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Responding to the BHIVA statement on potential safety signal in infants born to women conceiving on Dolutegravir - a service evaluation

Background

In May 2018, a preliminary unscheduled analysis of an on-going birth surveillance study reported an increased risk of neural tube defects (NTD) in children conceived on Dolutegravir (DTG)-based regimens. The study, looking at babies born to 11,558 HIV-infected women in Botswana, showed 0.9% of babies (4/426) whose mothers conceived on DTG-based regimens had a NTD, compared with 0.1% (14/11,173) conceived on non DTG-based regimens[1].

Whilst awaiting further evidence, on 22nd May 2018, BHIVA released a statement with recommendations on how to manage women at risk of pregnancy on DTG-based regimens[2].

We wanted to assess our service's response to this BHIVA statement.

Methods

Our service immediately reviewed DTG prescriptions for the 12 months prior to June 2018. We then identified and risk stratified women ≤50 years old on DTG by database and case-note review:

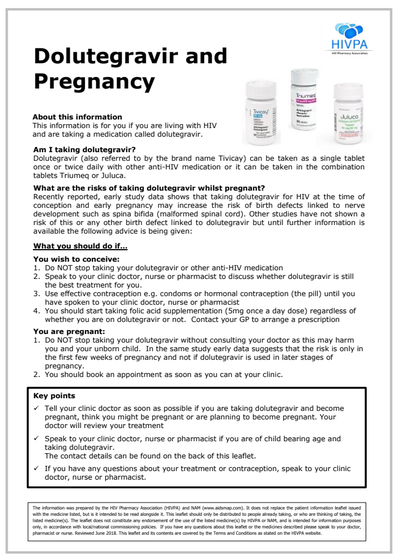
Category	Risk	Time to contact	Contact method
Red	Early pregnancy or high risk of pregnancy	Within 1 week	Urgent telephone call
Amber	Patients requiring clarification of partner and contraception status	Appointment within 1 month	Alert on patient record
		Appointment greater than 1 month away	Email to clinician to contact patient
Black	Patients with documented contraception, no sexual partner or late pregnancy	Within 6 months	Inform patient at next consultation

A second case-note review was performed in January 2019.

Spreading the word:

Copies of the HIV Pharmacy Association leaflet on *'Dolutegravir and Pregnancy'*[3] were given to patients in clinic, or sent to their mobiles via an SMS link.

Local third sector organisations were notified via email by our lead clinician. GPs and patients were also notified via our bi-annual service user newsletter.


Dolutegravir and Pregnancy

About this information
This information is for you if you are living with HIV and are taking a medication called dolutegravir.

Am I taking dolutegravir?
Dolutegravir (also referred to by the brand name Tivicay) can be taken as a single tablet once or twice daily with other anti-HIV medication or it can be taken in the combination tablets Triumeq or Juluca.

What are the risks of taking dolutegravir whilst pregnant?
Recently reported, early study data shows that taking dolutegravir for HIV at the time of conception and early pregnancy may increase the risk of birth defects linked to nerve development such as spina bifida (malformed spinal cord). Other studies have not shown a risk of this or any other birth defect linked to dolutegravir but until further information is available the following advice is being given:

What you should do if...

You wish to conceive:
1. Do NOT stop taking your dolutegravir or other anti-HIV medication
2. Speak to your clinic doctor, nurse or pharmacist to discuss whether dolutegravir is still the best treatment for you.
3. Use effective contraception e.g. condoms or hormonal contraception (the pill) until you have spoken to your clinic doctor, nurse or pharmacist
4. You should start taking folic acid supplementation (5mg once a day dose) regardless of whether you are on dolutegravir or not. Contact your GP to arrange a prescription

You are pregnant:
1. Do NOT stop taking your dolutegravir without consulting your doctor as this may harm you and your unborn child. In the same study early data suggests that the risk is only in the first few weeks of pregnancy and not if dolutegravir is used in later stages of pregnancy.
2. You should book an appointment as soon as you can at your clinic.

Key points
- ✓ Tell your clinic doctor as soon as possible if you are taking dolutegravir and become pregnant, think you might be pregnant or are planning to become pregnant. Your doctor will review your treatment
- ✓ Speak to your clinic doctor, nurse or pharmacist if you are of child bearing age and taking dolutegravir. The contact details can be found on the back of this leaflet.
- ✓ If you have any questions about your treatment or contraception, speak to your clinic doctor, nurse or pharmacist.

The information was prepared by the HIV Pharmacy Association (HIVPA) and NAM (www.aidsmap.com). It does not replace the patient information leaflet issued with the medicine listed, but is it intended to be read alongside it. This leaflet should only be distributed to people already taking, or who are thinking of taking, the listed medicine(s). The leaflet does not constitute any endorsement of the use of the listed medicine(s) by HIVPA or NAM, and is intended for information purposes only, in accordance with local/national commissioning policies. If you have any questions about this leaflet or the medicines described please speak to your doctor, pharmacist or nurse. Reviewed June 2018. This leaflet and its contents are covered by the Terms and Conditions as stated on the HIVPA website.

Conclusions

Over 95% of women on DTG-based regimens complied with the BHIVA statement recommendations. This evaluation demonstrates that our service is able to react swiftly to new BHIVA recommendations / safety alerts.

<5% of this cohort required a switch away from their DTG-regimen as planning pregnancy.

Since May 2018, three healthy babies have been born to women on DTG-based regimens. One first trimester miscarriage was identified, but this cannot be causally linked to the DTG-regime. We await further data to be published from the Botswana cohort.

Results

141 of 221 DTG prescriptions were dispensed to women ≤50 years old. 29/141 were repeat prescriptions. Five patients were excluded (1 trans-female, 2 temporary patients, 2 deceased) leaving 107 case-notes requiring review and risk stratification.

	Time to contact & documented discussion of BHIVA statement				
Category	**< 1 month**	**< 3 months**	**< 6 months**	**Not documented**	**Total (n)**
Red	8 (<1/52)	2	0	0	10
Amber	19	12	3	12	46
Black	23	12	5	11	51
	50	26	8	23	107

84/107 (79%) were contacted within 6 months and have documented discussions regarding the BHIVA statement. Of the 23 whereby risk discussion was not documented, 6 had disengaged with care, 9 were not sexually active and 3 had irreversible or long-acting methods of contraception.

Only 5 (<5%) patient records did not comply with BHIVA statement recommendations. These patients have scheduled appointments in the next four months and alerts have been added to their records.

Pregnancy summary:

Category	Pregnancies at baseline	Subsequent pregnancies
Red	1 x 12/40 - no NTD at birth 1 x 28/40 - no NTD at birth	1 x 1st trimester miscarriage. Using condoms initially. Now on folic acid, unwilling to switch.
Amber	0	0
Black	1 x 36/40 - no NTD at birth	1 x 8/40, using condoms initially. Referred by GP, switched to Raltegravir BD. Normal anomaly scan at 20/40.

Three pregnancies were identified at baseline review, all >12 weeks gestation, with no evidence of NTD at delivery.

Two women presented subsequently; one with miscarriage at 8 weeks despite having been informed of the BHIVA statement. The second, at 8 weeks, switched third agent to raltegravir. She was initially stratified within the 'Black category' reporting consistent condom use in February 2018. Detailed anomaly scan was normal at 20/40.

Pre-conception third agent switch summary:

Category	3rd agent switch	Viraemia
Red	1 x Raltegravir 1200mg	Remains undetectable, struggling to conceive. Will switch to BD Raltegravir upon conception.
	1 x Atazanavir/Ritonavir	Remains undetectable.
Amber	2 x Darunavir/Ritonavir	1 x viral rebound to 1,100 cp/ml, later suppressed without resistance.
		1 x remains undetectable.
Black	1 x Efavirenz	Viral blip November 2018, suppressed without resistance.

5/107 (<5%) switched from DTG-regimens as planning pregnancy. All third agent switches complied with BHIVA Pregnancy Guidelines and all remain virally suppressed. No pregnancies followed.

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References

1. BHIVA. BHIVA statement on Potential Safety Signal in Infants Born to Women Conceiving on Dolutegravir. Available at: https://www.bhiva.org/BHIVA-statement-on-Dolutegravir (Accessed 2nd January 2019).
2. 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.
3. HIVPA. Patient information leaflet: Dolutegravir and Pregnancy.. Available at: https://www.hivpa.org/wp-content/uploads/2018/09/Dolutegravir-and-Pregnancy-PIL.pdf (Accessed 2nd January 2019).