Dapivirine Ring, Dolutegravir, and Moving Forward with Pregnancy Research

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Introduction

- Justifications for pregnancy research
  - High HIV acquisition risk during pregnancy/PP (2-4X)
  - High MTCT risk with incident HIV in pregnancy (2-15X)
  - Ethical
    - Justice, Autonomy
    - Protect **through** research
  - Real-life scenarios
    - Every-day use, trials, etc.
    - **Inadvertent 1st tri pregnancy exposures**

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Making a case for studies involving pregnant women

- Drugs are often contraindicated in pregnant women because data to support their use in this population is lacking
  - Usually, a woman in a clinical trial must not be pregnant and must use contraception throughout
  - She must immediately stop using the product if she gets pregnant
  - These measure are intended to avoid potential risk to the developing fetus

- Drugs are used during pregnancy anyway
  - Roughly 2-5meds/pregnant woman
    - > 98% FDA-approved without human pregnancy data
  - Now the uncertainty sits with the health care provider

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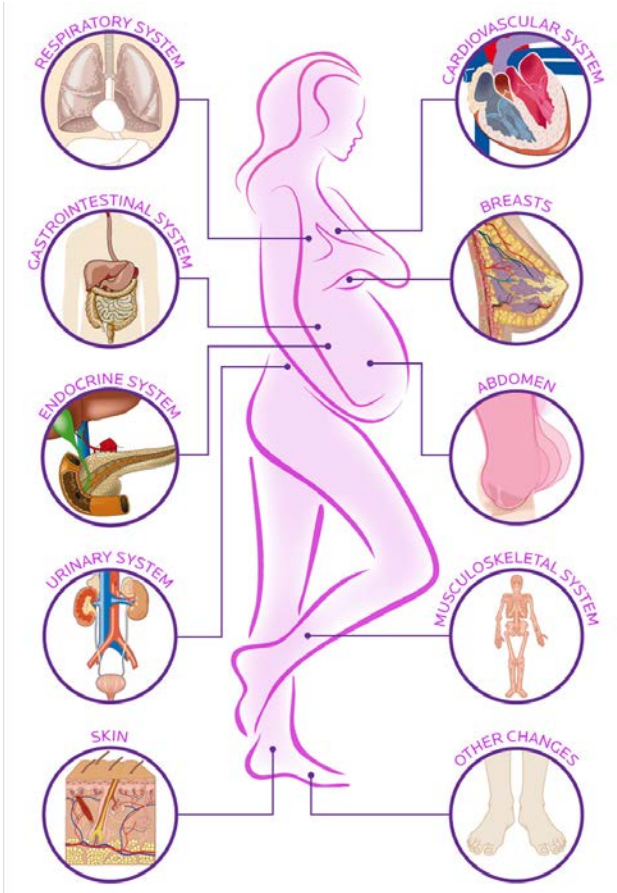
Why we should study drugs in pregnancy rather than leave safety to chance



- The body undergoes many changes during pregnancy
  - Physiology
  - Drug Metabolism
- A drug may work differently in a woman who's pregnant
- It may pass through the placenta and cause harm to the developing fetus or put the pregnancy (mother/fetus) at risk

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Duration of risk is substantial

	Malawi	South Africa	Uganda	Zimbabwe
A woman's average life expectancy	60 years	66 years	64 years	62 years
Total fertility rate per woman	5 children	2.3 children	5.7 children	3.9 children
Years pregnant/breastfeeding per pregnancy	1.75 years	1.75 years	1.75 years	1.75 years
Total time pregnant or breastfeeding	About 9 years	About 4 years	About 10 years	About 7 years
	15% of lifetime 26% of reproductive years	6% of lifetime 12% of reproductive years	16% of lifetime 29% of reproductive years	11% of lifetime 20% of reproductive years

Sources: World Bank ; http://www.worldlifeexpectancy.com/uganda-life-expectancy

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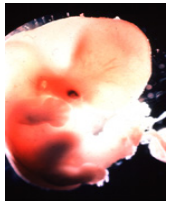
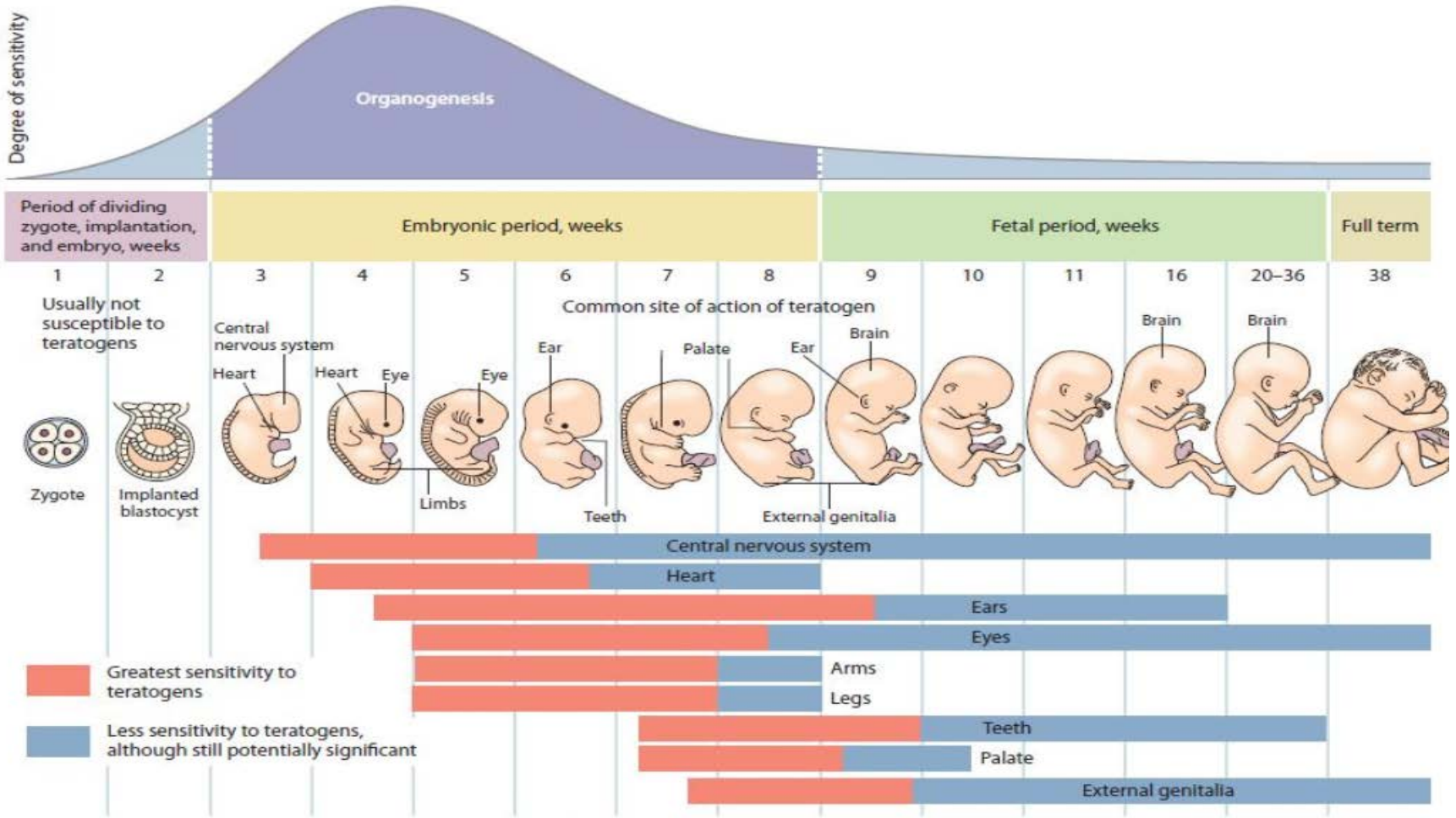


Timing of *In Utero* ARV Exposure and Fetal Risk



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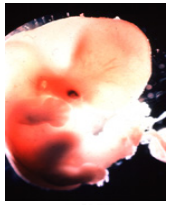

Timing of *In Utero* AD[illegible] Exposure and F[illegible]

Greatest risk for serious defects is not in women starting during pregnancy but in those who conceive while receiving drug - but most studies do not distinguish between 1st trimester and preconception exposure

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HIV, Pregnancy and ART

- HIV is associated with significant morbidity/mortality for the pregnant woman and her fetus/infant – treatment is required for both maternal health and to prevent MTCT
- Only limited data on ARVs in pregnancy/lactation; of the 31 approved ARVs, mean lag between approval→any pregnancy data is 5 years (no data 3/7 drugs approved since 2010)
- Big unknowns, particularly for newer drugs:
  - Pharmacokinetics and safety in pregnancy (and lactation)
  - Fetal/infant safety

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What is Predictive Value of Pre-Clinical Animal Studies?

- The molecular basis of birth defects with drug exposure is known for only a few drugs
- Most human teratogens were first identified by clinical/epidemiologic studies (e.g., thalidomide, diethylstibesterol, valproate)
- Animals can be *differentially sensitive* to drugs:
  - This is why currently FDA requires studies in ≥2 animal species

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What is Predictive Value of Pre-Clinical Animal Studies?

- To date, drugs known to be teratogenic in humans have shown teratogenic activity in mouse, rat or rabbit studies (often retrospectively) *(van der Laan JW et al. Reg Toxicol Pharmacol 2012;63:115-23).*
- However, while negative tests are reassuring, there is no absolute assurance that negative results obtained by testing drugs in these species can definitively predict that an agent will lack teratogenic effects in humans *(Ujhazy E et al. Developmental Toxicology: Safety Evaluation of New Drugs 2005)*
- Similarly, it cannot be said that agents teratogenic in animals will necessarily produce teratogenic effects in humans at therapeutic dose levels (e.g., EFV and CNS defects in monkeys but not in humans)

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MTN Approach

TFV 1% vaginal gel 1st steps:

- Data from antiretroviral pregnancy registry
- Pregnancy Category B
- Track record of safety in non-pregnant women

- How to balance population & scientific needs, ethics ??

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MTN-002 – First Step

- Primary: Assess term pregnancy maternal single-dose PK/Safety of TFV 1% vaginal gel - US
  - 16 women Cesarean delivery (2008 – 2010)
  - Findings:
    - Maternal PK similar to non-pregnant, 50-100x < than oral
    - Similar Cord:Maternal ratio (.53) as oral dosing
    - No safety signals (mom or baby)
- Findings justified more research

JID 2011;204:1527-31

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Next Step – MTN-008

- Expanded Safety Investigation of TFV 1% Gel in Pregnancy (& Lactation) – 2 US sites 2011-'13
  - Primary Objectives:
    - PK, Safety & tolerability of TFV gel for 7 days
  - Population
    - 90 Women
      - 45 term 1st (37-39 weeks) – **Interim Safety Review**
      - 45 near-term (34-37 weeks)
  - Design:
    - RCT, placebo-controlled (HEC gel), 2:1

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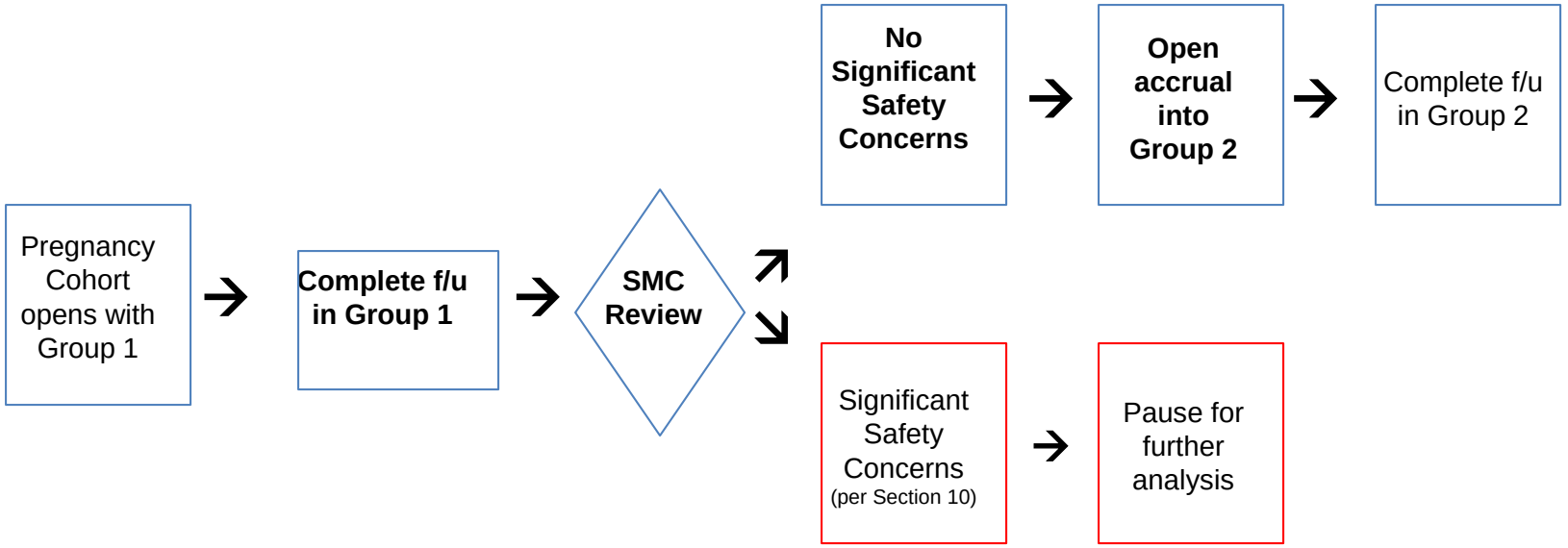
Important: Interim Safety Review



Next Step – MTN 019

- Proposed sequential next step with TFV 1% gel
  - 28 days of consecutive gel use in pregnancy
  - Approximately 100 women/gestational cohort
  - 3 sequential cohorts
    - 28-34 weeks → 20-26 → 12-18
  - ** Interim review planned for each cohort **
  - Tabled - lack of TFV gel efficacy
- Model "on shelf"…..Dapivirine Ring (042)

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Dapivirine: Safety in Pregnancy – Nonclinical findings

- No effects on embryo-foetal development in rabbits up to 90mg/kg or maternally non-toxic doses up to 20mg/kg in rats
  - Exposure levels > 1000-fold higher than expected human systemic exposure
  - Oral dapivirine (doses ≥ 80mg/kg) embryo-foetal development studies showed toxicity at maternally toxic doses in rats
- In rats oral dapivirine prenatal and post-natal development studies no effects were seen at 20mg/kg
- No maternal or embryo-foetal toxicity observed with dapivirine vaginal gel up to 3.3 mg/mL

Phase III Pooled Analysis: Pregnancy

Outcome data as at 30 Sept 2017

Pregnancy Outcome	Dapivirine Vaginal Ring n (%)	Placebo Vaginal Ring n (%)
Number of pregnancies	137	117
Live birth	80 (58.4%)	72 (61.5%)
Spontaneous abortion	28 (20.4%)	24 (20.5%)
Non-therapeutic abortion/elective termination of pregnancy	22 (16.1%)	15 (12.8%)
Stillbirth/intrauterine death	2 (1.5%)	3 (2.6%)
Ectopic Pregnancy	2 (1.5%)	1 (0.9%)
Maternal death	None	1 (0.9%)
Unknown	3 (2.2%)	1 (0.9%)

Phase III Data: Congenital Anomalies

Outcome data as at 30 Sept 2017

Anomaly Medical Concept	IPM 027		MTN-020	
	DPV Ring N=45 n (%)	PLA Ring N=21 n (%)	DPV Ring N=92 n (%)	PLA Ring N=96 n (%)
• Congenital inguinal hernia (bulge in the groin area)			1 (1.1%)	
• Congenital umbilical hernia (bulge at the belly button)			3 (3.3%)	3 (3.1%)
• Multiple congenital abnormalities		1 (4.8%)		
• Plagiocephaly (flattening of the head)			1 (1.1%)	
• Polydactyly (extra fingers or toes)	1 (2.2%)			1 (1%)
• Skeletal dysplasia (short legs and arms)			1 (1.1%)	

Abbreviations:
DPV = dapivirine
PLA = placebo
N = overall number of pregnancies per treatment group
n = number of pregnancies with anomaly

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Phase IIIb OLE Interim Pregnancy Data: as at 20 March 2018

- 22 pregnancies reported in IPM 032/DREAM
- 53 pregnancies reported in MTN-025/HOPE
- Pregnancy outcomes still accruing
- No new safety signals in respect of available pregnancy outcome data
- No congenital anomalies reported to date

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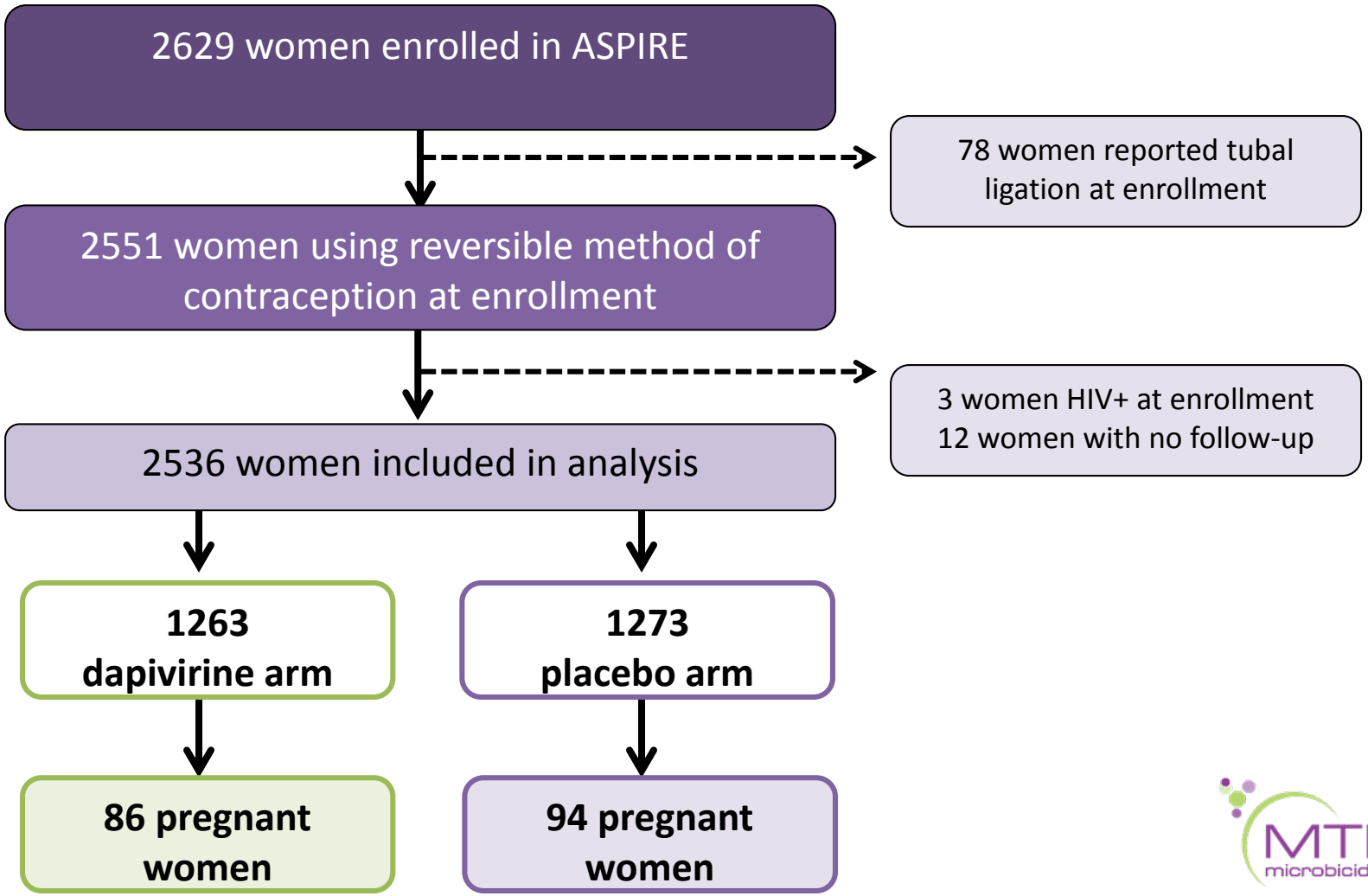
ASPIRE/MTN 020 Pregnancy Analysis



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Baseline characteristics of women who became pregnant in ASPIRE/MTN-020

	Became pregnant during follow-up N=180		Did not become pregnant during follow-up N= 2367	
Age	23	(21, 27)	26	(22, 31)
Married	65	(38%)	962	(40%)
Secondary education or greater	94	(56%)	1,093	(46%)
Number of live births	2	(1, 2)	2	(1, 3)

Data presented as N(%) or median (IQR)

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Pregnancy incidence by study arm

	Dapivirine	Placebo	Total
Number of pregnancies	86	94	180
Pregnancy incidence (per 100 p-yrs)	4.0 (3.1-5.1)	4.3 (3.4-5.5)	4.1 (3.5-4.9)

No difference noted in pregnancy incidence by arm (HR=0.93; 95% CI 0.68-1.26)

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Pregnancy outcomes by study arm

	Dapivirine N=86		Placebo N=94		Total 180	
Full term live birth	52	(60%)	53	(56%)	105	(58%)
Preterm birth	0	(0%)	9	(10%)	9	(5%0
Stillbirth/Intrauterine fetal demise	2	(2%)	2	(2%)	4	(2%)
Spontaneous abortion	18	(21%)	21	(22%)	39	(22%)
Therapeutic/elective abortion	13	(15%)	8	(9%)	21	(12%)
Ectopic pregnancy	1	(1%)	1	(1%)	2	(1%)

Distribution of pregnancy outcomes appears similar by study arm

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MTN 020: Suspectied infant congenital anomalies at birth

- Data available for 107 of 114 live births
- No difference noted in frequency of congenital anomalies* by arm
- No pattern of anomalies in the dapivirine arm vs. placebo

	Dapivirine N=48	Placebo N=59	Total N=107
Anomaly	4 (8%)	4 (7%)	8 (7%)
Physical defect	1 (2%)	3 (5%)	4 (4%)
Cranio-facial	1 (2%)	0	1 (1%)
Other	2 (4%)	1 (2%)	3 (3%)

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**Congenital anomalies as reported by site staff*

Infant analysis population

Dapivirine arm	Placebo arm
86 pregnant women	94 pregnant women
53 women enrolled in MTN 016	52 women enrolled in MTN 016
49 live births 49 infants enrolled	53 live births 50 infants enrolled
Infant follow-up Newborn = 30 (61%) Month 1 = 32 (65%) Month 6 = 44 (90%) Month 12 = 45 (92%)	Infant follow-up Newborn = 41 (82%) Month 1 = 42 (84%) Month 6 = 46 (92%) Month 12 = 47 (94%)

99 infants enrolled

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Infant Growth/Development

- Across all visits, no differences in infant weight, length or head circumference by study arm

- No reductions in infant growth among women with inadvertent exposure to dapivirine in early pregnancy compared to women in the placebo arm

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Dapivirine Pregnancy Data Summary

- Pre-clinical data: No signals
- Pregnancy rates similar between women randomized to dapivirine ring versus placebo
- Pregnancy outcomes and the frequency of site-identified congenital anomalies were also similar by arm
- Dapivirine use in the periconception period does not appear to be associated with adverse effects on pregnancy
- No effect on infant growth
- **Justifies further pregnancy research**

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Surveillance for Neural Tube Defects following Antiretroviral Exposure from Conception

Rebecca Zash, Lewis Holmes, Joseph Makhema, Modiegi Diseko, Denise L. Jacobson, Gloria Mayondi, Mompati Mmalane, Lynne Mofenson, Tendani Gaolathe, Chipo Petlo, Max Essex, Shahin Lockman and Roger L Shapiro

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

BOTSWANA HARVARD AIDS INSTITUTE PARTNERSHIP FOR HIV RESEARCH AND EDUCATION

Background

- **The Tsepamo Study started in August 2014**
  - Birth Outcomes Surveillance
  - 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**

Study Setting: Botswana

1. Ability to capture outcomes

- Antenatal record available at delivery for >99% of women
- >95% of women deliver in a healthcare facility
- Early termination extremely rare

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

Analysis Plan: 2014

- Original plan was for a 4-year analysis in August 2018 to compare the prevalence of neural tube defects in live-born and stillbirths (combined) among women on EFV at conception and other exposure groups

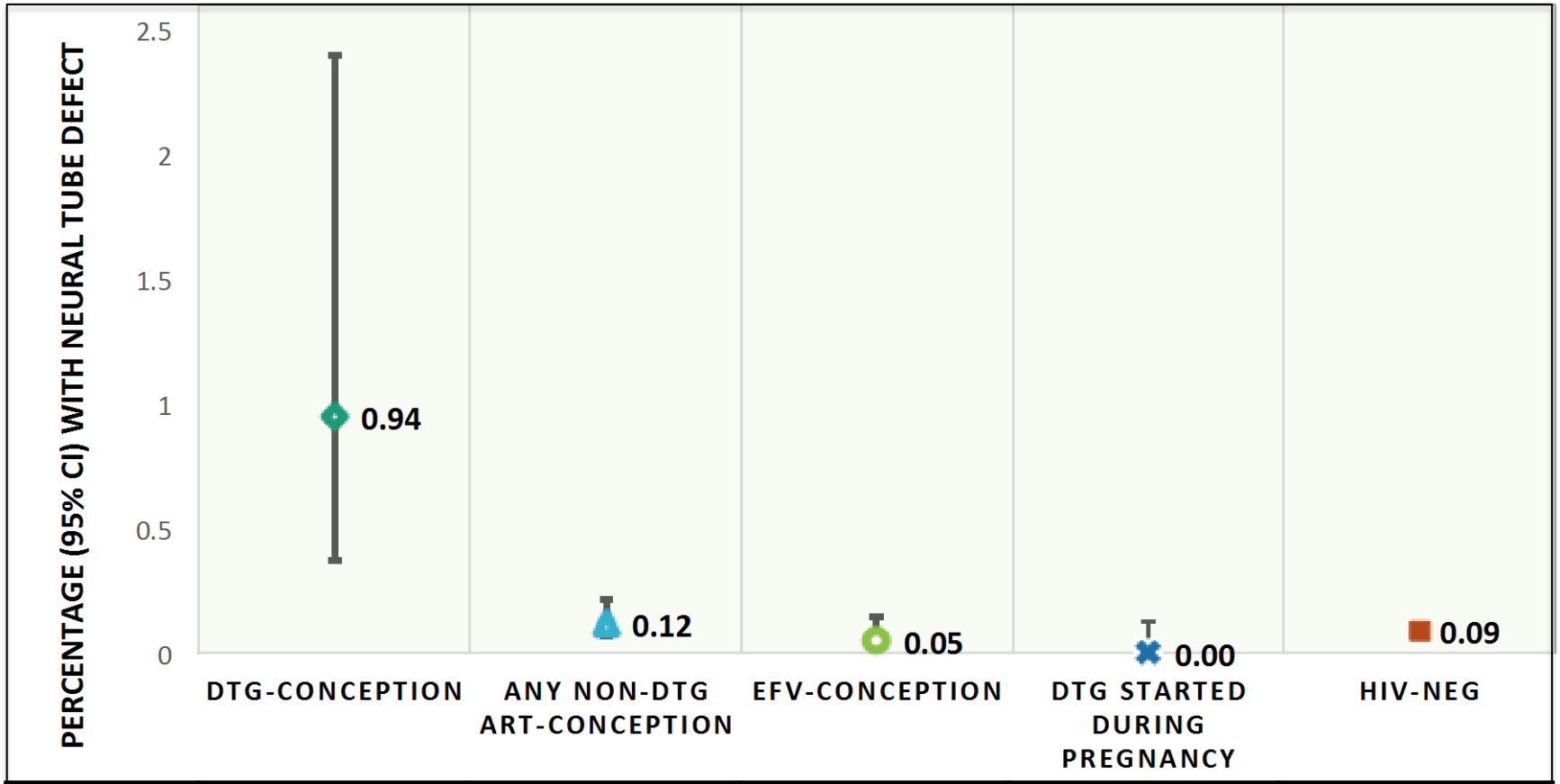
- In 2016, Botswana switched first line ART from TDF/FTC/EFV to TDF/FTC/dolutegravir (DTG) for all adults (including pregnant women)

Analysis Update

- Asked to provide any preliminary data available for May 2018 WHO HIV guidelines committee for outcomes among women ***who started DTG before pregnancy (pre-conception)***
  - Upon data review ID'd more neural tube defects than expected

- Then performed an unplanned analysis of NTDs comparing births to women on DTG-based ART started prior to conception to other exposure groups

NTD Prevalence Difference by Exposure



NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	**ref**	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Conclusion

- **Identified a concerning preliminary early signal for DTG and neural tube defects that requires further data to confirm or refute**
  - Based on only 4 cases (though 95% confidence intervals do not overlap with other exposure groups)
  - Absolute prevalence difference is small (~ 0.8%)
  - The 4 *different* defects among infants exposed to DTG at conception is unusual

Summary

- Compelling for continued pregnancy research
  - Societal needs + Dapivirine safety & efficacy
  - ARV choices & implications
  - Ethical justifications
- Stepwise backward approach fits current knowledge base
  - Periodic pause and evaluation key component
- MTN-042 ready to DELIVER
  - Landmark Study !

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