Creating a Better Understanding of Pregnancy Outcomes in Sub Saharan Africa: MTN-042B

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Affiliate Investigator, Fred Hutchinson Cancer Research Center

MTN Annual Meeting
February 10, 2020
DELIVER will provide critical information on the safety and acceptability of HIV prevention products used during pregnancy.

Participants who use TRUVADA® oral tablet daily and insert the dapivirine vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.
Global maternal & neonatal health indicators

- National data are available on key maternal and neonatal health indicators
  - Maternal mortality
  - Neonatal mortality
  - Low birth weight

https://www.who.int/data/maternal-newborn-child-adolescent/monitor
While national data are helpful, they may not reflect the prevalence in communities participating in research.

True population = 3/20 (15%)

Study population = 3/10 (30%)

If our communities are not representative of the larger population in the country, we may over or underestimate the background frequency of study outcomes.
Can published research studies inform estimates of pregnancy outcomes & complications?

Systematic Review - Number of Prevalence Estimates & Individuals

Slide courtesy of Dr. Erica Lokken
MTN-042B Study Design

- **Study Design:** Multi-site, chart review, cross-sectional study
- **Study Population:** All women delivering or receiving immediate postpartum care (within one week of delivery) at one or two facilities affiliated with each of the 4 sites, a primary care facility and a referral facility
- **Duration:** 8 weeks of abstraction at each delivery site
### To determine the frequency of...

<table>
<thead>
<tr>
<th>Pregnancy &amp; maternal outcomes</th>
<th>Pregnancy complications</th>
<th>Infant outcomes &amp; complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Full term live birth (≥37 weeks)</td>
<td>- Fever of unclear etiology</td>
<td></td>
</tr>
<tr>
<td>- Premature live birth (&lt;37 weeks)</td>
<td>- Chorioamnionitis</td>
<td></td>
</tr>
<tr>
<td>- Stillbirth/intrauterine fetal demise (≥20 weeks)</td>
<td>- Postpartum endometritis</td>
<td></td>
</tr>
<tr>
<td>- Maternal death</td>
<td>- Postpartum hemorrhage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Gestational hypertensive disorder (gestational hypertension, pre-eclampsia, eclampsia)</td>
<td>- Neonatal death (after delivery, before mother is discharged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neonatal ICU admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Congenital malformations</td>
</tr>
</tbody>
</table>
The heroes of MTN-042B

Blantyre

Chimwemwe Khonjera, Lonjezo Jemi, Hawah Mbali, pictured with Noel Kayange, Bonus Makanani, Frank Taulo

MU-JHU-Kampala

Birungi Harriet Mawanda, Kemigisa Everlyn, Atwebembire Prossy, Mirembe Ritah, Ekel Irene, Amany Spincious, Oloo Keziron Eric, Atukunda Mediaas, Naluggwa Abisagi, Helen Agoile Unzia, Anneett Miwanda

WRHI - Shandukani

Zinhle Tshabalala, Sarah Whittaker, Megan Dempster, Jean Leroux, Caroline Vika, Karabo Kongoane

UZCHS Zengeza

Fungai Murewa, Grecenia Ndlovu, Tsitsi Zinyengere, Vannessa Gatsi, Mary Mudavanhu, Moleen Matimbira
Data abstraction teams meticulously reviewed charts and abstracted data for deliveries occurring within the past 7 days.

7,345 charts abstracted

Final data for Malawi and Uganda

Data from South Africa and Zimbabwe through November 2019 and do not represent final estimates.
## Demographic characteristics by country

<table>
<thead>
<tr>
<th></th>
<th>Malawi</th>
<th>Uganda</th>
<th>South Africa</th>
<th>Overall*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2384</td>
<td>N=3505</td>
<td>N=1117</td>
<td></td>
<td>N=7345</td>
</tr>
<tr>
<td>Maternal age (mean ± SD)</td>
<td>25.7±6.7</td>
<td>25.5±5.6</td>
<td>28.7±6.2</td>
<td>26.1±6.2</td>
</tr>
<tr>
<td>Gravidity (mean ± SD)</td>
<td>2.5±1.6</td>
<td>2.6±1.7</td>
<td>2.6±1.3</td>
<td>2.6±1.6</td>
</tr>
<tr>
<td>Parity (mean ± SD)</td>
<td>1.4±1.5</td>
<td>1.4±1.6</td>
<td>1.3±1.1</td>
<td>1.4±1.5</td>
</tr>
<tr>
<td>Attended 4+ antenatal care visits</td>
<td>1070 (46.7%)</td>
<td>540 (38.9%)</td>
<td>772 (72.1%)</td>
<td>2501 (49.6%)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2008 (84.2%)</td>
<td>3013 (86.0%)</td>
<td>841 (75.3%)</td>
<td>6149 (83.7%)</td>
</tr>
<tr>
<td>Positive</td>
<td>311 (13.0%)</td>
<td>368 (10.5%)</td>
<td>273 (24.4%)</td>
<td>981 (13.4%)</td>
</tr>
<tr>
<td>Unknown or not documented</td>
<td>65 (2.7%)</td>
<td>124 (3.6%)</td>
<td>3 (0.3%)</td>
<td>215 (2.9%)</td>
</tr>
<tr>
<td>Number of infants at delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2327 (97.6%)</td>
<td>3387 (96.8%)</td>
<td>1089 (97.5%)</td>
<td>7134 (97.2%)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>57 (2.3%)</td>
<td>112 (3.2%)</td>
<td>28 (2.5%)</td>
<td>205 (2.7%)</td>
</tr>
</tbody>
</table>

*Overall includes data from Zimbabwe where data collection is still in progress*
Pregnancy outcomes & delivery mode

Global preterm birth estimates\(^1\) = 10.6%
- Malawi = 10.5%
- Uganda = 6.6%
- South Africa = 12.4%

Pregnancy outcomes not documented for 2.1% of outcomes

\(^1\)Chawanpaiboon et al. Lancet Global Health (2018)
## Serious maternal & infant outcomes

### Maternal deaths:
- **Malawi**: 7 (0.1%)
- **Uganda**: 0
- **South Africa**: 0

### Neonatal deaths:
- **Malawi**: 123 (1.7%)
- **Uganda**: 368 per 100,000
- **South Africa**: 47 per 100,000

<table>
<thead>
<tr>
<th>Country</th>
<th>MTN-042B Maternal deaths*</th>
<th>DHS Maternal death rate</th>
<th>MTN-042B Neonatal deaths*</th>
<th>DHS Perinatal death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malawi</td>
<td>n=7 (293 per 100,000)</td>
<td>439 per 100,000</td>
<td>n=61 (26 per 1,000)</td>
<td>31 per 1,000</td>
</tr>
<tr>
<td>Uganda</td>
<td>0</td>
<td>368 per 100,000</td>
<td>n=43 (13 per 1,000)</td>
<td>32 per 1,000</td>
</tr>
<tr>
<td>South Africa</td>
<td>0</td>
<td>47 per 100,000</td>
<td>n=12 (11 per 1,000)</td>
<td>29 per 1,000</td>
</tr>
</tbody>
</table>

*Data presented are not rates but prevalence in MTN-042B and transformed for comparability

1. Data from DHS reports 2015 and 2016; includes deaths within 42 days from delivery

2. For women 20-29, perinatal death rate includes stillbirths and deaths within 7 days of birth
Maternal complications

Hypertension-related complications

- Any hypertension
- Gestational
- Pre-eclampsia
- Eclampsia

Other complications

- Post Partum Hemorrhage
- Fever of Unclear Etiology
- Chorioamnionitis
- Post Partum Endometritis

Information not documented for <1% of outcomes
## Congenital anomalies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Malawi</th>
<th>Uganda</th>
<th>South Africa</th>
<th>Overall*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of records</strong></td>
<td>N=2442</td>
<td>N=3614</td>
<td>N=1146</td>
<td>N=7549</td>
</tr>
<tr>
<td><strong>Any malformation identified at delivery</strong></td>
<td>33 (1.4)</td>
<td>23 (0.6)</td>
<td>18 (1.6)</td>
<td>78 (1.0)</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>16 (0.7)</td>
<td>2 (0.1)</td>
<td>7 (0.6)</td>
<td>25 (0.3)</td>
</tr>
<tr>
<td>Musculoskeletal including clubfoot</td>
<td>6 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.1)</td>
<td>9 (0.1)</td>
</tr>
<tr>
<td>Cleft Lip and/or Palate</td>
<td>2 (0.1)</td>
<td>3 (0.1)</td>
<td>1 (0.1)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Umbilical Hernia</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>2 (0.2)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Neural tube defects and/or Hydrocephalus</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0 (0)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Esophageal, gastrointestinal, or anorectal</td>
<td>1 (&lt;0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0 (0)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Natal Tooth</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>5 (0.2)</td>
<td>12 (0.3)</td>
<td>7 (0.6)</td>
<td>25 (0.3)</td>
</tr>
</tbody>
</table>
Congenital anomalies: timing is everything

That vast majority of congenital anomalies attributed to a teratogen occur with exposure prior to 12 weeks gestation

DELLIVER will assess the safety of at different time points in pregnancy

12 weeks – delivery

• Data on congenital anomalies will be collected in all DELIVER cohorts
• Data from cohorts 1 through 3 will provide additional data on the background rate of congenital anomalies in our study population

https://clinicalgate.com/impact-of-age-on-pharmacology/
Congenital anomalies: Data in Context

• ~3% prevalence of any birth defect/congenital anomaly in the US and Europe\(^1\)

• Congenital anomalies in ASPIRE:
  – 8 (7%) suspected anomalies reported, 4 in each arm\(^2\)
  – Inguinal/umbilical hernia (5) most commonly reported

\(^1\)Moorthie et al. J Com Gen (2018); [https://www.cdc.gov/ncbddd/birthdefects/data.html](https://www.cdc.gov/ncbddd/birthdefects/data.html)
\(^2\)Makanani & Balkus et al. JAIDS (2018)
Congenital anomalies: Data in Context

**MTN-042B**
- Included a very short window of infant evaluation (within 7 days of delivery)
- Passive ascertainment of congenital anomalies (i.e. what was written in the chart)

**DELIVER**
- Infants followed for 12 months
- Active ascertainment of congenital anomalies (CRF questions about potential anomalies)
- External expert reviews by a geneticist

*Similar processes were implemented for ASPIRE and MTN-016*
How the data will be used by the DELIVER team?

Participants who use TRUVADA® oral tablet daily and insert the dapivirine vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

Prevalence of outcomes in populations where DELIVER will be conducted

Observed frequency of outcomes in DELIVER

Data from MTN-042B and systematic review will be used to generate the “target”
Summary

• Chart abstraction is not as easy as it sounds and requires dedicated teams, clear communication, and the ability to accept potentially “imperfect data”

• Data on key DELIVER outcomes were available for the majority of charts abstracted (<1% missing data)

• Site estimates of certain outcomes differed somewhat from other national data sources
  • Underlying differences in the study catchment area?
  • Differences due to the type of facilities included in MTN-042B?

• MTN-042B data will play a critical role in the conduct of DELIVER and will be a valuable resource for future studies conducted at participating sites that evaluate investigational products in pregnancy
THANK YOU!

MTN-042B protocol chairs & management team
MTN-042B site teams
Tanya Harrell, SCHARP
Moni Neradilek, SCHARP
Danny Szydlo, SCHARP
Elizabeth Brown, SCHARP
Ashley Mayo, FHI360
Rachel Scheckter, FHI360
Tara McClure, FHI360
Erica Lokken, UW
Acknowledgements

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.