Update on the Pregnancy Agenda Research: MTN-008 and MTN-016

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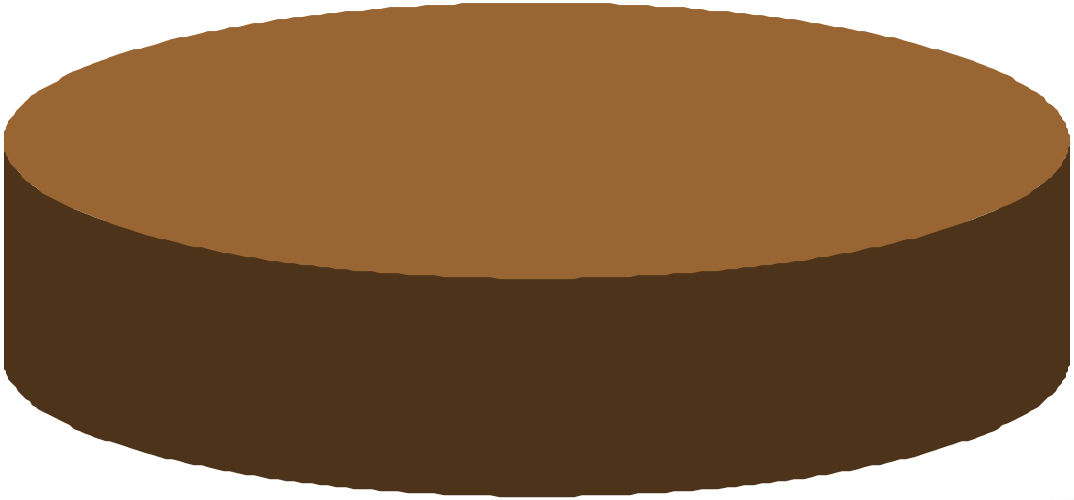
GOALS – MTN & PREGNANCY

- 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
  - MTN-002
  - MTN-008, MTN-016, (MTN-019)

Tenofovir Gel
Pregnancy/Lactation Data 2006

DATA FREE ZONE



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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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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**

JID 2011;204:1527-31

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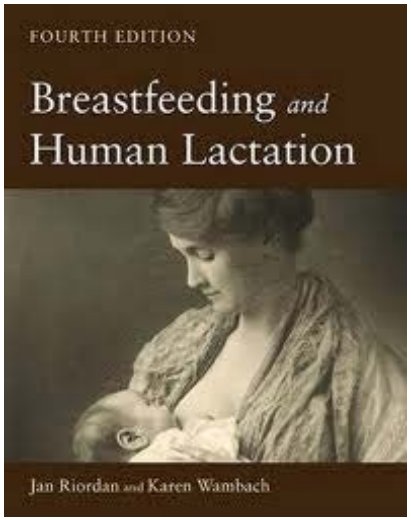
MTN-008

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



- **Primary Objectives:**
  - **Safety & tolerability** of TFV gel for 7 days
  - **PK** of TFV gel for 7 days
- **Secondary Objectives:**
  - Infant TFV
  - TFV gel impact on select organisms associated with neonatal sepsis → Pregnancy Cohort, (e.g., GBS, *E. coli*)
  - Adherence & acceptability TFV gel
- **Exploratory Objectives**
  - Measure vaginal flora changes with daily TFV gel
  - TFV gel effects 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 current evidence of maternal/fetal complications
  - RCT, placebo controlled, Blinded (HEC gel)
    - 2:1 Active/Placebo → 30:15 TFV/HEC

- **Group 1: 45 participants between 37 0/7 weeks and 39 1/7 weeks gestation (inclusive) on Study Day 0**
  - **Enrolled 52 women for 45 evaluable**
    - **Closed 3rd ¼ 2012**

- Group 2: 45 participants between 34 0/7 and 36 6/7 weeks gestation

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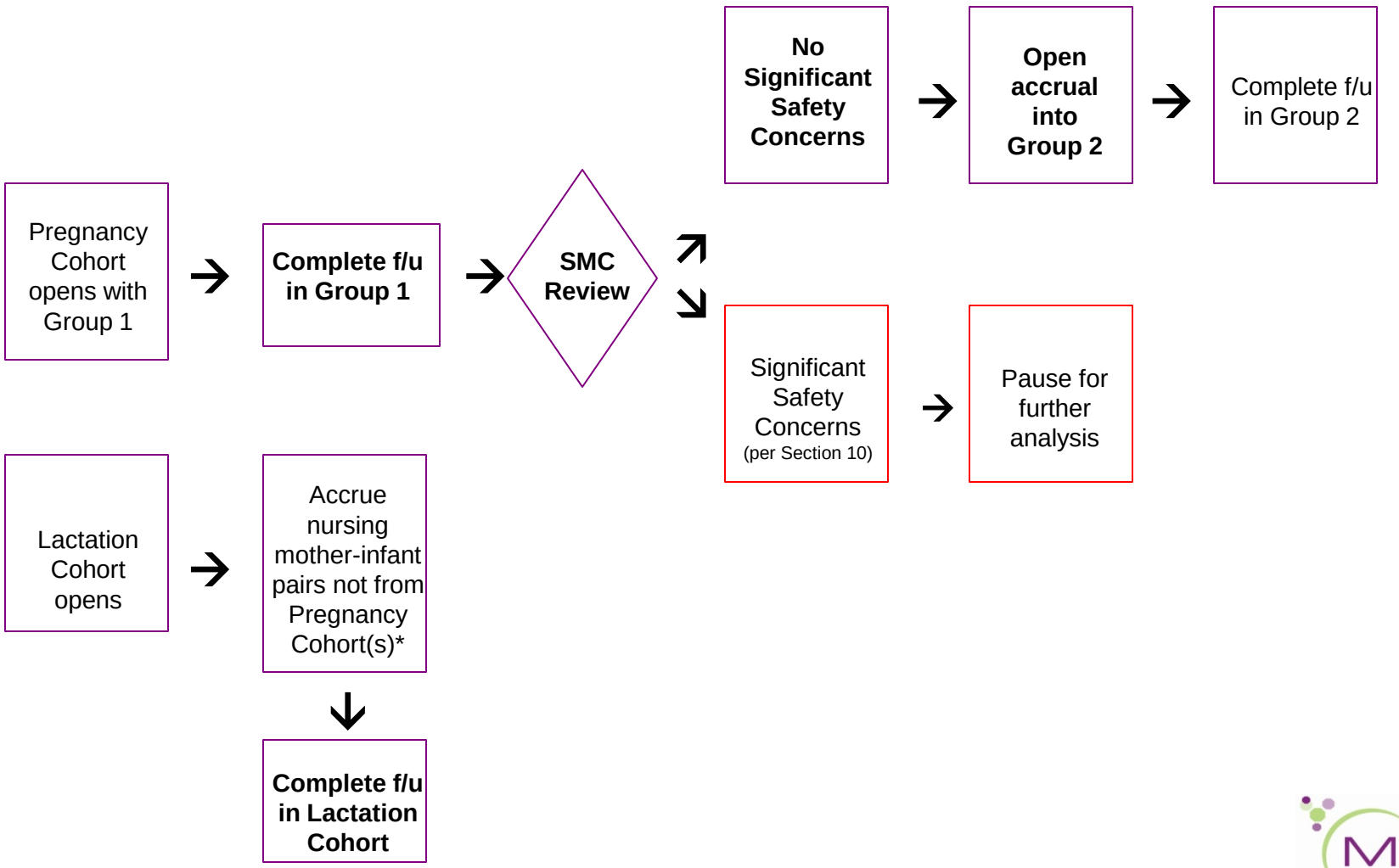
Pregnancy Cohort opens with Group 1
Complete f/u in Group 1
SMC Review
No Significant Safety Concerns
Open accrual into Group 2
Complete f/u in Group 2
Significant Safety Concerns
(per Section 10)
Pause for further analysis
Lactation Cohort opens
Accrue nursing mother-infant pairs not from Pregnancy Cohort(s)*
Complete f/u in Lactation Cohort

MTN-008 Interim SMC Review

- August 7, 2012
  - MTN-008 PSRT - no concerns on blinded review from cohort 1
  - ? Differences by study arm:
    - **PPH, PROM, Anemia**, Chorioamnionitis, Neonatal Sepsis, **VV irritative sxs**
      - Equal rates
    - Equal rates AE's
    - No grade 2 or higher lab abnormalities noted
    - No grade $\geq$ 3 AE's deemed related
  - No concern noted → Cohort 2

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MTN-008 Study Population

- Pregnancy Cohort
  - Healthy, 3rd trimester gestation, HIV-uninfected, pregnant women, 18 – 40 years old, without current evidence of maternal/fetal complications
  - RCT, placebo controlled, Blinded (HEC gel)
    - 2:1 Active/Placebo → 30:15 TFV/HEC

- **Group 2: 45 participants between 34 0/7 and 36 6/7 weeks gestation**
  - **Opened 3rd ¼ '12, project 3rd ¼ '13 closure**
    - **20 enrolled (approx ½ target)**

MTN-008 Study Population

- Lactation Cohort
  - Approximately 15 healthy women, 18 – 40 yrs, exclusively breastfeeding
  - Breastfeeding infants of women in the Lactation Cohort (4-26 weeks inclusive)
- **Closed enrollment 4th ¼ 2012**
  - Target met/exceeded (n=16)
  - Analysis planned soon

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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 + ASPIRE)**
  - 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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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

Objectives & Status

- **Exploratory Objectives**
  - Monitor for select risks of prevention agents
  - Prevalence & persistence of HIV drug resistance mutations in HIV-infected infants
  - Compare infant developmental milestones 1st year
- Status:
  - 292 Mothers
    - 214 (VOICE), 16 (002), 62 (008)
  - 258 Infants
    - 184 (VOICE), 16 (002), 58 (008)
  - Transitioning to ASPIRE
  - Analysis planning
    - Different nature/timing of exposures

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GOALS – MTN & PREGNANCY

- Proactively investigate HIV prevention agents during pregnancy
  - Delineate **Safety Profile** in real-time - **WIP**
  - Enable **Informed Use** during pregnancy - **WIP**
  - Delineate a **Paradigm Change** for studying therapeutics in pregnancy/lactation
    - Does not serve pregnant women well globally

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Paradigm Change

- Group effort: NIAID, NICHD, OAR
- Definite signs of progress
  - FDA engaged
  - NIH/NIAID/DMID:
    - 2011/'12 meeting series:
      - "Research of vaccines and antimicrobials in pregnancy"
        - Multidisciplinary input: FDA, NIH, Industry, Academia
        - Delineated paradigm and reccs for conduct of vaccine/antimicrobial trials in pregnancy

          - MTN expertise/experience pertinent and key input
        - Flu, Pertussis, GBS, ? RSV, ? CMV
- Progress is happening!

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