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10TH IAS CONFERENCE ON HIV SCIENCE

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Dolutegravir use at conception: Additional surveillance data from Botswana

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Disclosure: No conflicts of interest to declare
Botswana poised to provide data on dolutegravir (DTG)

Implemented DTG-based ART as first-line therapy in May 2016

Tsepamo study findings raised concerns about a possible association between neural tube defects (NTDs) and DTG use at conception

More data needed

Botswana was uniquely positioned as it had sufficient numbers of women with DTG exposure at conception

Expanding birth outcomes surveillance

Botswana’s Ministry of Health and Wellness (MoHW) initiated the NTD Surveillance Study

– Conducted in collaboration with:
  • US Centers for Disease Control and Prevention (CDC) – Atlanta and Botswana offices
  • Botswana University of Maryland School of Health Initiative (BUMMHI)

– Funding support from the US President’s Emergency Plan for AIDS Relief (PEPFAR)

– Informed by Tsepamo study methods
Coverage of birth outcomes surveillance

Tsepamo original
(8 sites: 45%)
Coverage of birth outcomes surveillance

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+  

Tsepamo expansion
(10 sites: 27%)

= 72 %
Coverage of birth outcomes surveillance

Tsepamo original (8 sites: 45%) + Tsepamo expansion (10 sites: 27%) = 72%

NTD Surveillance Study (22 sites) = 19%
Coverage of birth outcomes surveillance

Tsepamo original (8 sites: 45%) + Tsepamo expansion (10 sites: 27%) = 72%

NTD Surveillance Study (22 sites) = 19%

TOTAL: 91%
Study methods

Prospective NTD surveillance enrolled mothers who delivered infants (live births and stillbirths) >24 weeks gestation at the study sites from October 2018–March 2019. IRB-approved protocol.

MoHW Study Site Map:
- 22 sites – coverage of 19% of Botswana's deliveries
Methods: Prospective Surveillance for All Deliveries

At Maternity Unit

Delivery → Examination of infant → Completion of Coversheet and Maternal Obstetrical Record
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Delivery → Examination of infant → Completion of Coversheet and Maternal Obstetrical Record

Abstraction of data and entry into electronic data collection tool
Methods: Prospective Surveillance for Suspected NTDs

At Maternity Unit

Delivery → Suspected NTD → Examination of infant → Completion of Coversheet and Maternal Obstetrical Record

Consent for photographs and abstraction of additional information → Abstraction of data and entry into electronic data collection tool
Methods: Prospective Surveillance for Suspected NTDs

At Maternity Unit

1. Delivery
2. Suspected NTD
3. Examination of infant
4. Completion of Coversheet and Maternal Obstetrical Record
5. Consent for photographs and abstraction of additional information
6. Abstraction of data and entry into electronic data collection tool
7. Review of de-identified information and classification of the suspected NTD
Methods: Prospective Surveillance for All Deliveries

At Maternity Unit

- Delivery
- Examination of infant
- Completion of Coversheet and Maternal Obstetrical Record
- Abstraction of data and entry into electronic data collection tool
- Data quality review for deliveries at all sites

**SURVEILLANCE ASSISTANT**

**METHODS**

**delivery**

**examination of infant**

**completion of coversheet and maternal obstetrical record**

**abstraction of data and entry into electronic data collection tool**

**data quality review for deliveries at all sites**
Methods: Exposure definition

Exposure of interest = ART at conception

- HIV-positive women categorized as ART: exposed/not exposed/unknown

Last menstrual period used to determine periconceptional time frame

HIV-positive women exposed to ART at conception

- DTG-based regimen
- Non-DTG based regimen

- EFV-based regimen
- Non-EFV regimen
Methods: Outcome definition

Outcome of interest = NTD classification

1. Not NTD — photo/description/drawing sufficient to rule out NTD
2. Possible — description/drawing insufficient to determine NTD status
3. Probable — clear description/drawing and indication of surgical referral, if live-born
4. Confirmed — photo or clear description/drawing and/or surgical records, if live-born
Results: Pregnancies by HIV and ART status

3076 pregnancies in 22 surveillance sites
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- 3076 pregnancies in 22 surveillance sites
  - 742 (24%) with HIV-positive mother
  - 2328 (76%) with HIV-negative mother
  - 6 (<0.1%) with mother's HIV status unknown
Results: Pregnancies by HIV and ART status

3076 pregnancies in 22 surveillance sites

- 742 (24%) with HIV-positive mother
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- 544 (73%) with HIV-positive mother on ART at conception
- 176 (24%) with HIV-positive mother not on ART at conception
- 22 (3%) with HIV-positive mother with unknown ART status at conception
Results: Pregnancies by HIV and ART status

3076 pregnancies in 22 surveillance sites

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- 152 (28%) on DTG-based regimen at conception
- 381 (70%) on non-DTG-based regimen at conception

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11 (2%) on unknown regimen at conception
Results: Pregnancies by HIV and ART status

3076 pregnancies in 22 surveillance sites

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Results: Six suspected NTDs identified
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2 not NTDs: sacral dimples
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2 not NTDs: sacral dimples

1 possible NTD: unspecified lesion on side of head
Results: Six suspected NTDs identified

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1 possible NTD: unspecified lesion on side of head

2 probable NTDs: 1 spina bifida and 1 spina bifida with frontal encephalocele
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1 confirmed NTD: spina bifida
Results: Six suspected NTDs identified

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1 possible NTD: unspecified lesion on side of head

2 probable NTDs: 1 spina bifida and 1 spina bifida with frontal encephalocele

1 confirmed NTD: spina bifida

Probable and confirmed NTD cases (n=3) were included in the analysis
### Results: NTD prevalence by maternal exposure

<table>
<thead>
<tr>
<th></th>
<th>DTG</th>
<th>Any non-DTG ART</th>
<th>EFV</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of NTDs</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Number of Exposures</td>
<td>152</td>
<td>381</td>
<td>261</td>
<td>2328</td>
</tr>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.66% (0.02%, 3.69%)</td>
<td>0 (0, 0.79%)</td>
<td>0 (0, 1.15%)</td>
<td>0.09% (0.01%, 3.69%)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.66% (-0.73%, 4.16%)</td>
<td>0.66% (-1.25%, 4.16%)</td>
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Slide adapted from Rebecca Zash.
Results: NTD prevalence by maternal exposure

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Slide adapted from Rebecca Zash
Consideration: How do we monitor birth outcomes?
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- Surveillance
- Pharmacovigilance
Consideration: Surveillance

Surveillance is a reliable method to establish the DTG-NTD association

- Data collection methodology is continuous and systematic
- Provides a denominator to estimate the magnitude and scope of birth defects
- Starting point = outcome (delivery, NTD)
- Requires large sample size to detect rare outcome of birth defects
- Complex and resource-intensive
Consideration: Pharmacovigilance

Pharmacovigilance is a common post-marketing approach to capture adverse drug effects
- No comparison group
- Not designed to collect data from maternity wards
- Starting point = exposure (DTG at conception)
Conclusions

Small increased NTD prevalence among infants born to HIV-positive mothers on DTG at conception compared to infants born to HIV-negative mothers

Study was conducted for only 6 months, resulting in small number of deliveries

Data suggest that NTD risk with DTG exposure at conception remains <1%, consistent with Tsepamo study findings reported in 2018
Acknowledgements

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  – Gadzikanani Gokatweng
  – Chibuike Mark Ogbruabo
  – Ndwapi Ndwapi
Ke a leboga!
Thank you!
Retrospective study not feasible

Using standard obstetrical records:

- Unreliable outcome data → unable to validate NTDs
  - Missing records, unreliable exams, missing exams, unable to validate
- Incomplete exposure data—ART regimen at conception not captured
Prospective approach chosen

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<thead>
<tr>
<th></th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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**Reasons:**
- Able to capture needed data elements with additional tool
- Provides an accurate denominator
- Can compare NTD ratios among other groups of women (e.g., HIV negative and HIV-positive on other ARVs)
Would the results be different if the analysis had included the possible NTD case?

Possible NTD case occurred in an HIV-negative woman.

We conducted a sensitivity analysis to assess how inclusion of the possible NTD would affect the prevalence difference estimate and found there was no meaningful change.
Birth surveillance is complex and resource-intensive.

- Designated leadership
- New data tools
- Midwife training
- Cadre dedicated to data collection
- Commodities
- Logistics
- Ongoing oversight for procedural and data quality
- Data collection system