



MTN Research & International Considerations: Foundation For MTN-042

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Introduction

- Thinking behind pregnancy research
 - High HIV acquisition risk during pregnancy
 - High MTCT risk with incident HIV in pregnancy
 - Ethical justifications
 - Logistical justifications
 - Trials, every-day use, etc.
 - **Inadvertent 1st tri pregnancy exposures**



MTN Approach

Thoughtful, cautious yet bold approach

- TFV 1% vaginal gel 1st:
 - Reassuring safety data from antiretroviral pregnancy registry (oral use)
 - Pregnancy Category B (new system)
 - Track record of safety in non-pregnant women
- How to balance population & scientific needs, ethics, standard approach (inertia), reality ??



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

Next Steps ??

NIH Consultative Conference – 2010 (flu)

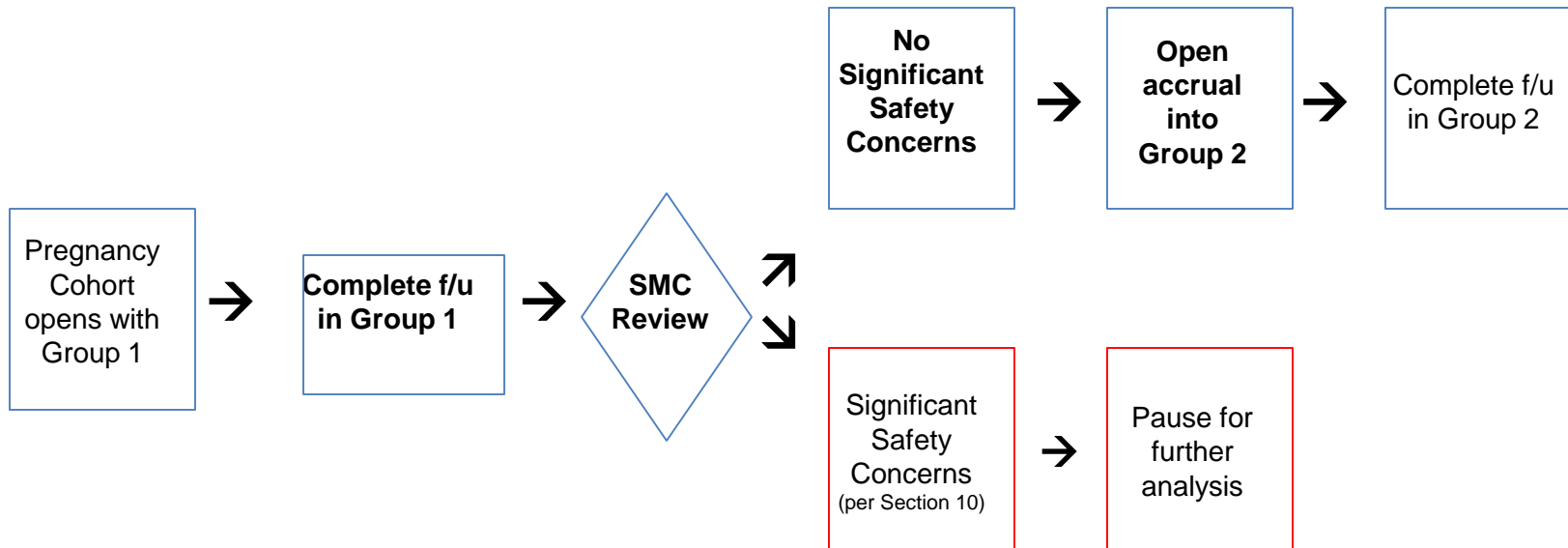
“Next Steps for Testing Microbicides & PrEP in Pregnancy”

- 50+ experts (NIH and Academics)
- Deliberated specifics:
 - Gestational age, oral vs. topical, Regs, Ethics, previous work, etc.
- Delineated paradigm - pregnancy research
 - Review of baseline available safety data
 - Progressive stepwise, backward approach

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

Important: Interim Safety Review



Final Results MTN-008

- PK:
 - Similar non-pregnant women
 - Low overall levels, no accum in mom/babies
- Safety:
 - No signals, equal AE's b/w arms/cohorts
 - Majority AE's related to pregnancy itself
- Tolerability
 - Well tolerated
- Justified Cont'd Research

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)

MTN-016

HIV Prevention Agent Pregnancy Exposure Registry (EMBRACE)

- Evaluation of Maternal & Baby Outcome Registry After Chemoprophylactic Exposure
- Prospective observational cohort:
 - Inadvertent exposures to microbicides and/or PrEP agents early pregnancy (**VOICE + ASPIRE + HOPE**)
 - Planned exposures during gestation (002, 008, **042**, etc.)
- Unique:
 - Real-time, built-in placebo arm, longer f/u (1 yr)
 - Less bias than traditional pregnancy registry
- Recruitment to date:
 - 421 women (87%)
 - 381 infants (95%)

MTN-016 Design

- Enroll mothers during pregnancy/ infants @ birth
 - Monitors For:
 - Adverse pregnancy outcomes
 - Growth of infant 1st year of life
 - Major Malformations
 - Follow newborns:
 - 4 visits: ≤ 10 dol, 3 mos, 6 mos, 12 mos (Growth)
 - Congenital anomalies
 - Site staff evaluation, if questions:
 - Pics taken - uploaded to central site
 - Protocol genetics expert adjudication



Paradigm Change

- NIH/GATES/CDC/WHO, etc.
- Additional areas of investigation
 - Maternal Immunization
 - NVAC, ACCV, ACIP, ACOG, Industry, etc.
 - 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
 - Flu, Pertussis, GBS, RSV, ZIKA, ? CMV, etc.



NVAC



30 Years Advising the National Vaccine Program

- Domestic vaccine policy
- 2012-2016
 - MIWG – 2 phases
 - 1st: Minimize barriers to Maternal Imm uptake
 - 2nd: Strategies to optimize maternal vaccine development
 - Key recommendation domains (→ 21st Century Cures Act)
 - Ethics & Regs- OHRP, IRB's, etc.
 - » Promote Inclusion & “Scientifically Complex”, not “Vulnerable”
 - VICP inclusions (offers protections to do research in pregnancy)
 - Pre-clinical & early clinical support (std. definitions)
 - Pharmacovigilance support & expansion



Maternal Immunization LMIC's

- Brighton Collaboration 2000 - Standardize
 - **GAIA** – Brighton + BMGF (2015-16)
 - Standardize terminology for Mat Imm LMIC's
 - Obstetric & Neonatal
 - **OB:** HTN, Mat death, NR fetal status, PTB, PPH)
 - **Neonatal:** Cong anomns, neonatal death & infection, PTB, stillbirth
 - More entities/terminology being developed

- Kochhar S. Vaccine 2017;35

- <http://gaia-consortium.net/international-consensus-conference-2016/>

- <http://gaia-consortium.net/>



Summary

- Progressive, backwards model for recruitment of pregnant women feasible
- Provides:
 - Reassurances in real-time during study – safety pull cord
 - Inward/outward validity of focus on safety
 - Innovative approach - challenging area
 - Nice fit for Dapivirine ring/042
- Maternal Immunization LMIC Standardization Template – Brighthon/GAIA
- 042 → Opportunity to bring 2 together

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