Real-world use of newly authorized antiretrovirals in pregnancy in the UK/Ireland and available safety data

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Background

In the UK and Ireland, MTCT rate is now 0.27% and nearly 90% of HIV+ women have undetectable virus by the time of delivery (2012-2014).

60% of women conceive under an ART regimen (2012-2014, the National Study of HIV in Pregnancy and Childhood (NSHPC))

- Pregnant women are often excluded from clinical trials and data are limited on safety of new ARV drugs including pregnancy outcomes.
- EU legislation No 1235/2010 and Directive 2010/84/EU, set out new prerequisites to better assess the risk of exposure to drugs in the post-authorisation phase, including in pregnancy and lactation.
- Following the new legislation, the European Medicines Agency (EMA) has been issuing detailed guidance regarding risk management requirements.
- The inverted black triangle (▼) is an EMA marker for products requiring additional monitoring due to being new to market or with limited data on long term use.

Aim and methods

- To examine the "real world" antenatal use and pregnancy outcomes of three newly authorized ARV: Rilpivirine (RPV), a NNRTI; Dolutegravir (DTG), an INSTI; and Cobicistat (COBI), a booster
- To evaluate the consistency between the EMA's safety information and recommendations on how to use these medicines in pregnancy and experience in clinical practice to date
- Safety data: EMA, using the European Public Assessment Reports and the Summary of Product Characteristics (SmPC)
- Real-world data: NSHPC, a comprehensive population-based surveillance study on all HIV-positive pregnant women seen for care in UK/Ireland
- Data on 4831 pregnancies reported with estimated date of delivery (EDD) from 1st January 2013 to 31st March 2017

Results

EMA

- EMA data showed distinct warnings and recommendations regarding pregnancy despite no preclinical findings of specific hazard(s).
- All the products had «no or limited data» from humans.
- Recommendations ranged from «talking to you doctor» to «unless clearly needed should not be given in pregnancy», with additional requirements to comply with contraceptive measures for Eviplera (FTC/TDG+ RPV) and Stribild (FTC/TDF+EVG/c) (Fig.1).
- ▼ label applies to both DTG (Tivicay/Triumeq) and COBI (Tybost/Stribild):
  - DTG crosses the placenta;
  - COBI, in reproductive toxicity studies in rats showed an increased risk of postimplantation loss.

NSHPC

- Between 2013 and 2016 the 3 assessed drugs saw a substantial increase in their usage.
- Of the 4526 pregnancies with EDD from 2013 to 2016, the number of pregnancies exposed to an RPV-containing or a DTG-containing regimen increased >10-fold from 0.5% in 2013 to 5.6% in 2016 and from 0.3% in 2015 to 3.3% in 2016 respectively (Fig. 3).
- Of 189 pregnancies with known outcomes, 6 (3%) had congenital anomalies (Table 2).

There is a gap between regulatory recommendations, requirements for marketing authorisation and what is happening in clinical practice. How best to address this gap?

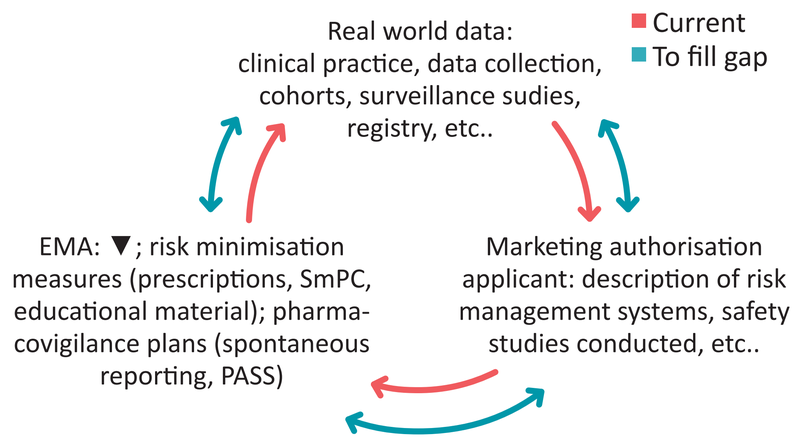


Figure 1. Example section of SmPC for Eviplera™

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

The use of Eviplera must be accompanied by the use of effective contraception (see section 4.5).

Pregnancy

There are no adequate and well-controlled studies of Eviplera or its components in pregnant women. There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of rilpivirine in pregnant women. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3) with the components of Eviplera.

As a precautionary measure, it is preferable to avoid the use of Eviplera during pregnancy.

Breast-feeding

Emtricitabine and tenofovir disoproxil are excreted in human milk. It is not known whether rilpivirine is excreted in human milk.

There is insufficient information on the effects of Eviplera in newborns/infants. Breast-feeding should be discontinued during treatment with Eviplera.

In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.

Fertility

No human data on the effect of Eviplera on fertility are available. Animal studies do not indicate harmful effects of emtricitabine, rilpivirine hydrochloride or tenofovir disoproxil fumarate on fertility.

Figure 2. Date of issue of marketing authorization valid throughout the EU

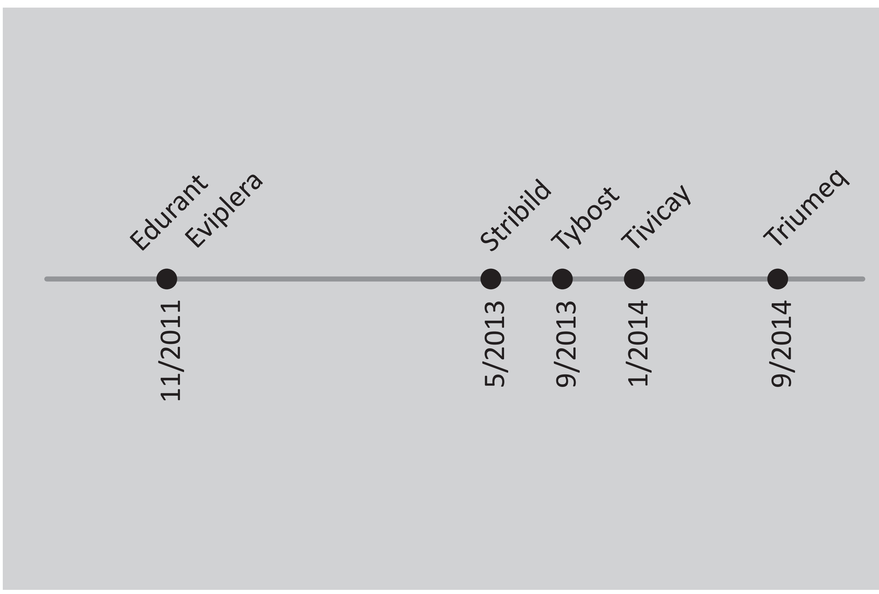


Table 1. Number of exposed pregnancies and pregnancy outcomes by drug

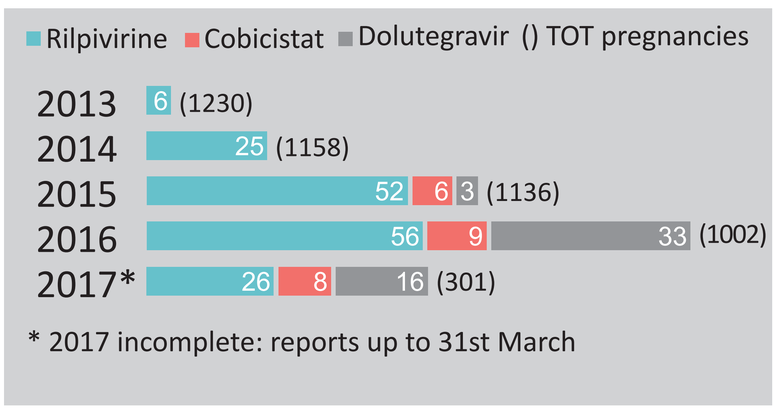
			Pregnancy outcomes* N (row%)					
Drug	N pregnancy	ART at conception	Livebirth	Spontaneous abortion	Elective TOP	Stillbirth	Ectopic pregnancy	TOT
DTG	112	52 (46.4%)	33 (91.6%)	2 (5.5%)	0	1 (2.7%)	0	36
COBI	33	23 (69.7%)	13 (81.3%)	1 (6.3%)	2 (12.6%)	0	0	16
RPV	198	165 (83.3%)	110 (80.3%)	19 (13.9%)	5 (3.6%)	1 (0.7%)	2 (1.4%)	137
TOTAL	343	240 (70%)	156 (82.5%)	22 (11.6%)	7 (3.7%)	2 (1.0%)	2 (1.0%)	189

* Excludes continuing pregnancies (N=51) and LTFU (N=1), TOP: Termination of Pregnancy

Table 2. Foetal / newborn abnormalities, by drug

	Outcome	Abnormalities	Treatment
1	Livebirth	Coartation of aorta	FTC/TDF + RPV
2	Livebirth	Down's Syndrome	FTC/TDF + RPV
3	Livebirth	Encephalocele	FTC/TDF + RPV
4	Livebirth	Extra digits (polydactyly)	ABC/3TC + DTG
5	TOP	Trisomy 18	FTC/TDF + EVG/COBI
6	TOP	Cystic hygroma	FTC/TDF + EVG/COBI

Figure 3. Number of exposed pregnancies, by year



* 2017 incomplete: reports up to 31st March

Conclusion

- Results show inconsistencies between regulatory recommendations - mostly advising avoidance of use whilst pregnant - and what is happening in clinical practice. Indeed, NSHPC findings showed a significant increase in the use of these newly authorized antiretrovirals not only with initiation in pregnancy but also use at conception.
- Results to date are reassuring regarding the risk of birth defects. However, numbers are small and preclude drawing stronger safety conclusions. Continued monitoring is critical and will be focus of future studies.
- There is a clear opportunity to develop this work further with the aim to draw stronger safety recommendations, to ensure better informed recommendations for patients and clinicians.

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