The Promise of HIV Prevention in Pregnancy

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Outline – Pregnancy/Lactation

- Brief background
- Where we were
- Where we are now
- Where we are going
- Where we will be

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Why Is This Necessary

- **Pregnancy high-risk**
  - HIV acquisition
  - OR = 15 for MTCT
    - Incident HIV in pregnancy
  - OR = 2.5 for *in utero* HIV transmission
    - "Recent Infection", Independent of Viral Load
  - HR = 2.5 for new HIV, when woman pregnant
    - Female to male transmission, Increased infectivity ?
    - **Incident HIV during lactation**
  - OR = 3-6X → MTCT

Gray R. Lancet 2005;366, Birkhead GS. Obstet Gynecol 2010;115
Taha T. AIDS 2011;25, Mugo N. AIDS 2011;25., Lockman S. JID 2009;200

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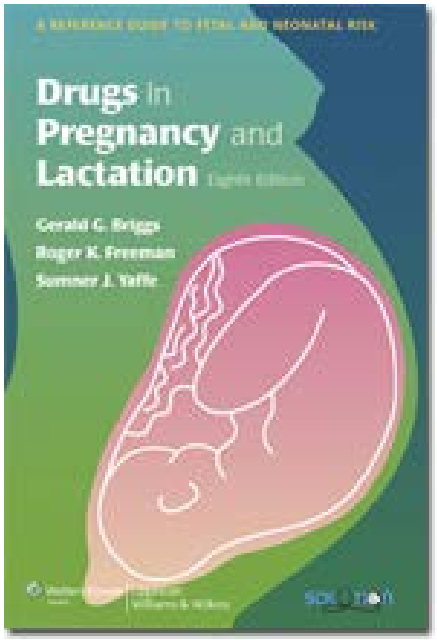
Background – Current Approach

- ≥ 99% of therapeutics **NEVER** studied during pregnancy (during R&D)
  - If done, late-stage & retrospective
    - Not controlled & variable participation → BIAS
  - Expose more pregnant women
- "Therapeutic orphans"
  - Pregnant women use therapeutics
    - Avg #: 2-5 meds used/pregnancy
  - Major Disconnect



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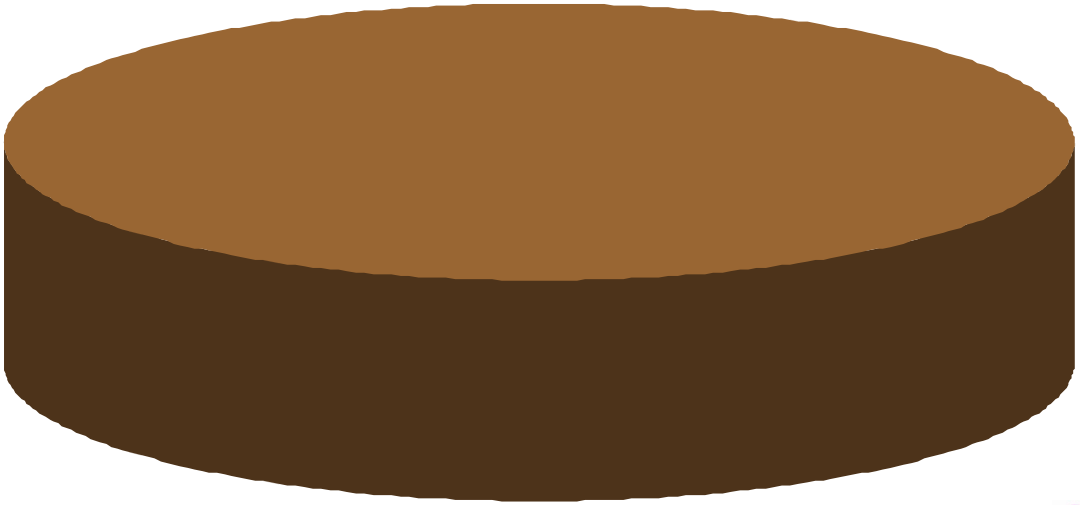
GOALS – MTN & PREGNANCY

- Proactively investigate HIV prevention agents during pregnancy
  - Delineate safety profile in real-time
  - Enable informed global use during pregnancy
  - Delineate a paradigm change for studying therapeutics in pregnancy
    - Challenge status quo
      - Does not serve pregnant women well globally

Tenofovir Gel
Pregnancy/Lactation Data 2006

DATA FREE ZONE



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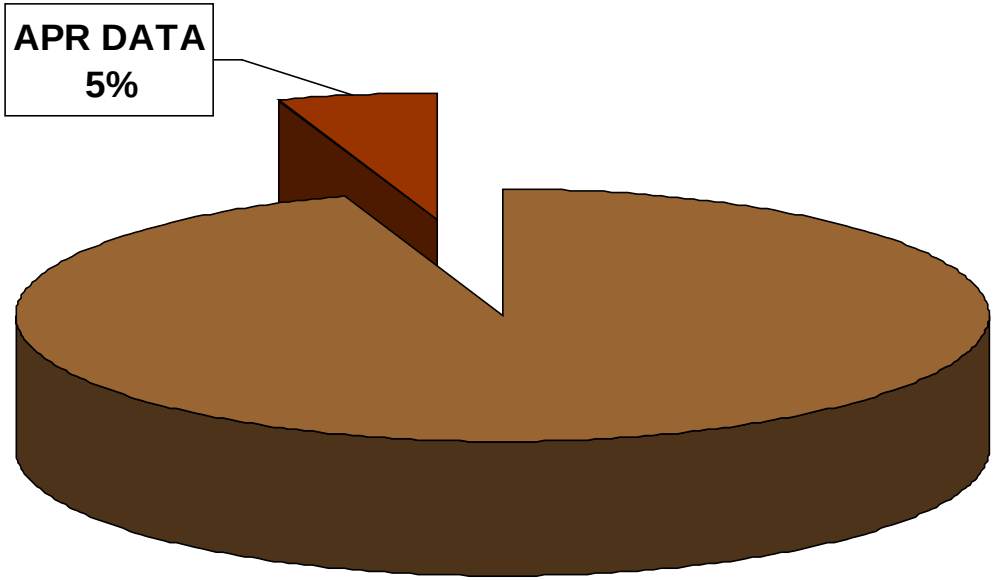
APR DATA - Tenofovir

APR-International Pregnancy Registry
for ARV's among HIV(+) women



Tenofovir = Pregnancy Category B

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MTN-002: Objectives

- **Primary:**
  - Assess term pregnancy maternal single-dose pharmacokinetics (PK) of Tenofovir (TFV) 1% vaginal gel
- **Secondary:**
  - Characterize the systemic safety profile
  - Compare 3rd trimester absorption of TFV gel to non-pregnant
  - Assess TFV: cord blood, amniotic fluid, endometrial tissue and placental tissue levels

Enrollment: August 2008 – January 2010

21 Women Enrolled

16 women received TFV gel (Target)

1 withdrawal prior to gel placement

4 delivered prior to gel placement

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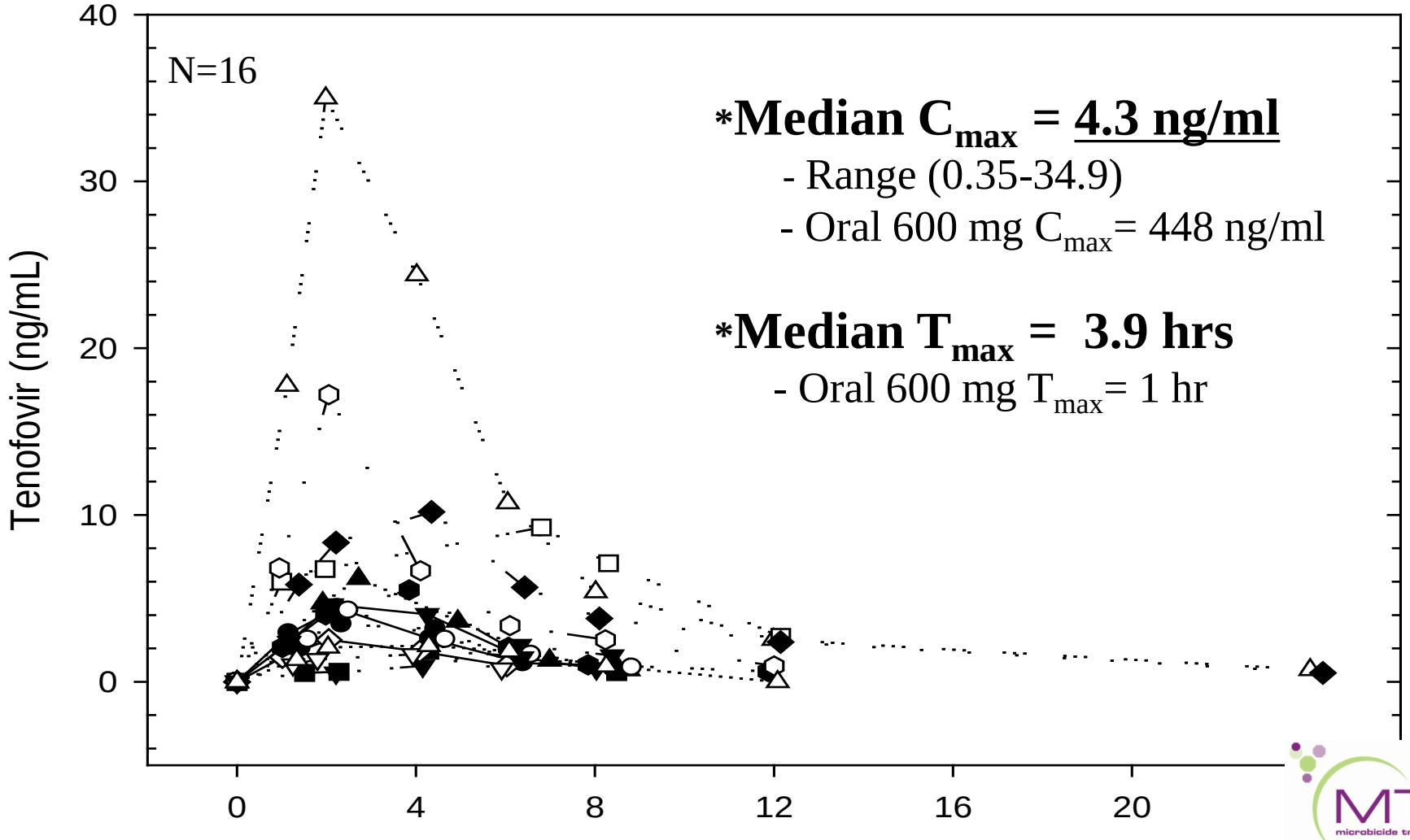
Results – Maternal TFV levels

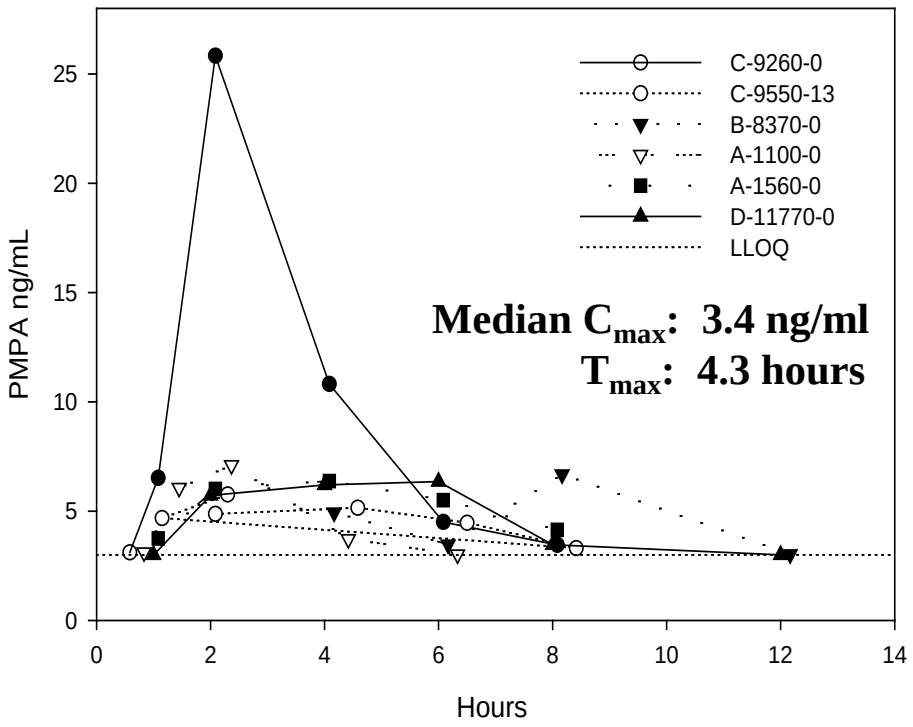


- **Median C_{max} = 4.3 ng/ml**
  - Range (0.35-34.9)
  - Oral 600 mg C_{max}= 448 ng/ml
- **Median T_{max} = 3.9 hrs**
  - Oral 600 mg T_{max}= 1 hr

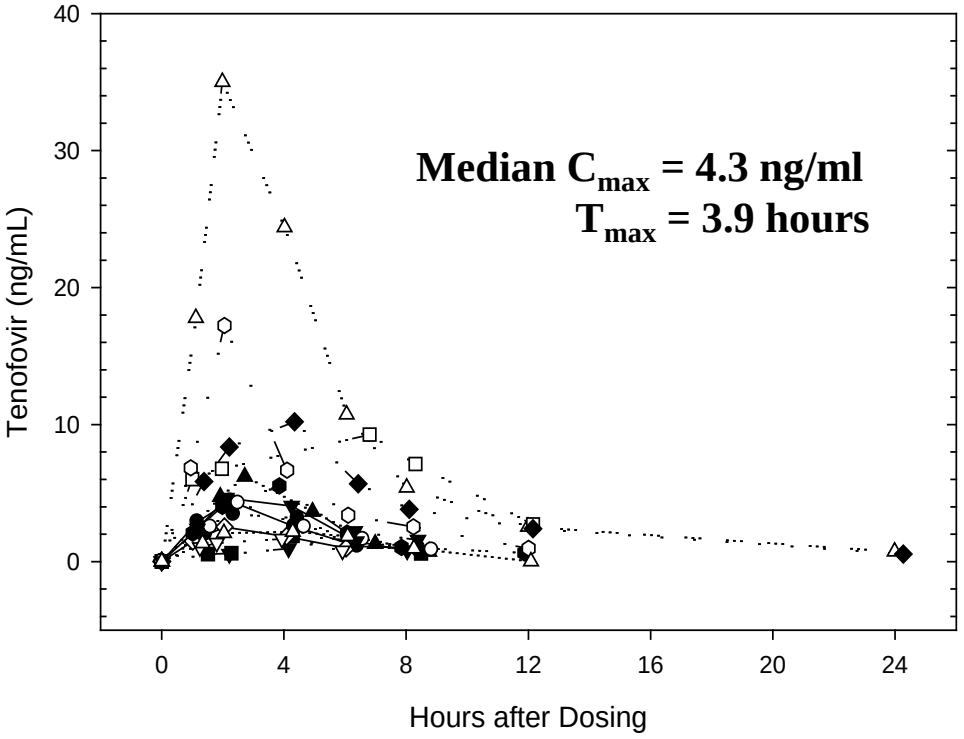
Beigi, et al. JID 2011;Epub

PK Comparison to Non-pregnant Women

*HPTN 050



MTN-002



****Similar absorption to non-pregnant women****

•Mayer. AIDS 2006;20.
•Beigi, et al. JID 2011;Epub

Summary

- **PK of single-dose TFV gel in term pregnancy:**
  - Similar to non-pregnant
  - Serum TFV 50-100X < standard oral dosing
- **TFV gets to fetal compartment**
  - Low overall cord levels (40X lower than oral dosing)
  - Similar Cord:Maternal ratio (.53) as oral dosing
  - No concentration in utero-placental tissues
- **Single dose TFV 1% Gel safe in term pregnancy**
  - **No concerning maternal or fetal AEs**
- **Findings + efficacy data justify more research**

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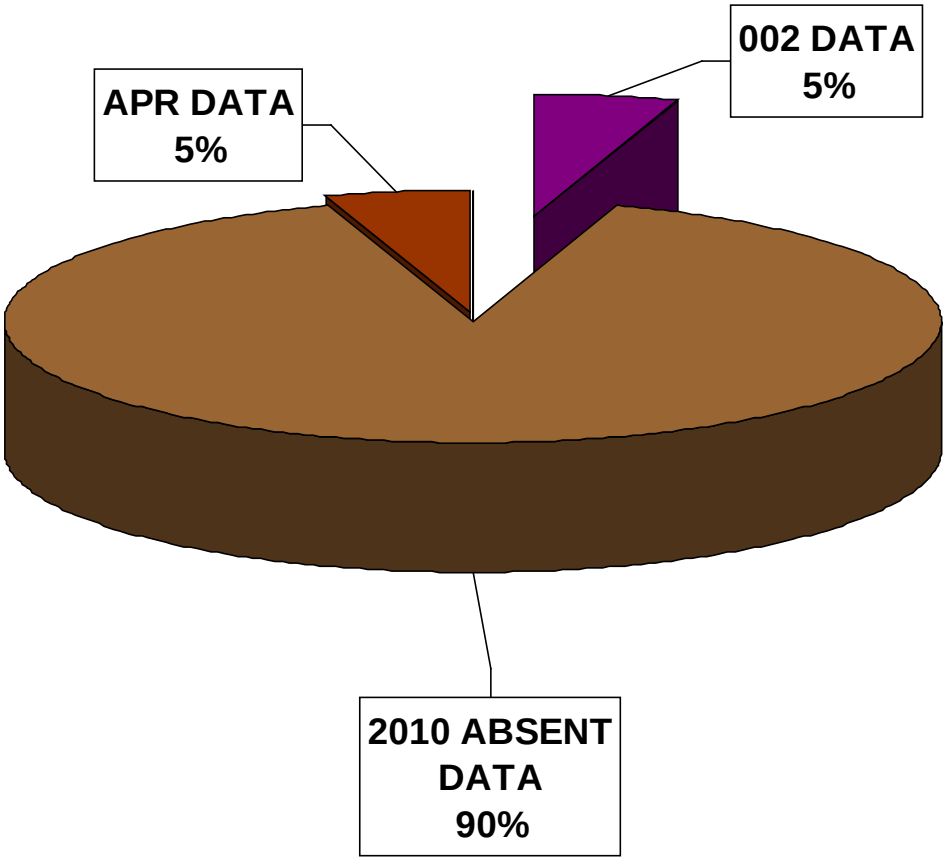
MTN-002: Minimal (Critical) DATA



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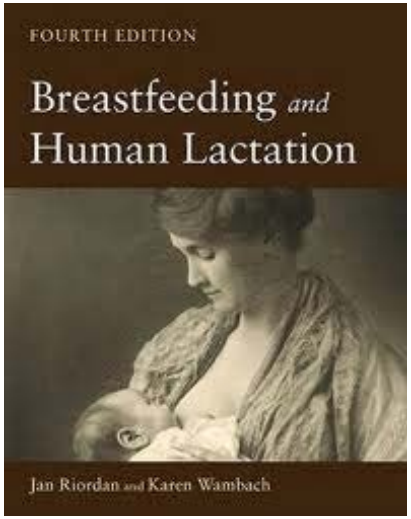
MTN-008

- **Expanded Safety Investigation of Tenofovir 1% Gel in Pregnancy and Lactation**



- **Primary Objectives:**
  - Safety & tolerability of TFV gel for 7 days
  - PK of TFV gel for 7 days
- **Secondary Objectives:**
  - Test for TFV in blood of infants
  - Impact of TFV gel on select organisms associated with neonatal sepsis → Pregnancy Cohort, (e.g., GBS, *E. coli*)
  - Adherence & acceptability TFV gel
- **Exploratory Objectives**
  - Measure vaginal flora and its changes with daily TFV gel use
  - Effects of TFV gel on vaginal and cervical biomarker expression

MTN-008 Study Population

- Pregnancy Cohort
  - Healthy, 3rd trimester gestation, HIV-uninfected, pregnant women, 18 – 40 years old, without evidence of maternal or fetal complications in the current pregnancy.
    - Group 1: 45 participants between 37 0/7 weeks and 39 1/7 weeks gestation (inclusive) on Study Day 0
    - Group 2: 45 participants between 34 0/7 and 36 6/7 weeks gestation (inclusive) on Study Day 0
  - RCT, placebo controlled, Blinded (HEC gel – Universal placebo)
    - 2:1 Active/Placebo → 30:15 TFV/HEC
    - Better control data for genital AE's, Lab AE's,
    - Pregnancy outcomes – combo of control group, MOMI and national data

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MTN-008 Study Population

- Lactation Cohort
  - Approximately 15 healthy women, 18 – 40 years old, currently exclusively breastfeeding an infant
  - Breastfeeding infants of women in the Lactation Cohort (4-26 weeks inclusive)
- **<u>Current Enrollment</u>**:
  - 20 Pregnant Women
  - 2 Lactating Women

} 20%

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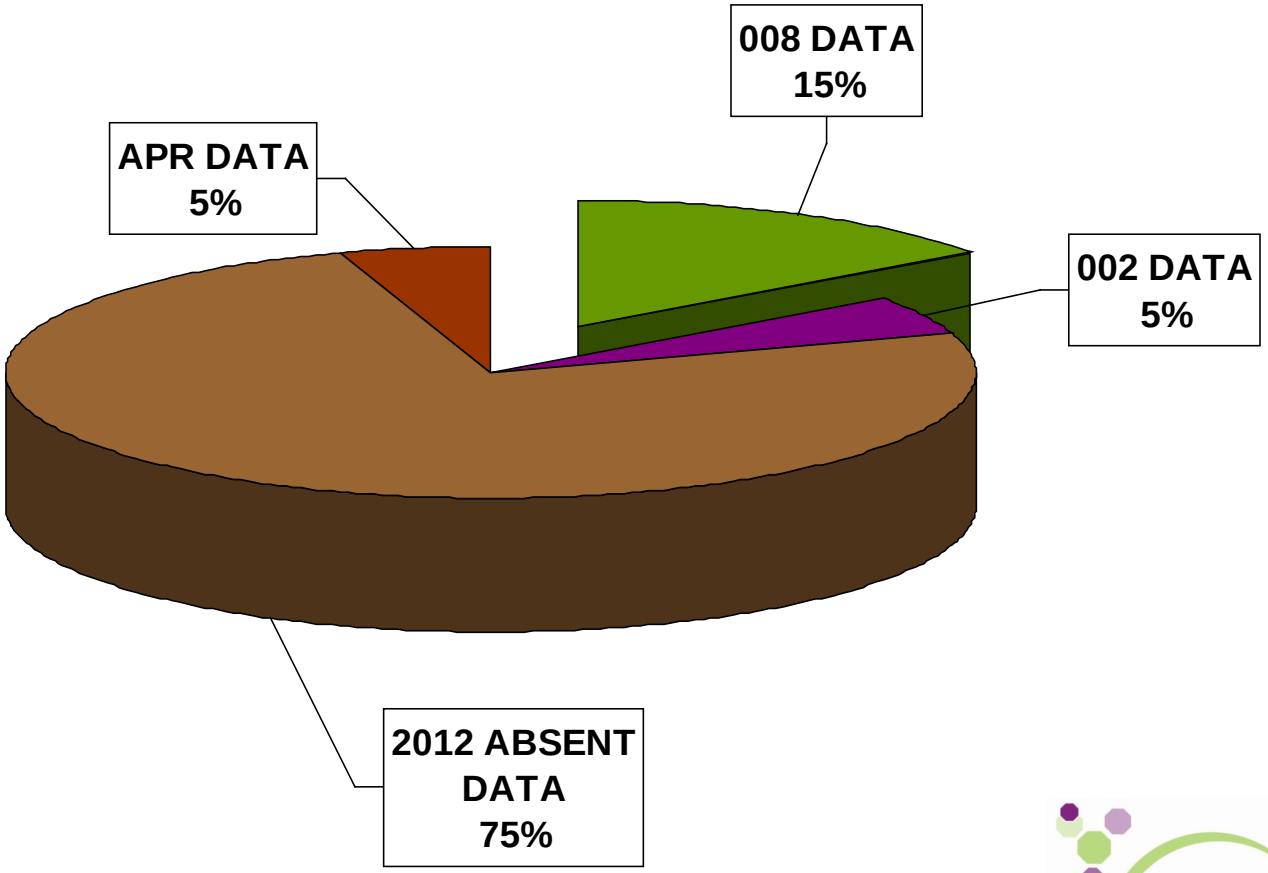
008 DATA



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MTN-016

MTN-016 – HIV Prevention Agent Pregnancy Exposure Registry (EMBRACE)

- **E**valuation of **M**aternal & **B**aby Outcome **R**egisty **A**fter **C**hemoprophylactic **E**xposure

- Prospective observational cohort:
  - Inadvertent exposures to microbicides and/or PrEP agents early pregnancy (**VOICE)**
  - Planned exposures late in gestations (MTN-002, MTN-008, etc.)
- Unique:
  - Real-time, built-in placebo arm, longer fu (1 yr),
  - Less bias

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MTN-016 OBJECTIVES

- **Primary Objectives:**
  - Pregnancy loss: mothers exposed/not exposed to an active study agent
  - Major malformations: infants exposed/not exposed to active study agent *in utero*

Secondary Objectives

- Adverse pregnancy outcomes
- Growth parameters in the first year of life among infants
- To provide a cohort of infants not exposed to active drug:
  - Represents background incidence of major malformations among babies born to women participating in HIV prevention trials

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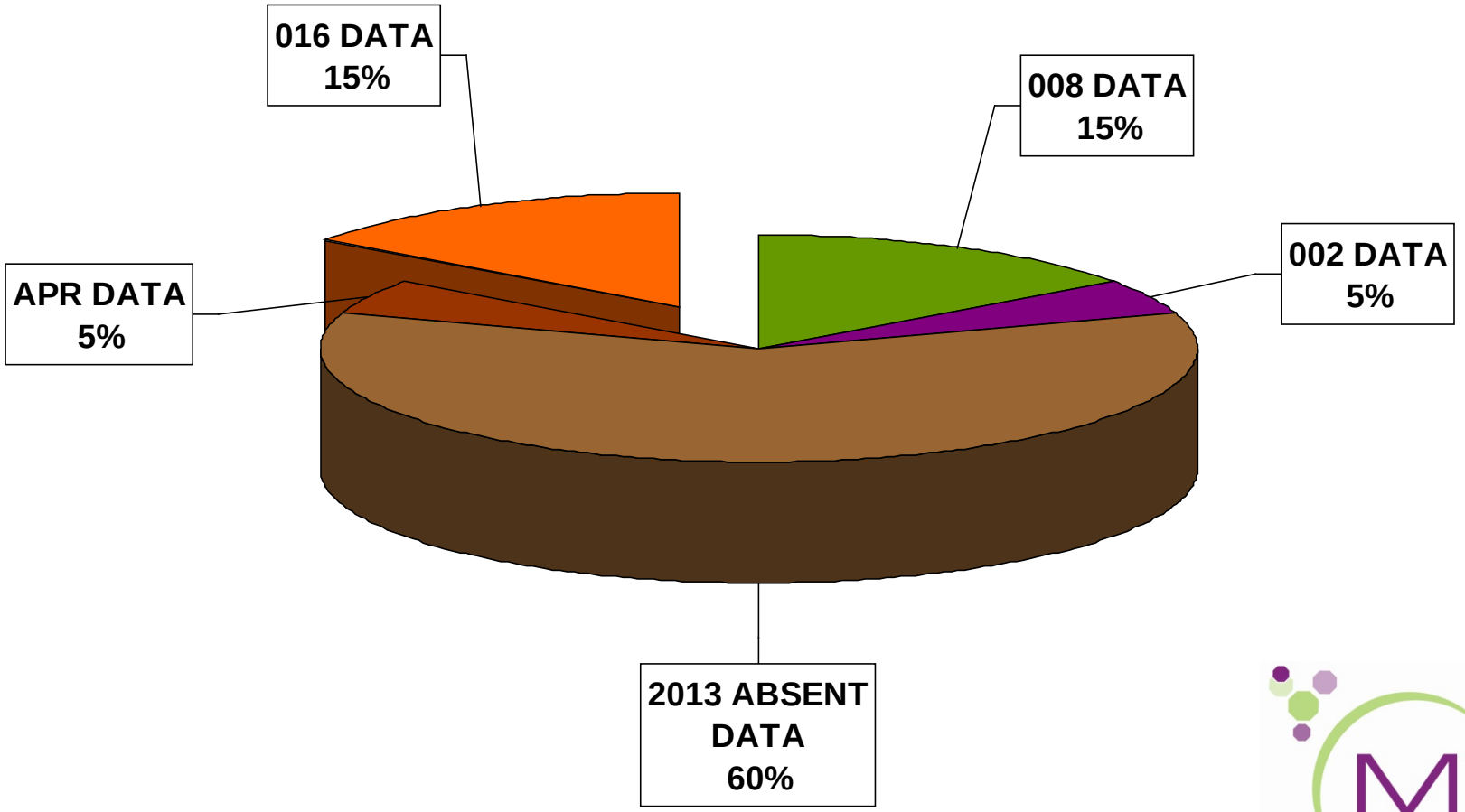
016 DATA



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Phase 2 Expanded Safety Study of Tenofovir Gel in Pregnancy

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MTN-019 Co-Chair/Site Investigator
University of Malawi College of Medicine
Blantyre, Malawi

Background / Rationale

- Pregnancy common within and outside of trials
  - Sexual activity during pregnancy
  - Unplanned sexual activity / pregnancy common
- Primary HIV in pregnancy
  - ⇧risk of *in utero* transmission
  - HIV seroconversion rates in pregnancy are high
- Primary HSV infection in pregnancy
- Oral tenofovir investigated for use in PMTCT
  - Antiretroviral Pregnancy Registry
- Potential licensure of 1% tenofovir gel

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Study Hypothesis

- 1% TFV gel used daily for up to 4 weeks during pregnancy will be safe and well-tolerated

Primary Objective

- To describe the safety profile of 1% tenofovir gel used daily per vagina for up to 28 days during different gestational age ranges during pregnancy

Primary Endpoints

- Maternal outcomes:
  - Grade 2 or higher AEs (lab, genital/pelvic, pregnancy)
  - Grade 3 or higher AEs not included above
  - Pregnancy outcomes
- Neonatal outcomes
  - All serious adverse events

Secondary Objectives

- **Pharmacokinetics.** To establish the peak blood concentration and the time course over the first 6 hours after a vaginal dose of tenofovir under steady-state vaginal dosing conditions during pregnancy
- **Adherence.** To assess the adherence to daily use per vagina of 1% tenofovir gel for 28 days among pregnant women

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Secondary Endpoints

- **Pharmacokinetics**
  - Maternal blood levels of tenofovir
- **Adherence**
  - Self-reported product use captured through questionnaires
  - Study drug levels
  - Count of returned unused applicators

Exploratory Objectives

- Changes in vaginal microenvironment
- Sexual activity, condom use and intravaginal practices
- Acceptability of study product use in pregnancy
- Pharmacokinetics

Exploratory Endpoints

- **Vaginal Microenvironment**
  - Gram stain, pH, vaginal microorganisms, biomarker expression in vaginal and cervical secretions
- **Behavior**
  - Self-report via questionnaire
- **Acceptability**
  - Self-report via questionnaire
- **Pharmacokinetics**
  - Tenofovir cord blood levels for infants of mothers who dosed <24 hours of arriving for delivery
- **Adherence**
  - # days study product used as reported electronically (at sites with capacity)

Study Design

- Multi-site, double-blinded, two-arm, randomized, placebo-controlled
- Daily vaginal use of 1% tenofovir gel vs. Universal HEC Placebo gel
- 2:1, active:placebo
- Approximately 30 months duration

Study Population

- Approximately 384 pregnant women
  - Blantyre, Harare/Chitungwiza, Kampala, Birmingham, Pittsburgh
- Onset of 28-day dosing period
  - Group 1: 36 0/7 weeks – 37 6/7 weeks (114 women)
  - Group 2: 28 0/7 weeks – 32 6/7 weeks (90 women)
  - Group 3: 20 0/7 weeks – 24 6/7 weeks (90 women)
  - Group 4: 12 0/7 weeks – 16 6/7 weeks (90 women)

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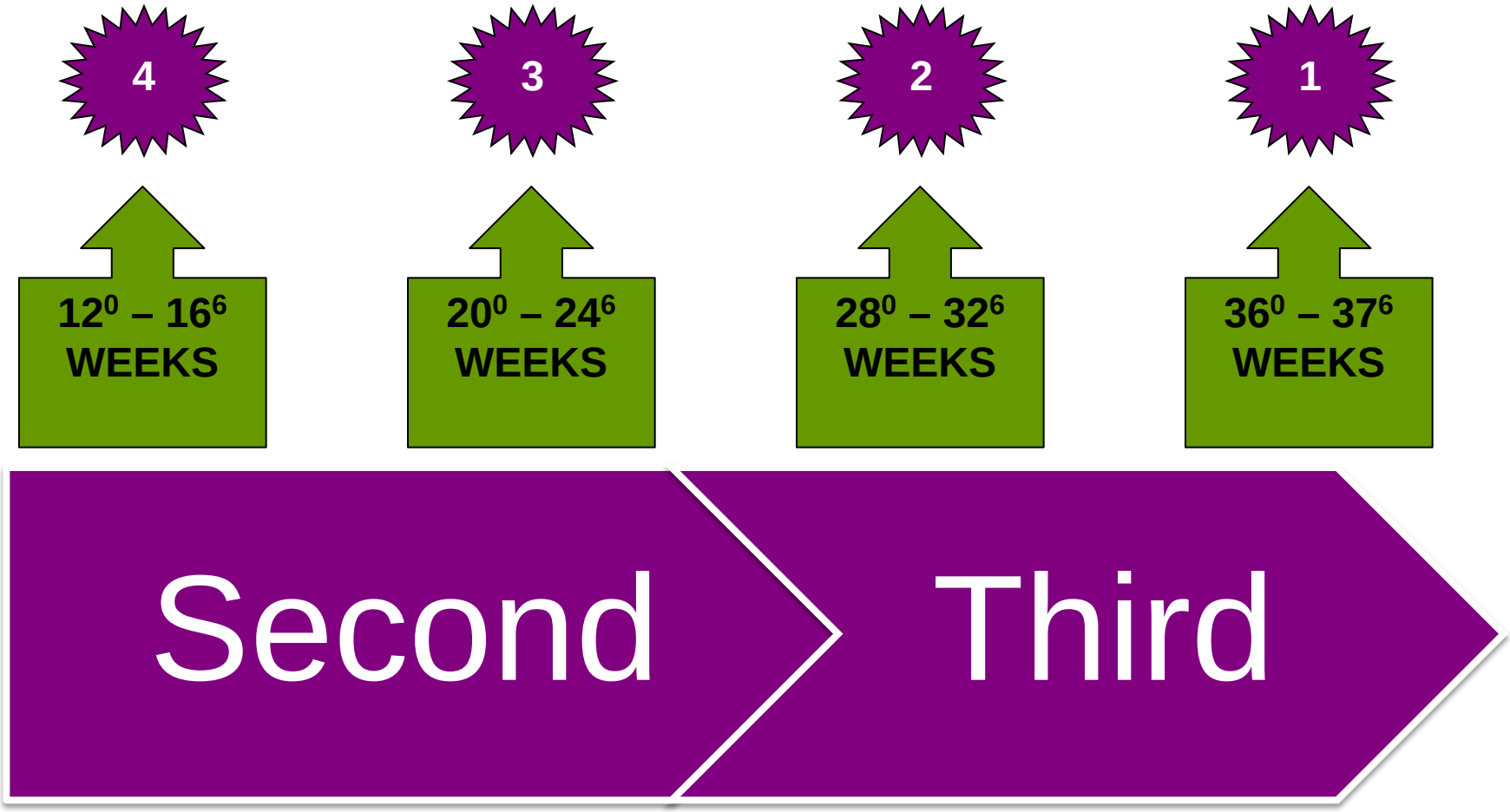
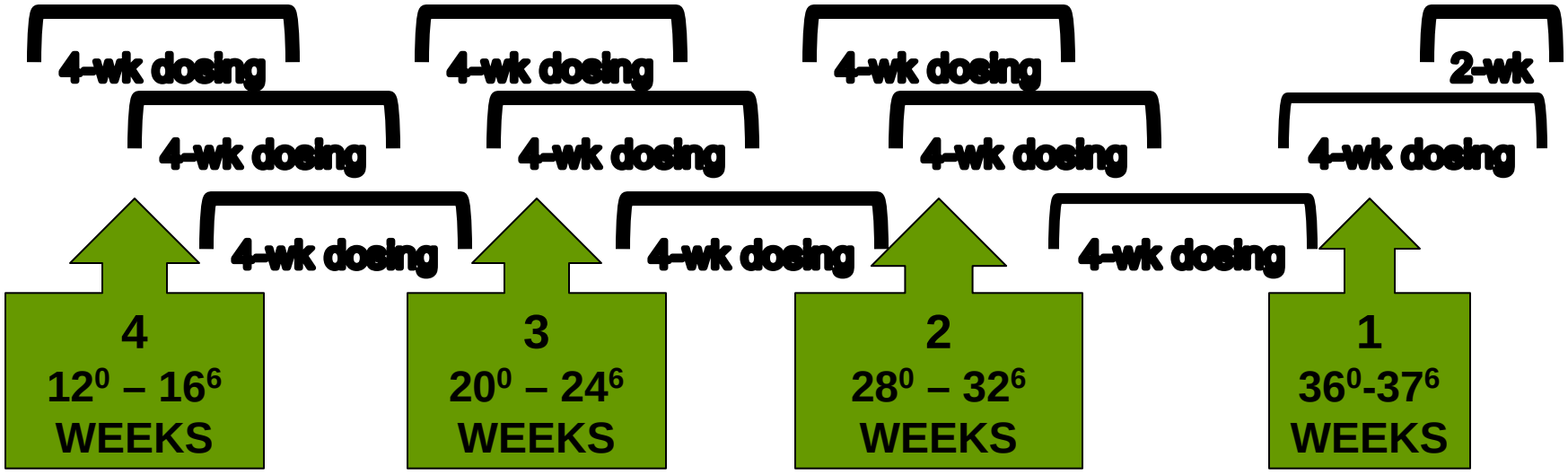
Why have “gaps” in groups?



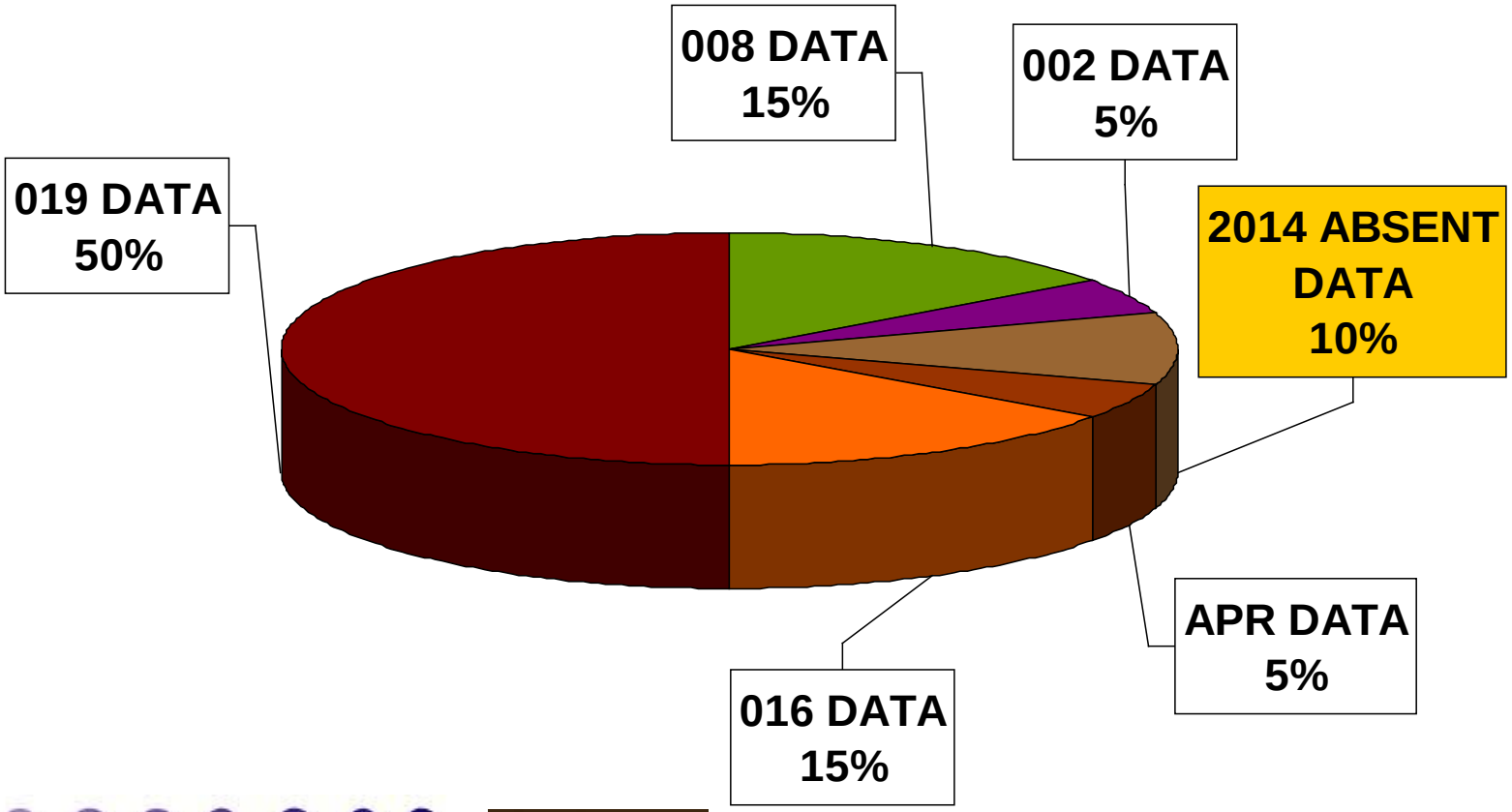
Not really gaps

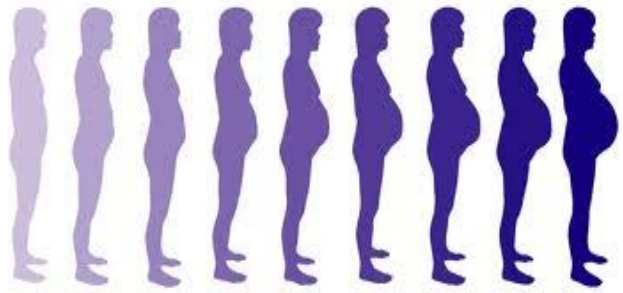


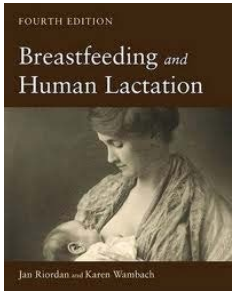
Second Third

TRIMESTERS

019 DATA







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CHOICE B
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