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Surveillance of congenital anomalies following exposure to Raltegravir or Elvitegravir during pregnancy in the UK and Ireland, 2008-2018

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Abstract

Background: The indisputable benefits of antiretroviral therapy (ART) in the reduction of mother-to-child-transmission of HIV (MTCT) have to be carefully balanced with the risks of embryo-foetal toxicities due to foetal exposure to maternal ART.

The recent report of a potential safety signal with Dolutegravir use in pregnancy and potential increased rate of neural tube defects (NTDs), has raised the question of a potential class effect for Integrase Strand Inhibitors. To contribute real-world evidence we evaluated data on pregnant women receiving Raltegravir (RAL) or Elvitegravir (EVG) in the UK and Ireland.

Methods: The National Study of HIV in Pregnancy and Childhood (NSHPC) is a comprehensive population-based surveillance study collecting data on all HIV-positive pregnant women and their children. We collected data on all pregnancies exposed to an ART regimen containing RAL or EVG resulting in livebirth, stillbirth and induced abortion with an expected date of delivery between September 2008 and April 2018. Pregnancies were stratified into three groups of earliest exposure.

Results: A total of 908 pregnancies were exposed to a RAL or EVG-based regimen (875 to RAL and 33 to EVG). There were 886 live-born infants exposed to RAL, eight pregnancies ended in stillbirth and nine in induced abortions. Among the 886 live-born infants there were 23 (2.59% 95% CI 1.65, 3.86) reported congenital anomalies, two nervous system defects but no reported NTDs. Of the 33 pregnancies exposed to EVG, 31 resulted in live-born infants with no congenital anomaly and the remaining two pregnancies ended in induced abortion.

Conclusions: The prevalence of congenital anomalies is consistent with national population estimates for 2008-2016 in the UK. More data are needed on safety of RAL and EVG in pregnancy.

Key words: HIV, pregnancy, birth defects, Raltegravir, Elvitegravir, Integrase Strand Transfer Inhibitors

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Introduction

Antiretroviral therapy (ART) is the most effective tool to reduce vertical transmission of HIV (VT), but pregnant women are a special and challenging population from a treatment-management perspective: the undeniable benefits of ART for maternal health and the prevention of VT have to be carefully balanced with safety concerns[1]. The increasing proportion of pregnant women living with HIV on ART regimens from conception and the growing proportion with suppressed HIV RNA viral loads (VL) throughout pregnancy are other factors to be considered in the risk-benefit evaluation. In the UK and Ireland in 2013-2015, around 90% of pregnancies were in women with an undetectable VL below 50 copies/mL within 30 days of delivery and around 65% of pregnancies were conceived on ART[2].

The recent report of a potential safety issue for Dolutegravir (DTG)[3,4] use in pregnant women living with HIV, specifically periconception use, has resulted in additional scrutiny of the entire Integrase Strand Transfer Inhibitors (INSTI) class regarding pregnancy use. Preliminary results from the ongoing Tsepamo surveillance study in Botswana indicated four neural tube defects (NTDs) among 426 women conceiving on DTG, a rate of 0.94% (95% confidence interval [CI] 0.37%, 2.4%) compared with that of 0.12% (95% CI 0.07%, 0.21%) in infants exposed to other antiretrovirals from conception[5]. Earlier results from this and other studies, based on smaller numbers and fewer DTG conceptions, showed no initial teratogenicity concerns[6]. Global efforts to gather additional, robust, prospective data on birth outcomes in women conceiving on DTG have ensued, coordinated by the World Health Organization (WHO). This had particular urgency given that WHO guidelines were being updated, recommending DTG-based regimens as first-line therapy, a policy that has been implemented in Botswana since mid-2016 and a number of other countries subsequently[7].

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Following the DTG-safety signal, WHO's interim guidance on HIV treatment was released in July 2018, recommending first- and second-line ART including DTG to everyone aged six years and above; these contained a note of caution on using DTG around conception and for adolescent girls and women of childbearing potential due to the safety signal[8].

The potential safety signal with DTG has raised questions around whether there might be a class effect for INSTIs. Raltegravir (RAL) and Elvitegravir (EVG), like DTG, have a strong trans-placental transfer and a consequent rapid and effective capacity to reduce maternal VL[9-11]. RAL, in particular, is highly effective in reducing VT risk for women presenting late to antenatal care and/or with high VL in late pregnancy[7, 12,13]. RAL is recommended by the British HIV Association guidelines for pregnant women in various scenarios, including for late-presenters when VL is unknown or known to be >100,000 copies/mL, in a three- or four-drug regimen [14]. EVG is a second generation INSTI, co-formulated with the booster Cobicistat (EVG/c), with very limited data from human studies in pregnancy. A recent systematic review[15] suggests that EVG/c/Emtricitabine/Tenofovir Alafenamide is a more effective option than NRTI-sparing regimens for treatment-naïve non-pregnant patients.

In order to contribute real world evidence regarding the safety of INSTIs other than DTG in pregnancy, we evaluated data on pregnant women receiving RAL and EVG in the UK and Ireland to assess potential risk of NTDs and other congenital anomalies.

Methods

The National Study of HIV in Pregnancy and Childhood (NSHPC) is a comprehensive ongoing surveillance study that collects data on all diagnosed pregnant women living with HIV, their infants, and children diagnosed with HIV seen for care in the UK and Ireland[16].

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All pregnancies are notified by a named respondent in each maternity unit through an active, quarterly surveillance scheme. Information on maternal demographics, pregnancy outcome, delivery, perinatal details and ART are collected from these maternity respondents and HIV-exposed infants are followed up through their paediatrician who provides information to confirm infection status, as well as infant feeding and any health concerns. The presence of birth defects is reported by both maternity and paediatric respondents.

For this analysis we included all pregnancies in women diagnosed with HIV before delivery meeting the following criteria: any exposure to an ART regimen containing RAL or EVG resulting in livebirth, stillbirth and induced abortion; expected date of delivery (EDD) between September 2008 and April 2018; and reported to the NSHPC by May 2018. We stratified pregnancies into three groups by earliest exposure to RAL or EVG: at conception, started in 1st trimester (T1), or 2nd/3rd trimester (T2/T3).

We analysed pregnancies (singleton and multiple) rather than women and a small number of sequential pregnancies in the same woman were included.

Definitions

T1 was considered to end at 12 completed gestational weeks. Maternal HIV diagnosis at delivery was defined as diagnosis made within two weeks before EDD. Baseline CD4 count was defined as the earliest reported measurement in pregnancy (classified as ≤350cell/mm^3 and >350cell/mm^3). Maternal VL at delivery was defined as a VL measured within 30 days before or 7 days after delivery. We classified congenital anomalies according to European Surveillance of Congenital Anomalies (EUROCAT) network definitions[17].

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Statistical analyses were conducted in R version 3.5.0 (R: Foundation for Statistical Computing). Binomial CI were calculated with the exact method.

Results

Overall, 908 pregnancies were exposed to RAL- or EVG-based ART regimens, of which 875 were RAL-exposed and 33 EVG-exposed. Maternal characteristics are presented in Table 1. Three-quarters of pregnancies were in women whose HIV-diagnosis was made before conception and 27% were on an INSTI-based regimen at conception (Table 1).

Raltegravir-exposed pregnancies

Of the 875 RAL-exposed pregnancies, 222 (25.4%) were exposed at conception, 34 (3.9%) started RAL during T1 and 600 (68.6%) during T2/T3, while for 19 (2.2%) exposure took place sometime during pregnancy. There were 886 live-born infants from 858 pregnancies, with 27 pregnancies resulting in multiple births (one set of triplets). Eight pregnancies (no multiple pregnancies) ended in stillbirth and there were nine induced abortions (Table 2). Among the live-born infants, 222 (25.0%) were RAL-exposed from conception, 40 (4.5%) from later in T1 and 602 (67.9%) from T2/T3. Of these 886 infants, 23 had a congenital anomaly (2.59% 95% CI 1.65, 3.86). Among the 222 infants exposed from conception, five (2.25% 95% CI 0.73, 5.17) had an anomaly, as did 17 of 602 exposed from T2/3 (2.82% 95% CI 1.65, 4.48) (Table 2). The relative risk of a congenital anomaly for RAL-exposure at conception relative to T2/T3 was 0.80 (95% confidence interval 0.30, 2.14).

Nearly half of the live-born infants with defects had either congenital heart defects or limb anomalies. There were two nervous system defects in infants exposed from T2/3 (one major brain malformation ending in neonatal death) but no reported NTDs. One of the nine pregnancies ending in induced abortion had a congenital anomaly reported (Down's syndrome). No congenital anomalies were reported among the eight stillbirths with RAL-exposure.

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Elvitegravir-exposed pregnancies

Of the 33 pregnancies exposed to EVG-based ART regimens, most (26, 78.8%) were exposed from conception with the remaining seven exposed from T2/3. Of the 31 live-born infants, none had a congenital anomaly. The remaining two pregnancies ended in induced abortion; both had EVG exposure from conception and had congenital anomalies (both genetic syndromes) reported as the reason for the termination.

Discussion

Using data from this comprehensive, population-based study of pregnant women living with HIV and their infants, we have provided "real-world" data on congenital anomalies in just over 900 pregnancies with RAL or EVG use, of which a quarter were conceived on either of these INSTIs. Our finding of an overall prevalence of anomalies in RAL-exposed pregnancies of 2.59% (95%CI 1.65, 3.86) is consistent with national population estimates for 2008-2016 in the UK (e.g. 2.0% among livebirths in 2010)[17], and also with historic prevalence in the NSHPC, with prevalence of 2.8% (95%CI 2.5%, 3.2%) in 1990-2007[18]. A recent pooled analysis from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) that included NSHPC data reported a birth defect prevalence of 2.3% (95%CI 2.0,2.7) in 8737 pregnancies exposed to ART at conception/T1 based on the EuroCAT definition (Begona Martinez de Tejada, personal communication). We observed no apparent clustering of specific anomalies, and no NTDs.

Although RAL is the INSTI with the most clinical data available in human pregnancy, this tends to be dominated by women initiating RAL later in pregnancy, consistent with clinical guidelines[14]. The Antiretroviral Pregnancy Registry (APR), an international voluntary-based, prospective registry monitoring rates of congenital birth defects associated with foetal exposure to ART, included data on 291 pregnancies with T1 RAL-exposure by January 2018 (prospective data), with a birth defect rate of 3.1% (95%CI 1.4,5.8)[19]. The French Perinatal

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Cohort reported a congenital abnormality rate of 4.2% (95%CI 2.4, 6.0) in all births and a T1 rate of 5.7% among 479 RAL-exposed pregnancies (with 140 T1 exposures)[20].

For EVG/c, there is very limited clinical experience in pregnancy; although embryo-foetal toxicity was not shown in preclinical animal models, caution is needed in extrapolating to humans. However, there are concerns regarding its pharmacokinetic profile of increased clearance and subsequent risk for virological rebound, particularly regarding pregnancy use[12,21,22].

The current analysis is restricted to RAL and EVG. Data from the NSHPC were included in an individual patient data meta-analysis from EPPICC on 101 pregnancies; this reported four congenital anomalies in 81/84 livebirths, with a prevalence of 4.9% (95%CI 1.4-12.2), heterogeneous anomalies and no NTD reports[6]. Additionally, in an NSHPC analysis evaluating DTG, Rilpivirine and Cobicistat use between 2013-2017, there were 112 (2%) pregnancies exposed to DTG-containing regimens, with 52 (46.4%) having DTG from conception and one birth defect (extra digits) among the 33 live births by time of analysis[23]. Data collection on outcomes following peri-conception DTG use is ongoing in Botswana, Kenya, Brazil and other countries to understand more about potential risk of NTDs[24].

The DTG and NTD safety signal has raised awareness of the large number of peri-conception exposures (at least 2000) needed to rule out an increased risk of NTD, due to it being a rare outcome[25]. Although NTDs occur in around 0.1% of pregnancies in the UK[26], the background rate may be considerably higher in resource-limited countries, particularly those without food folate supplementation. Despite RAL being used since 2008, prospective data on risk of congenital anomalies with peri-conception/T1 exposures remains limited, with only around 690 such pregnancies reported to date from the NSHPC, the French Perinatal Study and the APR combined (with potential for duplicated cases).

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The continued reduction in VT rates (currently <0.3% in the UK and Ireland)[2] is associated with growing proportions of women on suppressive ART regimens at conception (on increasingly diverse regimens) and earlier ART initiation in those starting antenatally. These trends have raised concerns regarding potential risk of teratogenic and embryo-foetal toxicity due to extensive foetal ART exposure. The need for pregnancy safety data on newer antiretroviral drugs is a key topic of discussion among stakeholders (e.g. policy-makers, researchers, the HIV community and regulators) including how to address the reasons behind this gap, such as the exclusion of pregnant women from registrational trials and the lack of post-marketing surveillance[27,28,29].

The strengths of our study include our comprehensive, population-based methodology, with good ascertainment of congenital anomalies by both obstetric and paediatric respondents within routine clinical care. We were also able to include pregnancies ending in induced abortion and stillbirth, resulting in less biased estimates. The use of EUROCAT definitions allows comparison with other studies.

However, this observational study has several limitations. The congenital anomalies were not assessed by a dysmorphologist and assessment of congenital anomalies may not have been blinded to maternal ART use. A major limitation in terms of interpretation of these findings in RAL-exposed pregnancies is the small number to date, particularly with peri-conception exposure, whilst the very few EVG-exposed pregnancies preclude any conclusions. A further limitation is the lack of a direct comparison between RAL-exposed pregnancies and those receiving other antiretrovirals; however, we have compared the overall rate of congenital anomalies in these pregnancies with national, NSHPC- and EPPICC-specific rates.

Administration of medicines in pregnancy in general is frequently complicated by the lack of sufficient data on which to inform risk-benefit decisions. In the case of antenatal ART, the

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individual and public health benefits are huge, with the exposed baby standing to benefit as well as the mother. The recent DTG signal detection has focussed global attention on the need for further pregnancy safety monitoring not only for INSTIs but for all antiretroviral drugs lacking safety data, and our results from a high-income setting on congenital anomalies in RAL- and EVG-exposed pregnancies add to the evidence base.

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APR Advisory Committee Consensus statement: In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of birth defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counselling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the use of new

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therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at SM_APR@INCResearch.com via the data forms available at www.APRegistry.com.

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Table 1. Maternal characteristics, by antiretroviral exposure

	Raltegravir		**Elvitegravir**	
	***n*=875**		***n*=33**	
Ethnicity	***n***	**%**	**n**	**%**
White	216	24.7	8	24.2
Black African	592	67.6	23	69.6
Other	67	7.6	2	6.1
Region of birth	***n*=873**		***n*=33**	
UK/ Ireland	165	18.9	5	15.1
Africa	566	64.8	23	69.7
Elsewhere/Not Known	142	16.3	5	15.1
Age at delivery, median (IQR)	***n*=875**		***n*=33**	
	33.2 years (Q_1=28.7 Q_3=37.1)		35.1 years (Q_1=31.8 Q_3=37.2)	
HIV acquisition route	***n*=873**		***n*=33**	
Heterosexual	755	86.5	28	84.8
Injecting drug use	16	1.8	0	0
Vertical	33	3.8	0	0
Other/Not Known	69	7.9	5	15.1
Timing of HIV diagnosis	***n*=875**		***n*=33**	
Before pregnancy	641	73.2	32	96.9
During pregnancy	225	25.7	1	3
At delivery	9	1	0	0
INSTI at conception	***n*= 875**		***n*=33**	
Yes	222	25.4	26	78.8
No	53	76.6	7	21.2
VL at delivery	***n*= 313**		***n*=6**	
Detectable (≥ 50 copies/ml)	108	34.5	1	16.6
Undetectable (< 50 copies/ml)	205	65.5	5	83.3
Baseline CD4 count, median cells/mm^3 (IQR)	***n*=843**		***n*=33**	
	403 (Q_1=250, Q_3=588)		442 (Q_1=3111 Q_3=593)	

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Table 2. Birth outcomes and congenital anomalies by organ/system[a] in pregnancies with Raltegravir use, by timing of exposure (875 pregnancies)

	Timing of exposure				Total
	At conception	Started in first trimester	Started in second/ third trimester	Timing unknown	
Pregnancies	222	34	600	19	875
Ending in stillbirth	3	0	5		8
Ending in induced abortion	5[b]	1	3		9
Live-born infants	222	40	602	22[c]	886[d]
Livebirths with a congenital anomaly	5 (2.25%)	0	17 (2.82%)	1	23 (2.59%)
Congenital Heart Defects	2		3		5
Respiratory			1		1
Oro-facial clefts			1		1
Nervous system			2[e]		2
Urinary			4		4
Limb	2		3	1	6
Other anomalies/syndromes	1		1		2
Chromosomal			2		2

[a]EUROCAT headings; ; [b]one with Down's syndrome; [c]5 newly diagnosed antenatally; [d]27 RAL-exposed pregnancies resulted in multiple births (one triplets); [e]one neonatal death

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