶Limited to births with weight >227 g.

HIV-negative women (3150 grams; IQR: 2785–3500) (Table 1). Compared with infants of HIV-negative women, a higher proportion of infants of WLHIV on ART were stillbirths (n = 507, 3.3% vs n = 5,622, 3.0%; $P < 0.006$), preterm deliveries (n = 2,953, 19.8% vs n = 28,957, 16.1%; $P < 0.001$), SGA (n = 1,777, 11.5% vs n = 15,624, 8.4%; $P < 0.001$), stunted (n = 884, 7.8% vs n = 8,568, 5.8%), and LBW (n = 1,043, 8.7% vs n = 8,945, 5.9%; $P < 0.001$). However, no significant differences were observed in spontaneous abortion, infant sex, ENND, or the overall occurrence of birth defects between infants of WLHIV on ART and HIV-negative women.

TABLE 2. Maternal Characteristics Among Women Living With HIV on Antiretroviral Therapy and HIV-Negative Women in Kampala, Uganda, August 2015–December 2021

Characteristic	Maternal HIV Status		Overall	*P*
	WLHIV on ART* N = 15,020 (7.6%)†	HIV-negative women N = 181,353 (92.4%)†	N = 196,373†	
Maternal age				<0.001‡
Median (IQR)	28 (24–32)	26 (22–30)	26 (22–30)	
Range	13–52	10–59	10–59	
Surveillance site, n (%)				<0.001§
Faith-based hospitals	1933 (12.9)	54,046 (29.8)	55,979 (28.5)	
Mulago hospital	13,087 (87.1)	127,307 (70.2)	140,394 (71.5)	
Surveillance yr, n (%)				<0.001§
2015‖	729 (4.9)	6065 (3.3)	6794 (3.5)	
2016	2476 (16.5)	21,332 (11.8)	23,808 (12.1)	
2017	2938 (19.6)	33,405 (18.4)	36,343 (18.5)	
2018	2775 (18.5)	36,657 (20.2)	39,432 (20.1)	
2019	2696 (17.9)	36,062 (19.9)	38,758 (19.7)	
2020¶	1277 (8.5)	17,295 (9.5)	18,572 (9.5)	
2021	2129 (14.2)	30,537 (16.8)	32,666 (16.6)	
Maternal age, yrs, n (%)				<0.001§
<20	700 (4.7)	17,322 (9.6)	18,022 (9.2)	
20–34	12,082 (80.4)	145,945 (80.5)	158,027 (80.5)	
≥35	2238 (14.9)	18,086 (10.0)	20,324 (10.3)	
Parity, n (%)				<0.001§
P0	2170 (14.4)	57,721 (31.8)	59,891 (30.5)	
P1-3	9742 (64.9)	99,133 (54.7)	108,875 (55.4)	
P≥4	3108 (20.7)	24,499 (13.5)	27,607 (14.1)	
Number of ANC visits, n (%)				<0.001§
None	232 (1.5)	4530 (2.5)	4762 (2.4)	
1–3 Visits	7905 (52.6)	90,150 (49.7)	98,055 (49.9)	
4+ Visits	6883 (45.8)	86,673 (47.8)	93,556 (47.6)	
Timing of 1st ANC visit, n (%)				0.012§
ANC 1 trimester	999 (9.3)	12,975 (9.8)	13,974 (9.8)	
ANC 2 trimester	4728 (44.2)	59,849 (45.1)	64,577 (45.1)	
ANC 3 trimester	4981 (46.5)	59,758 (45.1)	64,739 (45.2)	
Missing/implausible values#	4312	48,771	53,083	

*Women living with HIV (WLHIV) on antiretroviral therapy (ART).
†Median (IQR—inter quartile range) for continuous; n (%) for categorical.
‡Kruskal–Wallis rank sum test.
§Pearson χ^2 test.
‖Surveillance initiated in August 2015.
¶Study activities paused between March 27, 2020, and September 10, 2020, during the coronavirus pandemic.
#Missing/implausible date of ANC initiation.

Infant Exposure to Maternal Antiretroviral Use

Nearly two-thirds (n = 9,857, 63.3%) of infants of WLHIV on ART were exposed periconceptionally (Table 3). Most infants exposed to ART during the periconceptional period were exposed to NNRTI-based ART (n = 8706; 88.3%); while 7.6% (n = 752) were exposed to INT (DTG) and 4% (n = 399) were exposed to PI (ATV/r and LPV/r) (Table 3). Infants exposed during pregnancy were primarily exposed to NNRTI-based ART (n = 13,614; 87.5%), while only 9.7% (n = 1508) and 2.9% (n = 444) were exposed to INT (DTG) and PI (ATV/r and LPV/r), respectively (Table 3).

Prevalence of Major External Birth Defects by Maternal ART Exposure

A total of 44 (0.45%) infants with periconceptional ART exposure had a major external birth defect (Table 3). The most prevalent external birth defects (per 10,000 births) among infants exposed to maternal ART periconceptionally and HIV-negative women, respectively, were hypospadias (19.8 vs 19.5), talipes equinovarus (13.2 vs 13.4), and NTDs (14.2 vs 8.6) (Table 4).

After adjusting for maternal age, parity, and number of ANC visits, a higher prevalence was observed for spina bifida among infants born to WLHIV on ART periconceptionally compared with HIV-negative women (aPR = 2.45, 95% CI:

TABLE 3. ART Exposure Among Infants With or Without Major External Birth Defects and Other Adverse Birth Outcomes Born to Women Living With HIV on ART, Kampala, Uganda, August 2015–December 2021

	Periconceptional exposure to ART[a]				Exposure anytime during pregnancy to ART[b]			
Characteristic	Defect N = 44 (0.45%)*	No defect N = 9813 (99.6%)*	Overall N = 9857*	*P*-value	Other adverse birth outcomes, N = 6822 (43.8%)*	No other adverse birth outcome, N = 8744 (56.2%)*	Overall, N = 15,566*	*P*
ARV-based regimen, n (%)				0.005†				0.567‡
EFV + 2NRTI	35 (79.5)	7120 (72.6)	7155 (72.6)		3875 (75.7)	7965 (76.3)	11,840 (76.1)	
NVP+ 2NRTI	1 (2.3)	1550 (15.8)	1551 (15.7)		579 (11.3)	1195 (11.4)	1774 (11.4)	
DTG + 2NRTI	3 (6.8)	749 (7.6)	752 (7.6)		523 (10.2)	985 (9.4)	1508 (9.7)	
ATV/r + 2NRTI	4 (9.1)	365 (3.7)	369 (3.7)		133 (2.6)	280 (2.7)	413 (2.7)	
LPV/r + 2NRTI	1 (2.3)	29 (0.3)	30 (0.3)		12 (0.2)	19 (0.2)	31 (0.2)	
ARV drug class, n (%)				0.07†				0.303‡
NNRTI	36 (81.8)	8670 (88.4)	8706 (88.3)		4454 (87.0)	9160 (87.7)	13,614 (87.5)	
INT	3 (6.8)	749 (7.6)	752 (7.6)		523 (10.2)	985 (9.4)	1508 (9.7)	
PI	5 (11.4)	394 (4.0)	399 (4.0)		145 (2.8)	299 (2.9)	444 (2.9)	

*n (%) for categorical.
†Fisher exact test.
‡Pearson χ^2 test.
[a]ART exposure during the periconceptional period (i.e., 1 month before conception through first trimester).
[b]ART exposure during pregnancy. Other adverse birth outcomes defined as an infant presents with either a small for gestational age, early neonatal death, preterm live birth <37 weeks, stillbirth, or spontaneous abortion.

1.27, 4.33). Adjusted PRs were elevated but not statistically significant among WLHIV on ART periconceptionally compared with HIV-negative women for NTDs overall (aPR = 1.66, 95% CI: 0.91, 2.77), and omphalocele (aPR = 1.3, 95% CI: 0.51, 2.83) (Table 4). There were no statistically significant differences in the prevalence of the other major external birth defects comparing WLHIV on ART with HIV-negative women. Results were similar when comparing WLHIV on ART during pregnancy and HIV-negative women (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C415).

The prevalence of NTDs was significantly higher among infants whose mothers were on ART at conception compared with those who were not (aPR = 1.80, 95% CI: 1.04, 3.13). Within the category of NTDs, spina bifida showed a strong association, with infants exposed to maternal ART at conception being significantly more likely to have spina bifida compared with those unexposed (aPR = 2.64, 95% CI: 1.44 to 4.86) (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C415).

Prevalence of Major External Birth Defects Among Infants Exposed to Periconceptional ART

Analysis of birth defects by ART exposure during the periconceptional period was conducted for birth defects with ≥3 cases. After adjusting for maternal age, parity, and number of ANC visits, aPRs were elevated but not statistically significant among infants of WLHIV on NNRTI-based ART compared with infants of HIV-negative women for NTDs (aPR = 1.55, 95% CI: 0.88 to 2.74) and talipes equinovarus (aPR = 1.13, 95% CI: 0.64 to 2.00; Table 5). NTDs were more prevalent among infants exposed to EFV during the periconceptional period compared with infants of HIV-negative women (cPR = 1.86, 95% CI: 1.05 to 3.29; aPR = 1.85, 95% CI: 1.05 to 3.26), driven by an association with spina bifida (cPR = 2.55, 95% CI: 1.33 to 4.91; aPR = 2.46, 95% CI: 1.28 to 4.72); there was no association between NTDs and non-EFV-based regimens (cPR = 1.01, 95% CI: 0.76 to 1.33; aPR = 1.06, 95% CI: 0.80 to 1.41) (data not shown).

Other Adverse Birth Outcomes Among Infants With ART Exposure During Pregnancy

In a multivariable model that adjusted for maternal age, parity, and number of ANC visits, WLHIV on ART during pregnancy were more likely to have an infant that was SGA compared with HIV-negative women (NNRTIs: aPR = 1.46, 95% CI: 1.38 to 1.54; PIs: aPR = 1.74, 95% CI: 1.31 to 2.30; INT: aPR = 1.37, 95% CI: 1.16 to 1.62; Table 5). Infants exposed to NNRTI-based ART were more likely to be ENNDs compared with unexposed infants (aPR = 1.34, 95% CI: 1.03 to 1.74). Infants exposed to NNRTIs and INTs during pregnancy were also more likely to be preterm (NNRTI: aPR = 1.27, 95% CI: 1.21 to 1.32; INT: aPR = 1.61, 95% CI: 1.42 to 1.82) compared with infants of HIV-negative women. Post-term births were more likely to occur among infants exposed to NNRTIs (aPR = 1.23, 95%

TABLE 4. Prevalence of Major External Birth Defects Among Infants Exposed to Maternal ART Periconceptionally in Kampala, Uganda, August 2015–December 2021

	Number		Prevalence (95% CI)[1]		Prevalence Ratios (PR)	
Birth Defects	**WLHIV on ART**	**HIV-Negative**	**WLHIV on ART**	**HIV-negative women**	**cPR (95% CI)*,†**	**aPR (95% CI)***
NTDs‡	14	162	14.2 (8.5–23.8)	8.6 (7.4–10.1)	1.64 (0.91 to 2.73)	1.66 (0.91 to 2.77)
Anencephaly/craniorachischisis/ iniencephaly	1	51	1.0 (0.2–5.7)	2.7 (2.1–3.6)	NA	NA
Encephalocele	2	24	2.0 (0.6–7.4)	1.3 (0.9–1.9)	NA	NA
Spina bifida	12	92	12.2 (7.0–21.3)	4.9 (4.0–6.0)	2.48 (1.29 to 4.34)†	2.45 (1.27 to 4.33)†
Microcephaly	3	36	3.0 (1.0–8.9)	1.9 (1.4–2.7)	1.59 (0.38 to 4.39)	1.55 (0.47 to 5.09)
Anophthalmia/Microphthalmia	1	37	1.0 (0.2–5.7)	2.0 (1.4–2.7)	NA	NA
Anotia/microtia	1	32	1.0 (0.2–5.7)	1.7 (1.2–2.4)	NA	NA
Orofacial clefts	7	132	7.1 (3.4–14.7)	7.0 (5.9–8.3)	1.01 (0.43 to 2.00)	0.98 (0.45 to 2.10)
Cleft palate	2	14	2.0 (0.6–7.4)	0.7 (0.4–1.3)	NA	NA
Cleft lip with and without cleft palate	5	118	5.1 (2.2–11.9)	6.3 (5.3–7.5)	0.81 (0.29 to 1.77)	0.79 (0.28 to 1.75)
Imperforate anus	2	36	2.0 (0.6–7.4)	1.9 (1.4–2.7)	NA	NA
Hypospadias§	10	189	19.8 (10.8–36.4)	19.5 (16.9–22.4)	1.02 (0.50 to 1.82)	1.11 (0.55 to 2.00)
Talipes equinovarus	13	252	13.2 (7.7–22.6)	13.4 (11.9–15.2)	0.98 (0.53 to 1.64)	1.03 (0.56 to 1.73)
Limb deficiency	5	110	5.1 (2.2–11.9)	5.9 (4.9–7.1)	0.86 (0.31 to 1.91)	0.81 (0.28 to 1.79)
Omphalocele	6	78	6.1 (2.8–13.3)	4.2 (3.3–5.2)	1.46 (0.57 to 3.08)	1.33 (0.51 to 2.83)
Gastroschisis	0	40	NA	2.1 (1.6–2.9)	NA	NA

Owing to challenges in accurately determining a birth defect on small fetuses, only births with a weight more than 227 g were included in the analyses for birth defects. NA—not applicable (for cell counts <3).

*Denominator for infants exposed to ART = 15,566; denominator for infants among HIV-negative women = 187,526; prevalence=birth prevalence/10,000 births; (adjusted for maternal age (<20, 20–34, ≥35 years), parity (P0, P1-3, ≥P4), and number of ANC visits (none, 1–3 visits, ≥4 visits).

†$P < 0.05$.

‡NTDs—Two infants from WLHIV presented with both encephalocele and spina bifida; 4 infants from HIV-negative women presented with both encephalocele and spina bifida and 1 infant with both anencephaly and spina bifida.

§88 diagnosed as glandular hypospadias (Q54.0).

CI: 1.16, 1.32) but less likely if exposed to INT (aPR = 0.75, 95% CI: 0.58, 0.98) compared with infants of HIV-negative women.

DISCUSSION

Overall, we found no significant difference in the occurrence of the selected major birth defects of interest to our study among infants born to WLHIV on ART during pregnancy or periconceptionally compared with those born to HIV-negative women. These findings are similar to other smaller studies that have compared the overall association of ARV exposure during pregnancy with congenital anomalies.[11,12] However, in our large surveillance study, some differences by type of birth defect have been noted when the women are grouped by ART drug class and individual ART-based regimen compared with HIV-negative women. Previously, studies found no association between first-trimester use of EFV and birth defects,[8,20,21] including a recent study in South Africa that focused on the timing of ART during pregnancy[22] and a recent systematic review.[23] However, the systematic review reported a 10% increase of birth defects among births with PI exposure and a 60% increase with INTs exposure.[23] Differences between our study and others, like the Ford et al meta-analysis,[8] might be attributed to variations in study populations, ART regimens, geographical factors, methodologies, and focus on birth defects. Another review and network meta-analysis found that lopinavir-containing regimens were associated with the highest risks of adverse perinatal outcomes.[24] Our study had very few women on LPV/r containing ART and no differences were noted.

We found that periconceptional exposure to EFV was associated with a higher birth prevalence of NTDs, but a Botswana study found no such link.[5] Currently, most pregnant WLHIV are on DTG-based regimens rather than EFV. Ongoing BD surveillance for DTG exposure and its association with NTDs are essential for monitoring adverse pregnancy outcomes.

Although our results showed significant differences in various characteristics between infants of WLHIV on ART

TABLE 5. Associations of Infant ART Exposure During Pregnancy With Adverse Birth Outcomes and Infant ART Exposure Periconceptionally With Birth Defects by Drug Class, Kampala, Uganda, August 2015–December 2021

		NNRTI			PI			INT		
Characteristic	**Unexposed (n)N**	**Exposed (n)**	**PR (95% CI)*,†**	**aPR (95% CI)*,†**	**Exposed (n)**	**PR (95% CI)*,†**	**aPR (95% CI)*,†**	**Exposed (n)**	**PR (95% CI)*,†**	**aPR (95% CI)*,†**
Birth outcome										
Live births	180,194	13,063	—	—	431	—	—	1447	—	—
Stillbirths	5622	446	1.09 (0.99 to 1.20)	1.06 (0.96 to 1.16)	9	0.67 (0.35 to 1.30)	0.61 (0.32 to 1.18)	52	1.15 (0.87 to 1.52)	1.14 (0.86 to 1.50)
Spontaneous abortion	1710	105	0.86 (0.71 to 1.04)	0.98 (0.81 to 1.20)	4	0.98 (0.37 to 2.62)	0.87 (0.31 to 2.39)	9	0.66 (0.34 to 1.27)	0.79 (0.41 to 1.54)
ENND										
No	150,554	10,471	—	—	350	—	—	1105	—	—
Yes	682	56	1.17 (0.90 to 1.52)	1.34 (1.03 to 1.74)*	0	NA	NA	6	1.20 (0.54 to 2.67)	1.41 (0.63 to 3.14)
Gestational age										
Term (37–<42 weeks)	140,843	9639	—	—	326	—	—	1053	—	—
Preterm (<37 weeks)	28,957	2536	1.26 (1.20 to 1.31)***	1.27 (1.21 to 1.33)***	81	1.21 (0.95 to 1.54)	1.17 (0.91 to 1.49)	336	1.55 (1.37 to 1.75)***	1.61 (1.42 to 1.82)***
Post-term (42+ wk)	10,394	888	1.23 (1.15 to 1.32)***	1.23 (1.15 to 1.32)***	24	1.00 (0.66 to 1.51)	1.02 (0.67 to 1.55)	58	0.75 (0.57 to 0.97)*	0.75 (0.58 to 0.98)*
Size for gestational age										
AGA	164,160	11,507	—	—	368	—	—	1281	—	—
SGA	15,624	1562	1.39 (1.32 to 1.46)***	1.46 (1.38 to 1.54)***	57	1.63 (1.23 to 2.15)***	1.74 (1.31 to 2.30)***	158	1.29 (1.10 to 1.53)**	1.37 (1.16 to 1.62)***
LGA	6683	484	1.03 (0.94 to 1.13)	0.98 (0.89 to 1.07)	18	1.20 (0.75 to 1.93)	1.07 (0.66 to 1.71)	62	1.19 (0.92 to 1.53)	1.13 (0.88 to 1.46)
Birth defects‖,§										
NTDs	162	11	1.54 (0.85 to 2.78)	1.55 (0.86 to 2.81)						
Oral facial clefts	132	5	0.97 (0.40 to 2.33)	0.93 (0.39 to 2.24)						
Hypospadias¶	189	8	0.96 (0.48 to 1.91)	1.06 (0.53 to 2.12)						
Talipes equinovarus	252	11	1.05 (0.58 to 1.90)	1.13 (0.63 to 2.04)						
Limb deficiency	110	4	0.98 (0.37 to 2.61)	0.95 (0.35 to 2.52)						
Omphalocele	78	3	0.98 (0.32 to 3.04)	0.92 (0.30 to 2.84)						

The comparison group (unexposed) is the infants of HIV-negative mothers (n = 187,526). For analyses on birth outcomes and birth defects denominator for unexposed infants of HIV-negative women = 187,526; for analyses for ENND, denominator for unexposed live born term infants of HIV-negative women = 180,194; for analyses on gestational age, denominator for unexposed live born infants of HIV-negative women = 180,194; for analyses on gestational age, denominator for term live births exposed to mothers on NNRTI = 13,063; denominator for unexposed live born term infants of HIV-negative women = 18,6467.

*NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INT, integrase inhibitors.

†*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

§Birth defects exposures occurring during the periconceptional (before and during the first trimester) period; denominator for infants exposed to ART periconceptionally = 8706 for NNRTI, 399 for PI, 752 for INT; suppressed cells with cases less than 3; microcephaly major ear/eye defects, imperforate anus, and gastroschisis with cell counts of <3 were not displayed in this table.

‖Adjusted for maternal age (<20, 20–34, 35+ year), parity, and number of ANC visits (none, 1–3 visits, 4+ visits).

¶Includes hypospadias type I (Q54.0).

and HIV-negative women, the clinical relevance varies. Preterm birth and SGA are more clinically significant, while slight differences in stillbirth rates and birth weight may be less consequential in well-managed clinical settings.[25,26]

ART for all pregnant and breastfeeding WLHIV has significantly reduced VT of HIV. Previously, women were primarily on Option B+ that was an NNRTI-based regimen for pregnant mothers regardless of maternal CD4 cell counts throughout life, including throughout breastfeeding and subsequent pregnancies.[2] Since 2016, a treat-all approach (test and offer ART to all people living with HIV, regardless of CD4 or clinical stage) was adopted, replacing option B+.[27] In 2018, WHO recommended DTG-containing ART as the preferred first-line regimen for all people living with HIV,

including pregnant women.[28] Transition to DTG as the preferred ART regimen for women of reproductive age in low- and middle-income countries was slow following the initial NTD safety signal from a study in Botswana.[29,30] Updated data from the Botswana birth outcome surveillance system show a further reduction in NTD prevalence among infants exposed to periconceptional DTG. The Tsepamo study indicated that the NTD risk in these infants was similar to those in WLHIV on non-DTG ART regimens and HIV-negative women.[31] With the global commitment to reduce mother-to-child transmission of HIV to <5% by 2030, ART for pregnant women is essential with the hope of providing better health outcomes for mothers and their children. Surveillance programs such as the Botswana (Tsepamo) study and our program are needed to report maternal and birth outcomes, including rare events such as birth defects.

The Uganda birth defects surveillance program is one of the largest African programs, recording more than 200,000 births for a 6-year period. This large sample size has allowed us to analyze the associations of adverse birth outcomes—including birth defects—with ART exposure during the periconceptional period and pregnancy. Our results further support a recent review of pregnancy outcomes among WLHIV on ART, which reported that HIV-exposed infants were at higher risk of adverse outcomes, including preterm birth, poor growth, infectious morbidity, and death compared with infants born to HIV-negative mothers.[32] Studies have shown that adverse birth outcomes, such as stillbirth, ENND, preterm birth, and SGA, were higher among WLHIV.[33–36] We found that the risk of SGA was higher with periconceptional exposure to ARV. However, we did not find that those with PI exposure were at increased risk of preterm birth. This may be because the primary PI was atazanavir and not lopinavir/ritonavir, which has been reported to increase the risk of preterm birth[37–39]; however, other studies have also not shown an increased risk of preterm birth with maternal PI exposure.[32,40–42]

Strengths and Limitations

There were some limitations to this study, including inaccurate gestational age calculation based on maternal recall of LNMP and date of ART initiation. Although first-trimester ultrasound is the most reliable method for dating pregnancy and should be preferred over the last menstrual period when there is a significant discrepancy, most study participants attended their first ANC visit after the first trimester.[43] In addition, the largest proportion of women in this surveillance were on EFV-containing ART, and few women were on DTG and ATV/r-containing regimens. Our surveillance had fewer than 800 women with periconceptional exposure to DTG and only 1 NTD case; thus, there is a need for continued surveillance activities because DTG-based regimens are further scaled up with additional analyses. This surveillance system has several strengths, including a large cohort with 99% coverage of all eligible births, photographs and expert confirmation of birth defects coding and classification, active surveillance, and systematic collection of data for a 6-year period.

Implications

Because new antiretroviral medications and formulations are introduced for use among women of reproductive age and during pregnancy, surveillance systems can be used to determine the prevalence of adverse birth outcomes and association with birth defects or other rare outcomes.[3,44] Finally, adverse birth outcomes and birth defects have many causes, such as infections, poor nutrition, environmental exposure, and genetic factors[45]; surveillance systems can serve as a platform to assess potential causes and risk factors that may contribute to these adverse outcomes.[46] With continued support, this program can serve as a platform to assess the trend of birth outcomes because more women in Uganda are transitioned to dolutegravir or other newly introduced antiretrovirals (eg, long-acting injectable cabotegravir for PrEP, cabotegravir/rilpivirine for treatment and darunavir) in comparison with previous regimens.

CONCLUSIONS

In our study, WLHIV were primarily on EFV-based ART and were more likely than HIV-negative women to experience selected adverse birth outcomes. Furthermore, periconceptional exposure to EFV was associated with a higher risk of spina bifida, however, this result should be interpreted with caution because of the small number of cases and existing safety data. Because additional surveillance data become available, future analyses by ARV drug class and individual drugs with more cases will be able to refute or confirm the findings of maternal ARV use and adverse birth outcomes and birth defects.

REFERENCES

1. World Health Organization. *Update of Recommendations on First- and Second-Line Antiretroviral Regimens; Policy Brief*. Geneve, Switzerland; World Health Organization.
2. Astawesegn FH, Stulz V, Conroy E, et al. Trends and effects of antiretroviral therapy coverage during pregnancy on mother-to-child transmission of HIV in Sub-Saharan Africa. Evidence from panel data analysis. *BMC Infect Dis*. 2022;22:134.
3. Mofenson LM, Pozniak AL, Wambui J, et al. Optimizing responses to drug safety signals in pregnancy: the example of dolutegravir and neural tube defects. *J Int AIDS Soc*. 2019;22:e25352.
4. Rebecca Zash. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva: World Health Organization; June 2013.
5. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29:721–727.
6. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *Plos Med*. 2014;11:e1001635.
7. Martinez de Tejada B, Gayet-Ageron A, Winterfeld U, et al. Birth defects after exposure to efavirenz-based antiretroviral therapy at conception/first trimester of pregnancy: a multicohort analysis. *J Acquir Immune Defic Syndr*. 2019;80:316–324.
8. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2014;28(suppl 2):S123–S131.
9. Dorward J, Lessells R, Drain PK, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries:

uncertainties and opportunities for implementation and research. *Lancet HIV*. 2018;5:e400–e404.
10. Zash RM, Williams P, Holmes LB. What is the risk of major congenital abnormalities among women on antiretroviral therapy? *AIDS*. 2018;32: 403–404.
11. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381:827–840.
12. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med*. 2018;379:979–981.
13. Mofenson LM. In-utero ART exposure and the need for pharmacovigilance. *Lancet Glob Health*. 2018;6:e716–e717.
14. Mumpe-Mwanja D, Barlow-Mosha L, Williamson D, et al. A hospital-based birth defects surveillance system in Kampala, Uganda. *BMC Pregnancy Childbirth*. 2019;19:372.
15. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.
16. National Birth Defects Prevention Network (NBDPN). *Guidelines for Conducting Birth Defects Surveillance*. Atlanta, GA: National Birth Defects Prevention Network Inc.; 2004.
17. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Core Team; 2022.
18. Sjoberg D, Whiting K, Curry M, et al. Reproducible summary tables with the gtsummary package. *R J*. 2021;13:570–580.
19. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4:1686.
20. Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS*. 2010;24:1461–1470.
21. Martinez de Tejada B, Gayet-Ageron A, Winterfeld U, et al. Birth defects after exposure to efavirenz-based antiretroviral therapy at conception/first trimester of pregnancy: a multicohort analysis. *J Acquir Immune Defic Syndr (1999)*. 2019;80:316–324.
22. Mehta UC, van Schalkwyk C, Naidoo P, et al. Birth outcomes following antiretroviral exposure during pregnancy: initial results from a pregnancy exposure registry in South Africa. *South Afr J HIV Med*. 2019;20:971.
23. Alemu FM, Yalew AW. Does antiretroviral therapy cause congenital malformations? A systematic review and meta-analysis. *Epidemiol Health*. 2021;43:e2021008.
24. Tshivuila-Matala COO, Honeyman S, Nesbitt C, et al. Adverse perinatal outcomes associated with antiretroviral therapy regimens: systematic review and network meta-analysis. *AIDS*. 2020;34:1643–1656.
25. Chersich MF, Pham MD, Areal A, et al. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ*. 2020;371: m3811.
26. Christian P, Lee Se Fau-Donahue Angel M, Donahue Angel M, et al. *Risk of Childhood Undernutrition Related to Small-For-Gestational Age and Preterm Birth in Low- and Middle-Income Countries*:1464–3685. (Electronic).
27. WHO. Prevention of mother-to-child transmission - technical update. In Africa WROf. *WHO Regional Office for Africa*; Geneva: WHO; 2017.
28. Barlow-Mosha L, Serunjogi R, Kalibbala D, et al. Prevalence of neural tube defects, maternal HIV status, and antiretroviral therapy from a hospital-based birth defect surveillance in Kampala, Uganda. *Birth Defects Res*. 2022;114:95–104.
29. Romo ML, Patel RC, Edwards JK, et al. Disparities in dolutegravir uptake affecting females of reproductive age with HIV in low- and middle-income countries after initial concerns about teratogenicity: an observational study. *Ann Intern Med*. 2022;175:84–94.
30. Alhassan Y, Twimukye A, Malaba T, et al. Engendering health systems in response to national rollout of dolutegravir-based regimens among women of childbearing potential: a qualitative study with stakeholders in South Africa and Uganda. *BMC Health Serv Res*. 2020;20:705.
31. Rebecca ZLBH, Diseko M, Jacobson DL, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. *AIDS* 2022. Montreal, Quebec, Canada: 24th International AIDS Conference (AIDS 2022), Montreal, Quebec, Canada; July 29 to August 2, 2022.
32. Eckard AR, Kirk SE, Hagood NL. Contemporary issues in pregnancy (and offspring) in the current HIV era. *Curr Hiv/aids Rep*. 2019;16:492–500.
33. Zash R, Souda S, Chen JY, et al. Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana. *J Acquir Immune Defic Syndr (1999)*. 2016;71:428–436.
34. Goulding AN, Meeks K, Shay L, et al. Antiretroviral therapy in pregnancy: a 2023 review of the literature. *Curr HIV/aiDs Rep*. 2024; 21:1–10.
35. Hu F, Liang JJ, Lu JJ, et al. Effects of antiretroviral therapy and HIV exposure in utero on adverse pregnancy and infant outcomes: a prospective cohort study in guangzhou, China. *Biomed Environ Sci*. 2019;32:719–729.
36. Tan Y, Wu S, Yan Y, et al. Adverse pregnancy outcomes associated with antiretroviral therapy initiated before pregnancy and during pregnancy: a retrospective study in Hubei province, China. *Front Med (Lausanne)*. 2023;10:1158962.
37. Favarato G, Townsend CL, Bailey H, et al. Protease inhibitors and preterm delivery: another piece in the puzzle. *AIDS*. 2018;32:243–252.
38. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis*. 2011;204:506–514.
39. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis*. 2006;193:1195–1201.
40. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis*. 2012;54:1348–1360.
41. Koss CA, Natureeba P, Plenty A, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy. *J Acquir Immune Defic Syndr (1999)*. 2014;67:128–135.
42. Azria E, Moutafoff C, Schmitz T, et al. Pregnancy outcomes in women with HIV type-1 receiving a lopinavir/ritonavir-containing regimen. *Antivir Ther*. 2009;14:423–432.
43. Committee on Practice B-O. The American institute of ultrasound in M. Practice bulletin No. 175: ultrasound in pregnancy. *Obstet Gynecol*. 2016;128:e241–e256.
44. Renaud F, Mofenson LM, Bakker C, et al. Surveillance of ARV safety in pregnancy and breastfeeding: towards a new framework. *J Int AIDS Soc*. 2022;25(suppl 2):e25922.
45. Toufaily MH, Westgate MN, Lin AE, et al. Causes of congenital malformations. *Birth Defects Res*. 2018;110:87–91.
46. Botto LD, Mastroiacovo P. From cause to care: triple surveillance for better outcomes in birth defects and rare diseases. *Eur J Med Genet*. 2018;61:551–555.