

Introduction

Neural tube defects (NTDs) are one of the most common congenital malformations affecting births worldwide. The estimated NTD prevalence in Africa is 12 per 10,000 live births [95% confidence interval (CI) 5-75]; but data are limited (Zagajor et al, PLOS One 2016). Few studies have reported on the impact of antiretroviral therapy (ART) during pregnancy on the risk for birth defects in developing countries, however recent concerns have been raised about the potential increased risk of NTDs among women on dolutegravir at conception or during the first trimester (Zash et al. NEJM 2018).

As new antiretrovirals are introduced during pregnancy it is imperative to know the risk for birth defects and other adverse birth outcomes in the general population as well as among women on ART. Therefore ongoing birth defect surveillance is needed as part of pharmacovigilance. The objective of this analysis was to compare the prevalence of NTDs among infants of HIV infected women (on ART) and HIV negative women in the hospital based birth defect surveillance (BDS) program in Kampala, Uganda.

Methods

Design

A hospital-based birth defect surveillance program, with active case ascertainment in Kampala Uganda

Population

All eligible births at the four participating hospitals – Mulago, Nsambya, Mengo and Lubaga

Inclusion Criteria

All informative live births, stillbirths and abortions regardless of gestational age. Informative births are those in which the newborn is well formed so as to detect the presence or absence of a major external birth defects. Eligible newborns were examined by surveillance midwives for major structural external birth defects using active case ascertainment. Photographs of the birth defect were taken to confirm and classify the defect after consent.

Photos and narrative descriptions were reviewed by birth defect experts for confirmation of local expert diagnoses and coding of the birth defect using ICD-10 RCPH disease classification criteria. The prevalence of birth defects and 95% CI were calculated for HIV infected (on/off ART) and HIV negative women. Association of NTDs with HIV and ART was determined by logistic regression.

Results

Data was collected from the hospitals between August 2015 and December 2017. A total of 69,766 births were analyzed with 60,905 (90.2%) delivered by HIV negative, 6,494 (9.6%) by HIV infected women and 150 (0.2%) HIV unknown. Maternal median age was 25 years (IQR 22-30).

Total enrolled N = 69,766 births

Total mothers enrolled = 67,542

Maternal and infant demographics by Birth Outcome				
n (%)	Live n=66,793 (95.7%)	Still n=2,511 (3.6%)	Spontaneous Abortion N=462 (0.7%)	
Number of births	69,766 (100)	66,793 (95.7)	2,511(3.6)	462 (0.7)
Mother's HIV status				
Positive	6,494 (9.6)	6,239 (9.64)	225 (9.3)	30 (7.3)
Negative	60,906 (90.2)	58,392 (90.24)	2,145 (88.7)	369 (89.1)
Unknown	142 (0.2)	78 (0.12)	49 (2.0)	15 (3.6)
Maternal Antiretroviral therapy				
Yes	6,186(95.3)	5,954(95.4)	206(92.0)	26(86.7)
No	308(4.7)	286(4.6)	18(8.0)	4(13.3)
Antenatal visits				
No ANC	1,570 (2.3)	1,066 (1.6)	300 (12.4)	206 (49.3)
1-3 times	38,247 (56.6)	36,546 (56.5)	1,495 (61.8)	240 (49.7)
>=4 times	27,725 (41)	27,097 (41.9)	824 (25.8)	4 (1.0)
Sex				
Male	36,352 (52.1)	34,649 (51.9)	1,421 (56.6)	282 (61)
Female	33,401 (47.9)	32,137 (48.1)	1,084 (43.2)	180 (39)
Indeterminant	13 (0.02)	7 (0.02)	6 (0.2)	0 (0)
Birth Defect				
Yes	713 (1.0)	640 (0.96)	67 (2.7)	6 (1.3)
No	69,053 (99.0)	66,153 (99.0)	2,444 (97.3)	456 (98.7)

Birth Defect	No	Prevalence per 10,000 live births	Sex			Birth Outcome		Infant HIV Exposure			Maternal ART		Type of ART regimen		
			Male	Female	Indeterminant	Live Birth	Spontaneous Abortion	Positive	Negative	Unknown	Yes	No	EFV/TDF/3TC	ATV/rTDF/3TC	All Others
Anencephaly	19	2.7 (1.7-4.3)	5	13	1	11	6	2	1	17	1	1	0	1	0
Encephalocele	12	1.7 (1-3)	7	5	0	10	2	0	1	11	0	1	0	0	1
Spina bifida	41	5.9 (4.3-8)	28	12	1	35	6	0	3	38	0	3	0	1	2
Total	72	10.3(8.2-13)	40	30	2	56	14	2	5	66	1	5	0	2	3

Types of Neural Tube Defects	Number	Prevalence (95% CI)	
Anencephaly	Anencephaly	19	2.7 (1.7-4.3)
	Incomplete Anencephaly	14	2.0 (1.2-3.4)
		5	0.7 (0.3-1.7)
Encephalocele	Nasofrontal Encephalocele	12	1.7 (1-3)
	Orbital Encephalocele	4	0.6 (0.2-1.5)
	Occipital Encephalocele	4	0.6 (0.2-1.5)
	Encephalocele -other sites	2	0.3 (0.1-1)
		2	0.3 (0.1-1)
Spina bifida (SP)	Sacral SP without Hydrocephalus	41	5.9 (4.3-8)
	Lumbar SP without Hydrocephalus	12	1.7 (1-3)
	Lumbar SP with Hydrocephalus	11	1.6 (0.9-2.8)
	Sacral SP with Hydrocephalus	10	1.4 (0.8-2.6)
	SP, unspecified	6	0.9 (0.4-1.9)
	Unspecified SP with Hydrocephalus	1	0.1 (0-0.8)
All NTDs	72	10.3 (8.2-13)	

Type of Maternal ART Regimen + ZNRTIs	n(%)
Non-nucleoside Reverse Transcriptase Inhibitors (EFV/NVP)	5954(96.3)
Protease Inhibitors (ATV/r; LPV/r)	229(3.7)
Integrase Inhibitors (DTG)	1(0.02)
On ART Regimen Unknown	2(0.03)
Total	6,186

Prevalence of Neural Tube Defects among infants of mothers with known HIV status per 10,000 live births					
Common Birth Defects	Total cases	HIV unexposed infants cases	HIV exposed infants cases	Prevalence HIV unexposed infants (95% CI)	Prevalence HIV exposed infants (95% CI)
All NTDs	71	66	5	10.5 (8.3-13.3)	7.4 (3.2-17.4)

There was no significant difference in NTD prevalence among HIV-infected and HIV-uninfected women; AOR 0.91 (95% CI 0.3-2.4), p= 0.858

NTDs were not significantly associated with maternal age, HIV status, ART, or parity. Anencephaly was more common among females compared to males with site as an effect modifier [AOR of 5.9 (95%CI: 2.1-16.9), p=0.001]

Conclusions

NTDs are a common congenital malformation affecting births in Kampala. These findings are similar to the current estimates for Africa. ART was not associated with an increased risk for NTDs. With the introduction of new ART regimens during pregnancy, ongoing BD surveillance is critical.



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