Implications of the recent data on dolutegravir and birth defects

21 July 2018

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No conflicts of interest to report

Formal presentation of data will be presented at:
Safety of Dolutegravir in Pregnancy: Late breaking findings, interpretations and implications
Tuesday 24 July, 16:30-18:00
Elicium 2, RAI Amsterdam
How did we get here? And what should we do?
• The magnitude of ART exposure in pregnancy due to HIV in countries with high prevalence **outweighs** that seen for any other drug in history
Major Public Health Success: 75% Decrease in new pediatric HIV infections since 2000 in the 21 Global Plan countries because of increased availability of 3-drug ART in pregnancy.
Antiretroviral treatment in pregnancy

- 3-drug ART use in pregnancy *is critical*
  - Prevention of MTCT
  - Maternal Health
  - Decreasing transmission risk to uninfected partners (TasP)

- Is ART safe in pregnancy? Which ART is *safest*?
  - Birth defects, miscarriage, stillbirth, preterm, birthweight, neonatal/childhood death, long-term pediatric outcomes (neurologic, malignancy)
  - Gestational hypertension, pre-eclampsia and anemia
Women of reproductive age make up close to half of the worldwide population of HIV-infected people

- ~2 million HIV-infected women become pregnant every year
- Not really a ‘special population’

There are currently 31 approved ARVs but there is limited data on the safety during pregnancy
- The only ARV with FDA indication for pregnancy is AZT
Challenges to studying drug safety in pregnancy

- Lack of inclusion of pregnant women in clinical trials during drug development
- Most post-marketing surveillance is voluntary report by healthcare providers (not systematic)
- Reliance on safety data from observational data before any RCTs in pregnant women
  - Requires use of medications in pregnancy before data on safety
Challenges to studying drug safety in pregnancy

- The magnitude of ART exposure in pregnancy due to HIV in countries with high prevalence outweighs that seen for any other drug in history.

Majority of exposures are in countries where systematic surveillance for safety of drugs in pregnancy has is lacking.
Botswana

1. Ability to capture outcomes
   • Antenatal record available at delivery for >99% of women
   • >95% of women deliver in a healthcare facility
   • Almost no termination of pregnancy

2. Large # of exposures
   • High HIV prevalence (~25%)
   • High uptake of ART in pregnancy (>90%)
   • Multiple ART regimens in use concurrently
     • 52% start prior to conception
The Tsepamo Study

• Birth outcomes surveillance, started Aug 2014
  – 3\textsuperscript{rd} similar study done in Botswana since 2009
  – **Funding:** NIH/NICHD (R01, R Shapiro PI)

• **Primary aims:**
  – (1) Evaluate adverse birth outcomes by HIV-status and ART regimen
  – (2) Determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception
• Why were we interested in EFV and NTDs?

• Why were we focused on exposures to medications that started prior to conception?
Why were we interested in EFV and NTDs?

• For many years, EFV was avoided in women of reproductive age (FDA category D)
  – Animal data\(^1\): 3/20 infant monkeys had severe CNS defects (anencephaly, cleft palate, anophthalmia) after exposure to EFV from conception

• In 2011, TDF/FTC/EFV was seen as the best available ART and goal was to harmonize ART for all
  – Meta-analysis\(^2\) of 1437 women in 21 studies who fell pregnant taking EFV could rule out >4-fold increased risk for NTD

→ Starting in 2012, a rapid rollout of TDF/FTC/EFV as first-line ART in most high-burden countries and WHO guidelines

• Why were we interested in EFV and NTDs?

• Why were we focused on exposures to medications that started prior to conception?
Usually we talk about 1<sup>st</sup> trimester for teratogens?

**Weeks 3 to 8-12 Post Fertilization**

**Embryogenesis: Active Organogenesis**

most sensitive period to teratogens

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*Slide thanks to Lynne Mofenson*
But Neural Tube Defects develop in the first 28 days post-conception.

Fusion of the neural tube begins in the cervical region.

Fusion proceeds in both cephalad and caudal directions, forming anterior and posterior neuropores.

Cranial neuropore closes on the 25th day after conception; caudal neuropore normally closes ~2 days later.
Timing of *In Utero* Exposure Affects Fetal Risk
Critical Periods in Human Development

**Risk period for Neural Tube Defects is most often BEFORE a woman knows she is pregnant**

**Medications of concern most all started prior to conception**
The Tsepamo Study Methods

Tsepamo takes place at 8 of the largest maternity wards in Botswana
- ~45% of the total births in the country

Planned enrollment of 94,000 births over 4 years (2014-18)
- Sample size based on ability to detect a 2-fold increase in NTDs among women on EFV at conception and 0.1% prevalence of NTD
• Research assistants abstract data from the obstetric card for all consecutive in-hospital deliveries

• When midwives identify an infant with a congenital abnormality, they contact our research assistant who consents the mother for a photo of the abnormality
  – Photos reviewed by expert in Boston for diagnosis
Limitations of Surveillance for Abnormalities

• **Surveillance limited to abnormalities that were detected by surface exam at birth**
  – Unable to evaluate for cardiac defects (common) or other internal organ defects (rare)

• **Exclude defects that are not consistently and reliably evaluated during infant surface exams**
  – Undescended testes
  – Isolated cleft palate
  – Hip Dysplasia
Prior data from Tsepamo
2-yr analysis-Comparative safety of ART at conception

Zash et al JAMA Peds 2017

*Key Finding: Among women on ART from conception, TDF/FTC/EFV associated with fewer adverse and severe adverse birth outcomes

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC/EFV (N=2,503)</th>
<th>TDF/FTC/NVP (N=775)</th>
<th>ZDV/3TC/NVP (N=1,403)</th>
<th>TDF/FTC/LPV-r (N=237)</th>
<th>ZDV/3TC/LPV-r (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Birth Outcome aRR* (95% CI)</td>
<td>ref</td>
<td>1.2 (1.0,1.3)</td>
<td>1.3 (1.2,1.4)</td>
<td>1.3 (1.1,1.5)</td>
<td>1.2 (1.0,1.5)</td>
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<tr>
<td>Severe Birth Outcome aRR* (95% CI)</td>
<td>ref</td>
<td>1.4 (1.2,1.7)</td>
<td>1.7 (1.4,2.0)</td>
<td>1.6 (1.2,2.1)</td>
<td>1.9 (1.4,2.6)</td>
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In mid-2016, Botswana changed first line ART from TDF/FTC/EFV to TDF/FTC/DTG (including pregnant women) allowing us to provide the first data on safety of DTG when starting during pregnancy.

- No difference in any adverse birth outcome compared to women who started EFV during pregnancy.
- No increased risk of birth defects among a small number (280) women who started DTG in the first trimester.
DTG started PRIOR to pregnancy
The NTD signal

- It takes longer to accrue data on births to women on DTG at conception
  - To be included in surveillance, woman must start ART \( \rightarrow \) become pregnant \( \rightarrow \) deliver a baby

By May 1, 2018 we had accrued 426 births to women on DTG-conception
May 1 analysis

- 4/426 births with DTG-conception exposure had a NTD, 0.94%
- Almost 9x higher than expected (0.1%)
- about 9x higher than comparator groups
- prevalence difference was statistically significant compared to all comparator groups

Reported to WHO, ViiV, NICHD
The NTD signal

• There is an early signal for DTG at conception and neural tube defects that requires further surveillance to confirm or refute
  – Tsepamo is ongoing and we expect to have data on ~1200 births exposed to DTG from conception in mid-2019

• There is really no other comparable data from other parts of the world at the moment
  – Low HIV-prevalence settings accruing data, but still small numbers (UK, France)
  – High HIV-prevalence settings using DTG (Brazil and Kenya) working on getting more data
While the data collection continues...

- This is not an issue specific to pregnant women, but really for all women of reproductive potential.

- How to approach ART with women of reproductive age?
  - On DTG-based ART already (+/- already pregnant)
  - Presenting to initiate ART while not pregnant
  - Presenting to initiate ART while pregnant
  - Post-exposure prophylaxis (occupational, sexual, assault)
One size fits all approach is unlikely to work

- Harmonization of a single regimen for all adults, including pregnant women, is no longer obvious
  - If using DTG only, then might risk NTDs
  - If using EFV only, then might risk more ART failure/side effects
  - If using EFV for women and DTG for men, then risk inequity
  - No similar data on RAL—unknown if this could be a class effect
  - No similar data on modern PIs (darunavir, atazanavir) and lopinavir-r is associated with adverse birth outcomes
Individual approach

• **Barriers to individualized decision making**
  – The risk of NTD is still really unknown (is it true or not?)
  – The benefits of DTG vs. EFV in an individual are hard to predict
  – ~50% of pregnancies (or more) are unplanned and so hard to sort by ‘wanting pregnancy’ vs. ‘not wanting pregnancy’
  – Contraceptive access is poor in many settings with high HIV prevalence (particularly effective contraception like LARCs)
  – Accurate prenatal diagnosis of NTD and access to termination of pregnancy varies across settings
  – Accurate pregnancy dating varies across settings
  – The healthcare encounter is often insufficient and ineffective for a full discussion of risks and benefits
Current Approaches: 2 examples

- **Botswana updated guidelines**
  - DTG for women not planning a pregnancy with effective contraception
  - EFV for women wanting to get pregnant
  - EFV for pregnant women*
  - Women already on DTG should speak to their healthcare provider

- **DHHS updated guidelines (US)**
  - Pregnancy test prior to initiating ART
  - DTG ok for women not desiring pregnancy and on effective contraception
  - If want pregnancy or not on effective contraception use: RAL, ATZ, DVR, EFV or rilpivirine
  - Women <8 weeks pregnant should not start DTG
  - Women <8 weeks pregnant already on DTG should discuss risks and benefits with their provider, if good options for other ART, should be switched off DTG
  - Women >8 weeks pregnant can start or stay on DTG-based ART

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Conclusions

• The study of the safety of ART in pregnancy has not historically been a priority (but should be!)
• Tsepamo has previously shown DTG was as safe as EFV when started during pregnancy
• The signal for DTG and neural tube defects is preliminary and needs more data to confirm or refute
• This signal has put providers, country programs and women living with HIV in a difficult position with regard to ART treatment decisions
Thanks!

- NIH/NICHD
- Ministry of Health, Botswana
- Midwives, doctors and hospital administrators at all our study sites
- BHP admin
- Edith Moseki
- Cynthia Dube
- Rosemary Moremi
- Onkabetse Mokgosi
- Judith Mabuta
- Daphne Segobye
- Gosego Legase
- Patricia Mophuthegi