Use of dolutegravir in women of childbearing potential: a local response to preliminary data suggesting higher incidence of neural tube defects in women conceiving on dolutegravir-based regimens

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Background

- The integrase inhibitor dolutegravir (DTG) is one of the third agents recommended for use in people living with HIV by the British HIV Association (BHIVA) in conjunction with 2 nucleoside reverse transciptase inhibitor (NRTIs)[1]
- In May 2018 a preliminary unscheduled analysis of data from a birth surveillance study in Botswana reported a 0.9% incidence of neural tube defects (NTDs) amongst infants born to mothers on DTG based antiretroviral therapy (ART) compared to a 0.1% incidence in those on alternative regimens[2]
- Based on this early data BHIVA[3] (plus the European Medicines agency and WHO)[4,5] recommend a conception and contraception review of all women under 50 years on DTG
- In addition, all women who wish to conceive are recommended to start 5mg folic acid regardless of their ART regimens, and those on DTG are recommended to switch to an alternative effective regimen
- Currently the greatest amount of safety data available for ART in pregnancy is for efavirenz (EFZ) and atazanavir/ritonavir[6] (ATZ/r)
- Prior to this data 16 women in our unit have conceived on DTG-based therapy with no observed congenital abnormalities

Methods

- Women on DTG based ART under 50 years were identified by our pharmacy records
- For each patient clinic notes were reviewed with regards to pregnancy status, contraception and conception plans
- A clinical alert was placed on all electronic patient records with a clear plan for clinicians to offer contraception or a switch in ART if appropriate
- A letter was drafted by the antenatal team outlining the preliminary data and inviting women to clinic for further discussion
- For pregnant patients, those planning pregnancy or those not wishing to receive letters, patients were contacted directly for discussion
- After an intensive recall and review period of 4 months, the outcomes for all women under 50 on DTG were analysed and are presented below

Results

1. Demographics

- 112 women between the ages of 18-50 were identified who were on a DTG based regimen with a mean age of 29 years and a median age of 38 years (Figure 1)
- At the time of review the majority of women (73%) were on Triumeq or generic abacavir/lamivudine plus DTG (Figure 2)

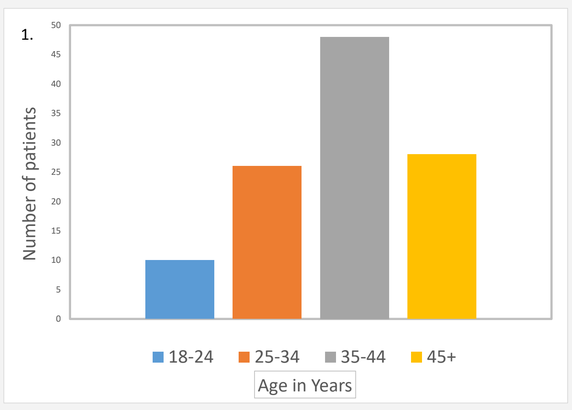

Figure 1: Bar chart to show age range of patients

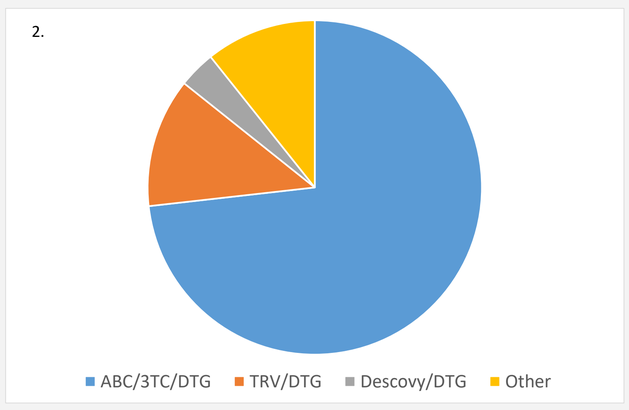

Figure 2: Pie chart to show ART regimens at the time of review. 'Other' regimens included quadruple therapy for treatment experienced women and DTG plus DRV/r

2. Contraception and conception review and pregnancy status

- 25 women (22%) already had an effective form of contraception, with 2 women having had tubal ligation, and 4 total abdominal hysterectomies (TAH) (Figure 3)

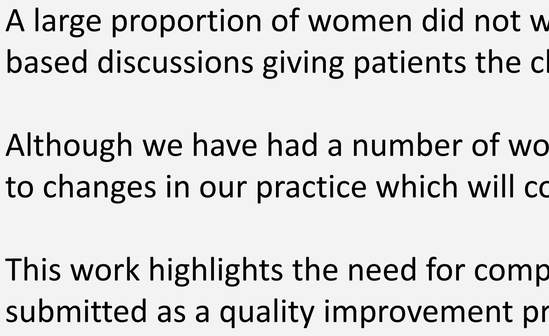

Figure 3: Pie chart to show contraception plus surgical procedures women in this cohort had undertaken. Abbreviations: COC (combined oral contraception); POP (progesterone only pill); IUS (intrauterine system); IUD (intrauterine device); TAH (total abdominal hysterectomy)

- 6 women had already conceived on DTG in the previous year prior to the new data on DTG
- 3 women in this cohort were already pregnant (all past the first trimester) and did not switch ART
- 12 women (5%) were peri or post menopausal
- 58% of women (65) were documented not to be using any form of contraception

3. Outcomes post recall and review process (currently 4 months and ongoing)

- Following an active review and recall process 30 women (27%) declined any contraception (excluding condoms) and opted to stay on DTG following either receipt of our letter outlining the pregnancy risks or face to face discussion with their clinician (Figure 4)
- In 9 women contraception was initiated based on a discussion of the risks of NTDs in early pregnancy with their clinician
- 12 women were documented as trying to conceive and actively recalled to check pregnancy status and switch off DTG
- For the majority of women there was no urgent action required due to effective contraception prior to the data as mentioned previously or peri/post menopausal women

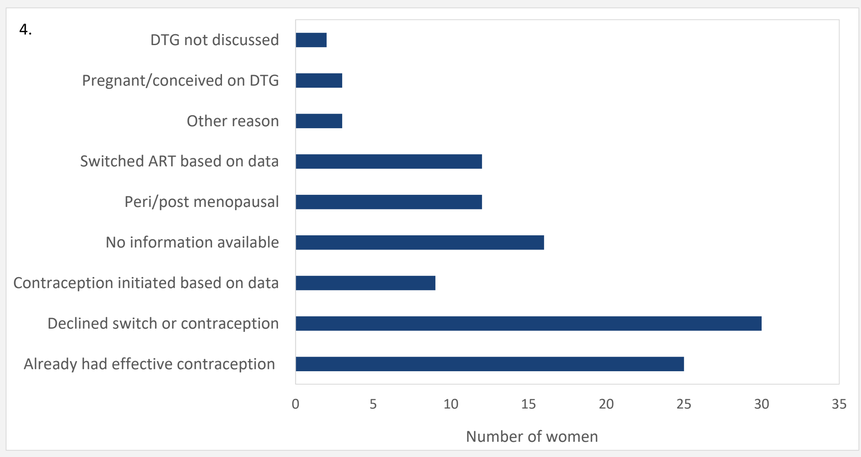

Figure 4: Cluster bar chart to show outcomes after review/recall process.
'Other reason' includes 1 patient who had never been sexually active therefore not switched or offered contraception; 1 patient with severe CNS pathology, deemed not to have capacity for discussion re DTG risks and was not sexually active; 1 patient who opted to stop ART during the review process.
'No information available' includes those LTFU or who have not yet attended clinic but have received a letter outlining risks.

4. ART switches

- 12 women were recalled to switch off DTG (trying to conceive). The majority were switched to either ATZ/r (5 women) or EFZ (2 women) as the third agent (Figure 5)

Figure 5: Pie chart to show switch of third agent for the 12 women trying to conceive. 'Other' agents were raltegravir 1200mg OD, rilpivirine 25mg OD and omitting DTG in a regimen consisting of TDF/DRV/r

5. Contraception initiated post review

- 9 women accepted contraception based on the preliminary data available. This included both oral and long-acting methods of contraception (Figure 6)

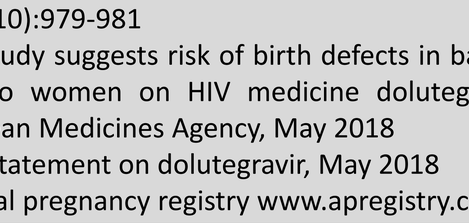

Figure 6: Pie chart to show contraception initiated post review

Conclusions

Our clinic was able to identify all women of childbearing potential on DTG based therapy in a timely manner, in line with current BHIVA recommendations. As this is new data, recall of our cohort is an ongoing process and in due course we hope to offer the majority either effective contraception or a switch in ART if appropriate

A large proportion of women did not wish to start contraception nor switch therapy highlighting the importance of clear evidence-based discussions giving patients the choice to make informed decisions

Although we have had a number of women in our unit conceive and delivery on DTG-based ART, this new preliminary data has led to changes in our practice which will continue under further information becomes available in the next year

This work highlights the need for comprehensive contraceptive history taking in women of childbearing potential and will be submitted as a quality improvement project, enabling us to better address the contraceptive needs of women in our unit.

References

1. BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy, 2015.
2. BHIVA statement on Potential Safety Signal in Infants Born to Women Conceiving on Dolutegravir (on behalf of the BHIVA HIV in Pregnancy Guidelines Committee), May 2018
3. Shapiro RL et al. Neural tube defects with dolutegravir treatment from the time of conception. N Engl J Med. 2018 Sep 6;379(10):979-981
4. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir, European Medicines Agency, May 2018
5. WHO statement on dolutegravir, May 2018
6. Antiviral pregnancy registry www.apregistry.com