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Prevalence of neural tube defects, maternal HIV status, and antiretroviral therapy from a hospital-based birth defect surveillance in Kampala, Uganda

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Abstract

Background: The estimated prevalence of neural tube defects (NTDs) in Africa is 11.7 per 10,000 live births; however, data on the impact of antiretroviral therapy (ART) during pregnancy and the risk for birth defects in Africa are limited.

Methods: Data from a hospital-based surveillance program at four hospitals in Kampala, Uganda were used to estimate the baseline prevalence of NTDs and assess potential associations with HIV status and ART use. All live births, stillbirths, and spontaneous abortions delivered at the participating hospitals affected with selected birth defects between August 2015 and December 2018 were included. Trained midwives collected data from hospital records, maternal interviews, photographs, and narrative descriptions of birth defects. We estimated NTD prevalence per 10,000 births (live, stillbirths, spontaneous abortions), prevalence ratios, and 95% confidence intervals (CIs).

Results: A total of 110,752 births from 107,133 women were included in the analysis; 9,394 (8.8%) women were HIV-infected and among those with HIV infection, 95.6% ($n = 8{,}977$) were on ART at delivery. Overall, 109 births were affected with NTDs, giving a prevalence of 9.8 (95% CI [8.2, 11.9]). Spina bifida ($n = 63$) was the most common type of NTD, with a prevalence of 5.7 (95% CI [4.4, 7.3]), followed by anencephaly ($n = 31$), with a prevalence of 2.8 (95% CI [2.0, 4.0]).

Conclusion: The prevalence of NTDs among births in Kampala, Uganda is consistent with current estimates for Africa. With the continued introduction

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of new medications that may be taken during pregnancy, sustainable birth defect surveillance systems and pharmacovigilance are indicated.

1 | INTRODUCTION

Neural tube defects (NTDs) are one of the most common congenital malformations worldwide with an estimated 300,000 cases per year (Christianson, Howson, & Modell, 2005). The neural tube is formed during the first 4 weeks after conception and failure to close by Day 28 of embryonic development results in defects of the brain and spinal cord (Copp & Greene, 2010). The three most common types of NTDs are spina bifida, anencephaly, and encephalocele; the spectrum of NTDs also includes craniorachischisis and iniencephaly, which are rare (Avagliano et al., 2019; Holmes, Toufaily, & Westgate, 2018). While the etiology of NTDs is not fully understood, the mechanism is thought to be a multifactorial interaction between genetic predisposition and potentially modifiable maternal or environmental risk factors, such as folate (Copp & Greene, 2010).

Few studies have reported NTD prevalence in low- and middle-income countries (LMIC). However, a recent systematic review of data from available literature, birth defect registries, and published reports between January 1990 and July 2014 from eight countries estimated the NTD prevalence in Africa to be 11.7 per 10,000 live births (Zaganjor et al., 2016).

In May 2018, the Botswana Tsepamo study raised concerns that the use of dolutegravir (DTG)-based antiretroviral therapy (ART) at the time of conception may be associated with an increased risk of NTDs (Zash, Makhema, & Shapiro, 2018). DTG, an integrase inhibitor used for treatment of HIV, was introduced to some LMIC in 2016 and is currently the World Health Organization's (WHO) preferred first-line regimen for all people living with HIV initiating ART, including women and adolescent girls of childbearing potential (WHO, 2019). An update to the initial concerns reported in the Tsepamo study showed that NTDs occurred in 3 per 1,000 deliveries among women on DTG at the time of conception compared to 1 per 1,000 deliveries among women taking other antiretroviral (ARV) regimens (Zash et al., 2019). As countries adopt DTG into their national HIV guidelines, WHO has recommended birth defect surveillance and pharmacovigilance is conducted to monitor birth outcomes (WHO, 2019). However, a key element of pharmacovigilance understands the baseline prevalence of NTDs among infants born to both HIV-uninfected and HIV-infected women in order to make comparisons and identify potential existing risk factors prior to the introduction of new treatments.

To estimate the prevalence of major external birth defects in Uganda, a hospital-based surveillance system was established at four hospitals in Kampala in 2015 (Mumpe-Mwanja et al., 2019). The purpose of this analysis was to provide an estimate of the baseline prevalence and factors associated with NTDs prior to the adoption of DTG-based regimens in Kampala, Uganda and assess the association with HIV status and ART use.

2 | METHODS

This analysis includes data for births that occurred from August 2015 to December 2018 from an ongoing hospital-based birth defects surveillance system at four urban hospitals in Kampala, Uganda. The methods have been described elsewhere (Mumpe-Mwanja et al., 2019). Briefly, all informative live births and fetal losses (stillbirths and spontaneous abortions) for which the presence or absence of a birth defect could be determined were included in the surveillance system, regardless of gestational age. Stillbirth was defined as fetal loss at 28 or more weeks gestation, and spontaneous abortion was defined as any informative loss less than 28 weeks gestation. Infants born at home (approximately 6% of births in Kampala; UBOS, 2017), or at nonparticipating health centers and referred to the surveillance hospitals for follow-up, were not included in the surveillance system.

2.1 | Data collection

Surveillance midwives collected birth defects surveillance data that included maternal demographic and reproductive characteristics (obstetric history, HIV status, HIV treatment) and infant characteristics (birth outcomes, birth weight, gestational age, and a detailed narrative description of the defect and photographs/drawings of the birth defect). Information on maternal HIV status and ART was obtained from antenatal records and inpatient hospital records. Information on all live births, stillbirths, and spontaneous abortions was collected between the time of birth and discharge which usually occurs within the first 24 hr after delivery.

All births were examined by surveillance midwives for the presence of birth defects. Infants identified with birth defects were confirmed by a surveillance doctor. Informed consent was obtained for photographs. An illustrative

drawing of the birth defect was done by the examining midwife for those pregnancies affected by a defect for which the mother declined to consent for photographs. All narrative descriptions, photographs, and drawings were reviewed by birth defect experts at U.S. Centers for Disease Control and Prevention (CDC). More details on data collection are published elsewhere (Mumpe-Mwanja et al., 2019).

2.2 | Statistical analysis

Prevalence was calculated by aggregating the number of infants affected with NTDs as the numerator, and the total number of live births, stillbirths, and spontaneous abortions delivered as the denominator, expressed per 10,000 births. All live births included mothers who had a live singleton birth or multiple live births. All stillbirths included mothers who had a singleton stillbirth or had multiple births with at least one stillborn. Spontaneous abortion included mothers who had at least one spontaneously aborted birth. Mothers were only counted once in the earliest outcome. Prevalence estimates were calculated for each type of NTD. Infants with more than one NTD were counted only once in the overall NTD prevalence estimate but included in each of the estimates for specific types of NTDs. Wilson's 95% confidence interval (CI) was calculated for each prevalence estimate. We also assessed whether the prevalence of NTDs differed by infant sex, birth outcome, maternal HIV status, maternal ART regimen at conception, maternal age, whether the mother was referred from another health center, the trimester of the first antenatal visit, and parity. Differences were assessed by calculating the crude prevalence ratios (PRs) with 95% CIs using a log-binomial regression model. Data were analyzed using STATA version 15 statistical software (StataCorp., 2017. College Station, TX: StataCorp LLC).

2.3 | Ethics considerations

This study was approved by the Joint Clinical Research Center institutional review board (IRB)/ethics committee, CDC IRB (protocol # 6606.0), and the Uganda National Council of Science and Technology (Ref: HS 1693). Informed consent to participate in the surveillance was waived by both the IRBs. However, written consent was obtained from mothers and/or legal guardians for photographs of newborns with birth defects.

3 | RESULTS

A total of 110,752 births from 107,133 women were included in this analysis (Table 1). The median maternal age was 26 years (interquartile range 22–30) with a range from 12 to 59 years. The majority of deliveries were to HIV negative women (n = 97,580; 91.1%) and to women who received antenatal care (ANC; n = 104,711; 97.7%). Approximately 8.8% (9,394) of women were HIV infected and only 0.1% (159) had unknown HIV status. Approximately, 4.4% (417) with known HIV were not treated with ART during pregnancy. Most of the women presented to ANC for the first time during the second (n = 41,883; 44.6%) or third (n = 44,592; 47.5%) trimester, with only 7.8% (n = 7,359) presenting in the first trimester. A few women (415) reported implausible dates of ANC and 10,462 women reported having received ANC but were unsure of the date it was received. Among HIV-infected mothers, 95.6% (n = 8,977) were on ART at the time of delivery, with 82.1% on efavirenz-based ART plus 2 nucleoside reverse transcriptase inhibitors (NRTI) (n = 7,374) and 14.4% on nevirapine-based ART plus 2 NRTIs (n = 1,292) (Table 1). Few HIV-infected women (n = 287; 3.2%) were on protease-inhibitor based ART, and only four women were on DTG-based ART (0.04%). ART was initiated prior to conception for over half of HIV-infected women (n = 5,255/8945; 58.8%), while thirty-two women initiated ART soon after the date of delivery but before discharge. Only 475 (5.3%) women initiated ART during the first trimester of pregnancy.

The majority of deliveries were live births (n = 105,438; 95.2%) and vaginal deliveries (n = 75,399; 68.1%) were approximately twice as common as deliveries by Cesarean section (n = 35,353; 31.9%) (Table 2). Approximately, 14.5% of infants had low birth weight (<2,500 g; n = 16,085) and 11.3% were born preterm (<37 weeks; n = 12,543). In addition, only 54.8% of those with a spontaneous abortion received prenatal care.

There were 109 infants diagnosed with at least 1 NTD, for an overall prevalence of 9.8 95% CI [8.2, 11.9] per 10,000 births (Table 3). Two infants had both spina bifida and encephalocele. Spina bifida (n = 63; 57.8%) was the most common type of NTD with a prevalence of 5.7 95% CI [4.4, 7.3] per 10,000 births. Approximately, 80% of infants with spina bifida were live born (n = 50; Table 2), and the majority of affected births had the lesion in the lumbar (n = 35; 56%) or sacral (n = 25; 40%) regions of the spine. Anencephaly was the second most common NTD observed in this population (n = 31; 28.4%; prevalence: 2.8 per 10,000 births; 95% CI [2.0, 4.0]). While approximately half (n = 15, 48.4%) of the anencephaly cases were live born, all died soon after birth (Table 2). Encephalocele was the third most common NTD (n = 15; 12.6%; prevalence: 1.4 per 10,000 births; 95% CI [0.8, 2.2]). The majority of infants with encephalocele were live born (80.0%; n = 12) and the location of the encephalocele was primarily in the

TABLE 1 Maternal characteristics by birth outcome, from a hospital-based birth defects surveillance system in Kampala Uganda, August 2015–December 2018[a]

	Total	Live birth	Stillbirth	Spontaneous abortion
	n **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**
Total	107,133(100)	101,990 (95.2)	3,436 (3.2)	1,707 (1.6)
Hospital of delivery				
Lubaga	7,027 (6.6)	6,765 (6.6)	146 (4.3)	116 (6.8)
Mengo	8,971 (8.4)	8,805 (8.6)	107 (3.1)	59 (3.4)
Nsambya	8,744 (8.1)	8,454 (8.3)	156 (4.5)	134 (7.9)
Mulago	82,391 (76.9)	77,966 (76.4)	3,027 (88.1)	1,398 (81.9)
Maternal age, median (IQR)	26 (22–30)	26 (22–30)	26 (22–30)	25 (21–30))
<20 years	10,783 (10.0)	10,200 (10.0)	357 (10.4)	226 (13.2)
20–29 years	67,041 (62.6)	63,905 (62.7)	2,101 (61.2)	1, 035 (60.6)
30–39 years	27,798 (26.0)	26,455 (25.9)	915 (26.6)	428 (25.1)
>40 years	1,511 (1.4)	1,430 (1.4)	63 (1.8)	18 (1.1)
Singleton/multiple deliveries				
Singleton	103,376 (96.5)	98,617 (96.7)	3,208 (93.4)	1,551 (90.9)
Multiple	3,757 (3.5)	3,373 (3.3)	228 (6.6)	156 (9.1)
Maternal HIV status				
Infected	9,394 (8.8)	8,952 (8.8)	323 (9.4)	119 (7.0)
Un-infected	97,580 (91.1)	92,963 (91.1)	3,087 (89.8)	1,530 (89.6)
Unknown	159 (0.1)	75 (0.1)	26 (0.8)	58 (3.4)
Maternal antiretroviral therapy ($n = 9{,}394$)				
Yes	8,977 (95.6)	8,584 (95.9)	297 (92.0)	96 (80.7)
No	417 (4.4)	368 (4.1)	26 (8.0)	23 (19.3)
Type of maternal ART regimen[b] ($n = 8{,}977$)				
EFV + 2NRTI	7,374 (82.1)	7,047 (82.1)	249 (83.8)	78 (81.3)
NVP+ 2NRTI	1,292 (14.4)	1,239 (14.4)	41 (13.8)	12 (12.5)
ATV/r + 2NRTI	261 (2.9)	250 (2.9)	6 (2.0)	5 (5.2)
LPV/r + 2NRTI	26 (0.3)	25 (0.3)	0 (0.0)	1 (1.0)
DTG + 2NRTI	4 (0)	4 (0.0)	0 (0.0)	0 (0.0)
Other[c]	15 (0.2)	15 (0.2)	0 (0.0)	0 (0.0)
Unknown	5 (0.1)	4 (0.0)	1 (0.3)	0 (0.0)
Time of maternal ART initiation ($n = 8{,}945$)				
Before conception[d]	5,255 (58.8)	5,009 (58.6)	174 (59.2)	72 (75.0)
First trimester	475 (5.3)	452 (5.3)	19 (6.5)	4 (4.2)
Second trimester	1,371 (15.3)	1, 310 (15.3)	45 (15.3)	16 (16.7)
Third trimester[e]	1,844 (20.6)	1, 783 (20.8)	56 (19.0)	4 (4.2)
Referred from other health centers[f]				
Yes	47,997 (44.8)	44,172 (43.3)	2,584 (75.2)	1,241 (72.7)
No	59,136 (55.2)	57,818 (56.7)	852 (24.8)	466 (27.3)
Received any antenatal care				
Yes	104,711 (97.7)	100,524 (98.6)	3,252 (94.6)	935 (54.8)
No	2,422 (2.3)	1,466 (1.4)	184 (5.4)	772 (45.2)

TABLE 1 (Continued)

	Total	Live birth	Stillbirth	Spontaneous abortion
	n (%)	*n* (%)	*n* (%)	*n* (%)
First antenatal visit ($n = 93{,}834$)[g]				
First trimester	7,359 (7.8)	6,990 (7.7)	223 (8.6)	146 (20.2)
Second trimester	41,883 (44.6)	40,265 (44.5)	1,105 (42.7)	513 (71.1)
Third trimester	44,592 (47.5)	43,266 (47.8)	1,263 (48.7)	63 (8.7)
Parity				
Primipara	33,003 (30.8)	31,532 (30.9)	966 (28.1)	505 (29.6)
Multipara (P2-3)	59,236 (55.3)	56,518 (55.4)	1, 814 (52.8)	904 (53.0)
Multipara ($p \geq 4$)	14,894 (13.9)	13,940 (13.7)	656 (19.1)	298 (17.4)

Abbreviations: ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; IQR, Interquartile range; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine.

[a]In this table, all live births included mothers who had live singleton birth or multiple live births. All stillbirths included mothers who had a singleton stillbirth or had multiple babies in which at least one infant was stillborn and no infants were spontaneously aborted. Spontaneous abortion included mothers who had at least one baby spontaneously aborted. A mother is only counted once in the more severe category.

[b]ART regimen prior to hospital discharge.

[c]Incomplete ART regimen; Aluvia $n = 2$, Lopinavir $n = 1$, Tenofovir $n = 11$, and Tenofovir/Lamivudine $n = 1$.

[d]Before conception was defined as months on ART more than gestation age.

[e]Excluded 32 mothers who mentioned had started ART after the date of delivery.

[f]Mothers who received antenatal care at a different health center (self-referral) or referred by a health worker to surveillance hospital for delivery from an alternative health center.

[g]Excluded 415 mothers who mentioned implausible dates of antenatal care (ANC) and 10,462 mothers who reported receiving ANC care, but not the date it was received.

TABLE 2 Infant characteristics and number of neural tube defects by birth outcome, from a hospital-based birth defects surveillance system in Kampala Uganda, August 2015–December 2018

	Total	Live birth	Stillbirth	Spontaneous abortion
	n (%)	*n* (%)	*n* (%)	*n* (%)
Births	110,752 (100%)	105,438 (95.2%)	3,463 (3.1%)	1,851 (1.7%)
Infant sex				
Male	57,390 (51.8)	54,407 (51.6)	1,930 (55.7)	1,053 (56.9)
Female	53,335 (48.2)	51,020 (48.4)	1,524 (44.0)	791 (42.7)
Indeterminate	27 (0.0)	11 (0.0)	9 (0.3)	7 (0.4)
Mode of delivery				
Vaginal delivery	75,399 (68.1)	71,508 (67.8)	2,178 (62.9)	1,713 (92.5)
Cesarean delivery	35,353 (31.9)	33,930 (32.2)	1,285 (37.1)	138 (7.5)
Infant birth weight (g)				
Less than 2,500	16,085 (14.5)	13,024 (12.4)	1,242 (35.9)	1,819 (98.3)
2,500 or more	94,667 (85.5)	92,414 (87.6)	2,221 (64.1)	32 (1.7)
Gestational age				
36 weeks or less	12,543 (11.3)	9,651 (9.2)	1,041 (30.1)	1,851 (100.0)
More than 36 weeks	98,209 (88.7)	95,787 (90.8)	2,422 (69.9)	0 (0.0)
Type of NTD[a,b]	109	76 (69.7)	26 (23.9)	7 (6.4)
Spina bifida	63	50 (79.4)	11 (17.5)	2 (3.2)
Anencephaly	31	15 (48.4)	12 (38.7)	4 (12.9)
Encephalocele	15	12 (80.0)	2 (13.3)	1 (6.7)
Craniorachischisis	2	1 (50.0)	1 (50.0)	0 (0.0)

Abbreviation: NTD, neural tube defect.

[a]Two infants had both spina bifida and encephalocele.

[b]NTDs are presented as row percentages.

TABLE 3 Prevalence of neural tube defects by subtype per 10,000 births from a hospital-based birth defects surveillance system in Kampala Uganda, August 2015–December 2018

Neural tube defects	*n*	Prevalence (95% CI)
All neural tube defects[a]	109	9.8 (8.2, 11.9)
Spina bifida	**63**	**5.7 (4.4, 7.3)**
Lumbar spina bifida with hydrocephalus	17	1.5 (1.0, 2.5)
Sacral spina bifida with hydrocephalus	9	0.8 (0.4, 1.5)
Spina bifida with hydrocephalus, site unspecified	1	0.1 (0.0, 0.5)
Lumbar spina bifida without hydrocephalus	18	1.6 (1.0, 2.6)
Sacral spina bifida without hydrocephalus	16	1.4 (0.9 - 2.4)
Spina bifida, site unspecified	1	0.1 (0.0, 0.5)
Thoracic spina bifida with hydrocephalus	1	0.1 (0.0, 0.5)
Anencephaly	**31**	**2.8 (2.0, 4.0)**
Anencephaly, NOS	25	2.3 (1.5, 3.3)
Incomplete anencephaly	6	0.5 (0.2, 1.2)
Encephalocele	**15**	**1.4 (0.8, 2.2)**
Frontal encephalocele	2	0.2 (0.0, 0.7)
Nasofrontal encephalocele	3	0.3 (0.1, 0.8)
Occipital encephalocele	4	0.4 (0.1, 0.9)
Encephalocele of other sites	3	0.3 (0.1, 0.8)
Orbital encephalocele	1	0.1 (0.0, 0.5)
Parietal encephalocele	2	0.2 (0.0, 0.7)
Craniorachischisis	**2**	**0.2 (0.0, 0.7)**

Note: The values marked in bold is to indicate the overall prevalence for each subtype of spina bifida.
Abbreviations: CI, confidence interval; NOS, not otherwise specified.
[a]Two infants had both encephalocele and spina bifida.

occipital ($n = 4$; 26.6%) and nasofrontal ($n = 3$; 20.0%) regions of the skull. Two cases of a rare type of NTD, craniorachischisis, were also identified during the surveillance period (prevalence: 0.2 per 10,000 births; 95% CI [0.0, 0.7]).

Spina bifida was less common among females compared to males (PR: 0.6; 95% CI [0.3, 1.0]) though not statistically significant, while anencephaly was more common among females with a PR of 2.8 (95% CI [1.3, 6.4]) (Table 4). There was no significant difference in the prevalence of NTDs among infants born to HIV-infected mothers compared to HIV-uninfected mothers (PR: 0.7; 95% CI [0.3, 1.5]) (Table 4). Among mothers with HIV infection who delivered an infant with an NTD, six or seven were on ART at conception or during the first trimester—the relevant exposure period for birth defect risk. Four mothers (57.1%) were on an efavirenz based regimen (TDF/3TC + EFV) and two mothers (28.6%) were on an atazanavir/ritonavir (TDF/3TC + ATV/r) based ART at conception. There was a significant difference in the prevalence of spina bifida between infants exposed to maternal atazanavir-based ART (PR 8.2; 95% CI [2.0, 33.0]) compared to HIV negative women (Table 4). However, there were only two infants born with spina bifida whose mothers were on ATV/r-based ART at conception, and the overall number of births among women on ATV/r-based ART was small ($n = 261$), so results are unstable. There were no differences in the overall prevalence of NTDs by maternal age or parity. The prevalence of NTDs among deliveries to women who were referred from another health center was 2.2 times higher than among those who were not referred (95% CI [1.4, 3.3]).

4 | DISCUSSION

The prevalence of NTDs globally has been reported with great variability (range: 0.3–199.4 per 10,000 births), even in different regions within the same country (Zaganjor et al., 2016). Our results are similar to the median NTD prevalence (11.7 per 10,000 live births) from a few select countries in Africa reported in a systematic review (Zaganjor et al., 2016; Zash et al., 2019). However, the data included in the systematic review were available from only eight African countries using hospital-based retrospective case reviews, which have limitations in generalizability and accuracy of birth defect diagnoses. In addition, our prevalence estimate included stillbirths and spontaneous abortions in the denominator and not live births only as reported in the systematic review. The prevalence of NTDs from this hospital-based surveillance system with active case ascertainment provides a more accurate estimate for Kampala compared to previous studies in Uganda with small sample sizes or retrospective data collection (Ndibazza et al., 2011; Ochieng, Muanbi, & Ibingira, 2011; Simpkiss & Lowe, 1961). However, our surveillance data captured only 55% of facility-based births in Kampala, including referrals from other hospitals due to a prenatal diagnosis of a birth defect. Therefore, the prevalence of NTDs in our surveillance system is likely to be higher than in the general population in Kampala, and also may not be generalizable to the country as a whole (Mumpe-Mwanja et al., 2019). In a sensitivity analysis we excluded deliveries to women who referred to one of the surveillance hospitals and the NTD prevalence was 6.4/10,000.

TABLE 4 Crude prevalence ratio (PR) of neural tube defects by selected maternal and infant characteristics from a hospital-based birth defects surveillance system in Kampala Uganda, August 2015–December 2018

	Spina bifida ($N = 62$)		Anencephaly ($N = 30$)		Encephalocele ($N = 15$)		Total NTDs ($N = 107$)[a]	
	n (%)	PR (95% CI)	*n* (%)	PR (95% CI)	*n* (%)	PR (95% CI)	*N* (%)	PR (95% CI)
Sex								
Male	39 (62.9)	1.0	8 (26.7)	1.0	7 (46.7)	1.0	54 (50.5)	1.0
Female	21 (33.9)	0.6 (0.3, 1.0)	21 (70.0)	2.8 (1.3, 6.4)	8 (53.3)	1.0 (0.7, 1.5)	50 (46.7)	1.0 (0.7, 1.5)
Unclear	2 (3.2)	109.0 (27.7, 429.0)	1 (3.3)	265.7 (34.4, 2052.2)	0 (0.0)	—	3 (2.8)	118.1 (39.3, 354.6)
Birth outcome								
Live birth	49 (79.0)	1.0	14 (46.7)	1.0	12 (80.0)	1.0	74 (69.2)	1.0
Stillbirth	11 (17.7)	6.8 (3.6, 13.1)	12 (40.0)	26.1 (12.1, 56.4)	2 (13.3)	5.5 (1.2, 25.0)	26 (24.3)	10.7 (6.9, 16.7)
Spontaneous abortion	2 (3.2)	2.3 (0.6, 9.6)	4 (13.3)	16.3 (5.4, 49.4)	1 (6.7)	5.2 (0.7, 40.1)	7 (6.5)	5.4 (2.5, 11.7)
Maternal HIV status[b]								
Negative	56 (90.3)	1.0	28 (93.3)	1.0	15 (100.0)	1.0	99 (92.5)	1.0
Positive	6 (9.7)	1.1 (0.5, 2.6)	1 (3.3)	0.4 (0.1, 2.7)	0 (0.0)	—	7 (6.5)	0.7 (0.3, 1.6)
Unknown	0 (0.0)	—	1 (3.3)	21.6 (3.0, 157.6)	0 (0.0)	—	1 (0.9)	6.1 (0.9, 43.5)
Maternal ART regimen before second trimester								
HIV negative ($n = 100,853$)	56 (91.8)	1.0	28 (96.6)	1.0	15 (100.0)	1.0	99 (94.3)	1.0
EFV + 2NRTI ($n = 4,404$)	3 (4.9)	1.2 (0.4, 3.9)	1 (3.4)	0.8 (0.1, 6.0)	0 (0.0)	—	4 (3.8)	0.9 (0.3, 2.5)
ATV/r + 2NRTI ($n = 249$)	2 (3.3)	14.5 (3.6, 58.9)	0 (0.0)	—	0 (0.0)	—	2 (1.9)	8.2 (2.0, 33.0)
Maternal age (years)								
<20	3 (4.8)	0.5 (0.1, 1.5)	2 (6.7)	0.5 (0.1, 1.5)	4 (26.7)	3.1 (0.9, 10.4)	9 (8.4)	0.9 (0.4, 1.7)
20–29	41 (66.1)	1.0	17 (56.7)	1.0	9 (60.0)	1.0	66 (61.7)	1.0
30–39	15 (24.2)	0.9 (0.5, 1.6)	11 (36.7)	0.9 (0.5, 1.6)	2 (13.3)	0.6 (0.1, 2.8)	29 (27.1)	1.1 (0.7, 1.6)
>40	3 (4.8)	3.2 (1.0, 10.4)	0 (0.0)	3.2 (1.0, 10.4)	0 (0.0)	—	3 (2.8)	2.0 (0.6, 6.3)
Referred from other health center								
Yes	36 (58.1)	1.7 (1.0, 2.8)	22 (73.3)	3.3 (1.5, 7.5)	10 (66.7)	2.2 (0.7, 6.5)	69 (64.5)	2.2 (1.5, 3.3)
No	26 (41.9)	1.0	8 (26.7)	1.0	5 (33.3)	1.0	38 (35.5)	1.0
Parity								
0	17 (27.4)	1.0	7 (23.3)	1.0	6 (40.0)	1.0	30 (28.0)	1.0
1–3	34 (54.8)	1.1 (0.6, 2.0)	17 (56.7)	1.3 (0.6, 3.2)	8 (53.3)	0.6 (0.2, 1.9)	59 (55.1)	1.1 (0.7, 1.7)
≥4	11 (17.7)	1.4 (0.7, 3.0)	6 (20.0)	1.9 (0.6, 5.6)	1 (6.7)	0.4 (0.0, 3.0)	18 (16.8)	1.3 (0.7, 2.4)

Abbreviations: ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; CI, confidence interval; EFV, efavirenz; NRTI, nucleoside reverse transcriptase inhibitor; PR, prevalence ratio.

[a]One infant with anencephaly exposed to an unknown HIV status.

[b]Two infants had craniorachischisis, and two infants had both encephalocele and spina bifida.

Our results are consistent with those of the Tsepamo study regarding the NTD prevalence reported among women without HIV infection (Zash et al., 2019). It is important to note that the NTD prevalence found in urban areas may not reflect the prevalence in rural areas, where there may be higher rates of folate nutritional deficiency that could influence NTD prevalence (Kancherla & Black, 2018). In addition, countries with mandatory folic acid fortification regulations have reported lower NTD prevalence than those with voluntary or no fortification (Atta et al., 2016). Uganda passed legislation for food fortification of wheat and maize flour with folic acid, iron, zinc, and other B vitamins in 2011; however, compliance has been reported as variable (Kyamuhangire et al., 2013; Uganda MOH, 2011; SPRING, 2018). While folic acid is provided and recommended to all pregnant women once they present for ANC, the majority of the women ascertained for the birth defects surveillance system present after the first trimester and, thus, may not gain from the protective benefit that folic acid has in helping to prevent NTDs.

As of 2019, DTG-based ART is recommended as the preferred treatment by WHO for all people living with HIV, including for pregnant women in order to prevent transmission of HIV to their infants and for their own health (WHO, 2019). Prior to this recommendation, EFV-based ART was recommended as the WHO preferred ART regimen for pregnant women since October 2012 (WHO, 2019). This analysis was conducted prior to the adoption of DTG-based ART in the national ART guidelines with over 80% of women receiving EFV based ART and only four women receiving DTG. Currently, HIV-infected pregnant women in LMIC are primarily treated with EFV, protease inhibitors, and DTG-based ART. To monitor pregnancy outcomes and ART safety, registries, such as the Antiretroviral Pregnancy Registry (APR) (Covington, Tilson, Elder, & Doi, 2004; Scheuerle & Covington, 2004), were established to collect information on pregnancy outcomes among women who are exposed to ARTs during pregnancy (Antiretroviral Pregnancy Registry Steering Committee, 2019). Data from the APR and other studies have since documented no observed increased risk of major birth defects for babies delivered to women on ART compared to the general population (Antiretroviral Pregnancy Registry Steering Committee, 2019; Covington et al., 2004; Knapp et al., 2012). Unfortunately, many LMIC in Africa lack national ARV pregnancy registries and established birth defect surveillance systems or regulations for mandatory reporting of suspected cases by health providers (Blencowe, Kancherla, Moorthie, Darlison, & Modell, 2018; Zaganjor et al., 2016).

Our results support studies that have not observed an increased prevalence of NTDs among HIV-infected women overall, and more specifically among those on EFV-based ART. Spina bifida was more prevalent among women on ATV/r-based ART; however, there were only two cases born to mothers with this exposure, and the total number of HIV-infected women on ATV/r is small in the current data, leading to imprecise estimates and warranting further follow-up. Therefore this finding may be random or entirely due to chance. ATV/r is primarily given as second-line ART therapy in LMIC, and women on this ART regimen may have other unmeasured risk factors for NTDs associated with chronic HIV infection that could have contributed to the higher NTD prevalence. A higher prevalence of birth defects, though not specifically spina bifida or other NTDs, has been observed in some (Williams et al., 2015) (Knapp et al., 2012), but not all (Antiretroviral Pregnancy Registry Steering Committee, 2019) previous studies that have assessed this exposure during pregnancy. Results from these studies and our findings suggest the need for continued pregnancy pharmacovigilance and surveillance of birth outcomes among women on ART.

This hospital-based surveillance system has several strengths, including large size, completeness of information, active case ascertainment, and classification of defects by trained experts (Mumpe-Mwanja et al., 2019). Passive surveillance systems tend to have incomplete data resulting in under ascertainment of NTDs. Voluntary registries, such as the APR, may also have under ascertainment of birth defects. Nevertheless, the limitations of the surveillance include short ascertainment period limited to birth and time of hospital discharge, referral bias, potentially missing spontaneous abortions that are managed at home, and lack of rural hospital participation. Rural setting factors, such as access to health facilities, nutritional status, home births, use of herbal medication and others risk factors, may also contribute to a variance in the prevalence of NTDs, and data on these factors, such as folic acid supplement use, are not routinely available in these surveillance data. While we found the prevalence of NTDs was two times higher among women who were referred, 85% of the women were referred from the urban and periurban areas surrounding Kampala and not the rural areas. In addition, Mulago Hospital is the major referral/teaching hospital in Kampala therefore some women may have been identified as high risk at lower health centers and referred for care.

Our findings indicate that the prevalence of NTDs among births in Kampala, Uganda is similar to the current estimates for Africa. The data from this active surveillance system provide background NTD prevalence estimates in Uganda prior to the designation of DTG-based ART as the preferred first-line treatment for people

living with HIV, which started in August 2018. However, DTG-based ART has now been adopted as the preferred regimen for first- and second-line treatment of all people living with HIV, including pregnant women. In addition, some women who may fail first-line treatment or not tolerate DTG may be changed to ATV/r as an alternative treatment regimen. Therefore with time, as the number of women using DTG and ATV/r captured in the surveillance system increases, we will be able to better assess potential risks for adverse pregnancy outcomes associated with use of these medications during pregnancy, as well as those associated with other new ARV medications that are introduced and may be taken during pregnancy (Dorward et al., 2018) (Mofenson, 2018; Schomaker, Davies, Cornell, & Ford, 2018; Zash et al., 2018). Furthermore, data from birth defect surveillance (Botto & Mastroiacovo, 2018) are important to assess risk factors other than ARVs, to identify potential preventive interventions, and to inform healthcare and other services needed for affected children (Zash et al., 2018).

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CONFLICT OF INTEREST

The authors declared no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Linda Barlow-Mosha took the lead in writing of the manuscript and is accountable for ensuring that questions related to any part of the work are appropriately addressed. Philippa Musoke, Joyce Namale Matovu, Daniel Mumpe-Mwanja, Dhelia Williamson, and Diana Valencia made substantial contributions to conception and design of the study. They were involved in drafting the manuscript and revising it critically for important intellectual content. Dennis Kalibbala, Sarah C. Tinker, Robert Serunjogi, Diana Valencia, Michelle R. Adler, Cynthia A. Moore, and Lisa Nelson were involved in drafting the manuscript and revising it critically for important intellectual content. All authors approved the final manuscript version submitted.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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