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BHIVA HIV in Pregnancy Guidelines

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Disclosures

- I have received Honoraria for educational meetings and advisory boards from ViiV, Janssen and Gilead

Introduction

- Reporting systems for HIV in pregnancy
- New changes which have consensus
- Still in draft form following public consultation
 - Respond to comments

Summary of new changes

- We have expanded the section on 'The psychosocial care of women living with HIV during and after pregnancy' and moved its position within the guidelines
- Changed some recommendations for ARV therapy in pregnancy
- Hepatitis: information added on tenofovir alafenamide for hepatitis B and direct acting agents for hepatitis C
- Length of infant PEP has been shortened where risk of vertical transmission is VERY LOW
- We have updated infant feeding advice to include new data on breastfeeding and the emotional impact not breastfeeding may have on women
- We have added a section on the postnatal management of women living with HIV
- We discuss the use of cabergoline in non breastfeeding women

Reporting and long-term follow-up

National Study of HIV in Pregnancy and Childhood (NSHPC)

- This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, based at the UCL Great Ormond Street Institute of Child Health, London.
- It is the responsibility of clinicians caring for women with living HIV and their children to report them prospectively to the NSHPC.
- Prospectively collected
- Longer term data on infected children are subsequently collected through the Collaborative HIV Paediatric Study (CHIPS).
- For further information see the NSHPC website (www.ucl.ac.uk/nshpc), the CHIPS website (www.chipscohort.ac.uk)

National Study of HIV in
NSHPC
Pregnancy and Childhood

The image shows three overlapping forms from the National Study of HIV in Pregnancy and Childhood (NSHPC). The top form is the 'NSHPC confidential paediatric notification' form, which is blue and white. It contains sections for 'PART 1: CHILD INFORMATION' (including date of birth, hospital no., and home postcode) and 'PART 2: DETAILS OF EXPOSURE TO INFECTION (MATERNAL OR OTHER)' (including maternal history, date of birth, and source of infection). The middle form is the 'Infected pregnancy' form, which is yellow and white. It contains sections for 'Infected pregnancy' (including date of delivery, sex, and planning to breastfeed) and 'Infected pregnancy' (including date of delivery, sex, and planning to breastfeed). The bottom form is the 'Infancy notification' form, which is purple and white. It contains sections for 'Infancy notification' (including date of arrival, sex, and stillbirth(s)/term(s)).

Reporting and long-term follow-up

Antiretroviral Pregnancy Registry (APR)

- Aggregated data tables from the UK and Ireland of antiretroviral exposure and congenital malformations are regularly sent to the Antiretroviral Pregnancy Registry (APR).
- Individual prospective reports should also be made to the APR antenatally with postnatal follow-up.
- Antiretroviral Pregnancy Registry Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA
- In UK call Tel: 0800 5913 1359; Fax: 0800 5812 1658; For forms visit: www.apregistry.com

Section 4: The psychosocial care of women living with HIV during and after pregnancy



- Comments on additional factors which may affect a woman
 - Family
 - Asylum status
 - Confidentiality
- Antenatal HIV care should be delivered by a multidisciplinary team (MDT), the precise composition of which will vary
- Assessment of antenatal and postnatal depression should be undertaken at booking, and 4–6 weeks postpartum and 3–4 months postpartum in accordance with NICE guidelines
- Post natal contraception, breast feeding and cabergoline use should also be addressed antenatally

Section 6: ARVs, Pharmacokinetics & Safety data

- Prescribing: all women are recommended to start on treatment and remain on it lifelong as per BHIVA Adult Treatment Guidelines
- As this includes Elite Controllers this section has been removed

Section 6: ARVs, Pharmacokinetics & Safety data

- Raltegravir 400mg bd maintains therapeutic levels in the majority
- Raltegravir 1200mg od – no data therefore not recommended
- Elvitegravir/cobicistat
 - Results from IMPAACT P1026s study group showed exposure was lower and clearance higher during pregnancy, compared to postpartum
 - Viral load at delivery was <50 HIV RNA copies/mL for 14/19 women (74%)
 - Infant blood showed undetectable levels of cobicistat and a similar elvitegravir elimination half-life for infants in comparison to adults
 - The Writing Group therefore recommends that if a woman becomes pregnant with an undetectable viral load on elvitegravir/cobicistat, it may be continued, with close follow up of maternal viral load in the third trimester but not enough data to recommend commencing in pregnancy



Section 6: ARVs, Pharmacokinetics & Safety data

- Dolutegravir 50mg od appears to be safe
 - Andrew Hill et al systematic review

Table 2. Prevalence of pregnancy outcomes and birth defects in mothers taking ARVs, from six studies of dolutegravir and four control databases

| Trial location and year [ref] | n | Congenital anomalies (%) | Still birth (%) | Preterm birth <37 weeks (%) | Small for gestational age (%) |
|---|--------|--------------------------|-----------------|-----------------------------|-------------------------------|
| Control databases | | | | | |
| France 2017 [22] | 13,272 | 4.4 | 0.7 | 14.0 | |
| Botswana 2012 [23] | 9504 | 2.3 | 4.6 | 23.7 | 18.4 |
| SA/Zambia 2014 [24] | 600 | 6.2 | 2.0 | 24.0 | – |
| Zambia 2012 [25] | 1229 | – | 2.6 | 16.3 | – |
| UK 2017 [26] | 6073 | 2.9 | – | 10.4 | – |
| DTG studies [ref] | | | | | |
| APR [28] | 142 | 3.0 | 0.0 | 10.9 | 11.8 |
| EPPICC/NEAT/PANNA [30] | 81 | 4.9 | 1.0 | 13.9 | 18.7 |
| Botswana [27] | 845 | 0.0% | 2.1 | 17.8 | 18.7 |
| DTG post-marketing surveillance [11,31] | 67 | 7.5 | – | – | – |
| DTG Phase 3 trials [11,31] | 30 | 3.3 | – | – | – |
| IMPAACT P1026S [32] | 15 | 13.3 | – | – | – |

Section 6: ARVs, Pharmacokinetics & Safety data

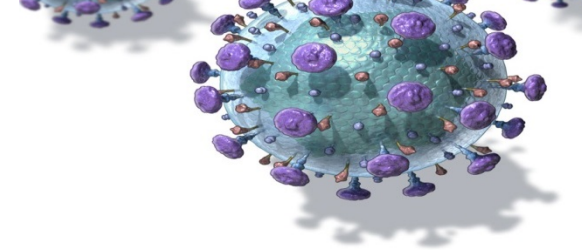
Table 3. Pregnancy outcomes from the Botswana cohort

| Botswana | DTG/TDF/FTC (n=845) | | EFV/TDF/FTC (n=4593) | |
|--|------------------------|-------|-------------------------|-------|
| Stillbirth | 18 | 2.1% | 105 | 2.3% |
| Neonatal death | 11 | 1.3% | 60 | 1.3% |
| Preterm birth (<37 weeks) | 149 | 17.6% | 844 | 18.4% |
| Preterm birth (<32 weeks) | 35 | 4.1% | 160 | 3.5% |
| Small for gestational age (<10th percentile) | 156 | 18.5% | 838 | 18.3% |
| Small for gestational age (<3rd percentile) | 51 | 6.0% | 302 | 6.6% |
| Congenital anomalies | 0/116 | 0.0% | 1/396 | 0.3% |

Table 5. Ongoing randomised clinical trials of DTG in pregnant women [11]

| Clinical trial | Treatment arms | Sample size | Inclusion | Time expected first results |
|----------------|---|-------------|--|-----------------------------|
| DOLPHIN-1 | TDF/FTC/EFV 600 TDF/FTC/DTG | 60 | Pregnant women Uganda, South Africa | 2Q2018 |
| DOLPHIN-2 | TDF/3TC/EFV 600 TDF/3TC/DTG | 250 | Pregnant women Uganda, South Africa | 2Q2019 |
| VESTED | TDF/FTC/EFV 600 TDF/FTC/DTG TAF/FTC/DTG | 550 | Pregnant women International | 2Q2019 |
| ING20026 | TDF/FTC/ATV/r TDF/FTC/DTG | 25 | Pregnant women International Sub-study of ARIA | 2020 |

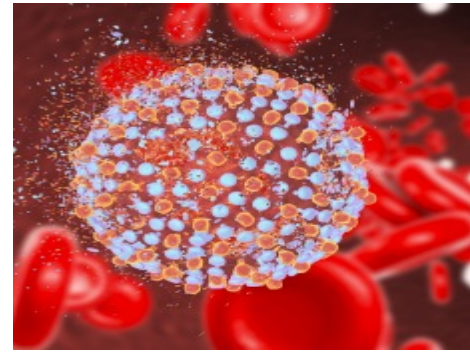
Section 7: Hepatitis B



- For tenofovir-DF, emtricitabine and lamivudine, APR and the Development of Antiretroviral Therapy Study (DART) have not identified any increased risk in prevalence or any specific pattern of anomaly, even when administered in the first trimester
- When a patient becomes pregnant on an anti-HBV viral agents as part of their ART, treatment should be continued as the potential risk to the fetus from drug exposure is outweighed by that of a
 - hepatitis flare
 - liver disease progression or
 - HIV/HBV virological rebound and risk of vertical transmission
- Whilst the experience with tenofovir-AF in pregnancy is limited, animal data do not indicate direct or indirect harmful effects with respect to reproductive toxicity [1]

1. eMC. SmPC Vemlidy 25 mg film coated tablets (tenofovir alafenamide fumarate). Available at: <https://www.medicines.org.uk/emc/medicine/32756> (accessed December 2017)

Section 7: Hepatitis C



- Women living with HIV/HCV should not be treated for HCV with ribavirin-based DAA therapies, and all women who discover they are pregnant while receiving treatment should discontinue both therapies immediately
- Women living with HIV/HCV of child-bearing age wishing to get pregnant should be prioritised for DAA-based HCV therapy

Section 8: Duration of Rupture of membranes

- There is no significant difference in vertical transmission rates between ROM <4 hours and ≥ 4 hours <24 hours in women of all viral loads
 - vertical transmission rates were 0.34% and 0.64% respectively; OR 1.90 and 95% CI 0.45-7.97)
- However, transmission rates were 0.13% in women with viral load <50 copies/ml (2/1519)
 - 2.05% in women with viral load 50-999 copies/ml (3/146),
 - 23.1% in women with viral load >10000 copies/ml (3/13)
- Treat as HIV negative woman but maximum recommended duration of ROM even if HIV VL<50c/ml is 24 hours

Section 9: Neonatal Post Exposure Prophylaxis

VERY LOW RISK

Two weeks ZDV monotherapy

- Mother has been on cART for >10 weeks AND
- Two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart AND
- Maternal HIV viral load <50 HIV RNA copies/mL >36 weeks

LOW RISK

4 weeks ZDV monotherapy

- If VERY LOW RISK criteria are not all fulfilled but
- Maternal HIV VL is <50 HIV RNA copies/mL at or after 36 weeks
- If baby born <34 weeks but most recent maternal HIV VL is <50 HIV RNA copies/mL

HIGH RISK

- Use combination PEP if maternal birth HIV VL known to be or likely to be >50 HIV RNA copies/mL on day of birth, if uncertainty about recent maternal adherence or if VL not known

Section 9: Infant feeding

- In the UK and other resource rich settings the safest way to feed infants born to mothers with HIV is with formula milk, as this eliminates on-going risk of HIV exposure after birth.
- There are no data on the risk of HIV transmission via breast milk in resource rich settings

| HIV transmission (95% CI) | | |
|---------------------------|---------------------------|----------------------------|
| | Bispo, et al ¹ | PROMISE study ² |
| At 6m | 1.08 (0.32-1.85) | 0.3% (0.1–0.6) |
| At 12m | 2.93% (0.68–5.18) | 0.6% (0.4–1.1) |

1. Bispo S, et al. *J Int AIDS Soc* 2017; 20: 1–8. 2. Taha T. *International AIDS Conference. Durban, South Africa*. 3. Becquet R. *PLoS One* 2009; 4: e7397. 4. Rollins N. *Sex Transm Infect* 2012; 88 Suppl 2.

Section 9: Infant feeding



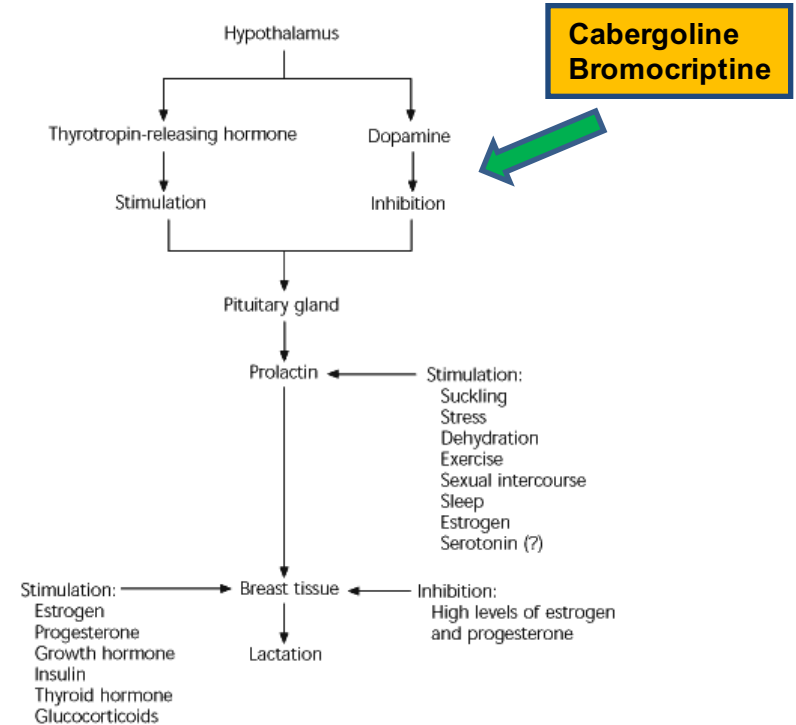
- Factors that increase the risk of breast milk HIV transmission when women are not on cART include
 - detectable viral load
 - advanced maternal HIV disease
 - longer duration of breastfeeding (0.16%/month)
 - breast and nipple infection/inflammation
 - infant mouth or gut infection/inflammation
- Mixed feeding, in particular solid food given to infants less than 2 months of age³
 - Exclusive breastfeeding risk is 9/100 child-years
 - Predominantly breast milk with liquid other risk is 9.5/100 child years
 - Early solid foods transmission risk is **41.2/100** child-years
- Whether this risk still ⁴ holds when women breastfeed on effective cART with is not yet known

Section 10: Postnatal Care

- New section
- Opportunity to provide guidance on mental health assessment post partum at 4-6 weeks
- Ensure cytology and contraception provided or planned for
- Testing of partner and/or other children if not already done
- Women not breastfeeding their infant by choice, or because of HIV RNA > 50 HIV RNA copies/mL, should be offered cabergoline to suppress lactation

Cabergoline

- Cabergoline is an ergot derivative introduced in the mid-1990s to inhibit puerperal lactation
- A single dose of 1 mg of cabergoline may be used to inhibit lactation on Day 1 postpartum giving the equivalent effect of two weeks of bromocriptine
- A small prospective study in Canada looked at 22 women who received cabergoline postpartum
 - successfully suppressed lactation with absence of pain, swelling or nipple discharge in over 86% of women
- Side effects were common most frequently dizziness and hand or foot numbness, hand or foot pain, and nausea
- Overall women were satisfied with the treatment and would recommend its use to a friend



And finally..

- We have significantly changed the language used in the text preferring for example
 - vertical transmission vs MTCT
 - woman living with HIV to HIV positive or infected woman
 - well received in public consultation



Thank you

- All my co-authors
- Fiona Creagh
- Mediscript
- BHIVA Guidelines Committee
- External guidelines reviewers
 - Fiona Lyons
 - Karoline Aebi-Popp
- All of you who took the time to read and comment on our guidelines
- The guidelines are being redrafted in response to comments
- We hope to publish Summer 2018