

# Pregnancy in HIV Prevention Research: The MTN Approach

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# Why Need to Consider Pregnancy?

- Major challenge to the performance and interpretation of HIV Prevention trials
  - 2008 IOM Report – “Major Methodological Challenge to HIV Prevention Research”
  - Safety, Statistical Design, Analysis, etc.
- HIV Prevention (Microbicide/PrEP) trials require ongoing sexual activity among participants:
  - Pregnancy natural consequence
    - 85%/yr – non-contraceptive users
    - 0.5-15%/yr – Typical users of all different methods
    - Preg rate: 16-64/100 woman-years – ongoing

Darroch. Fam Planning Perspect 1999;31.

Trussel Contraception 2004;70.

Ranjit. Fam Planning Perspect 2001;33. Raymond. STD's 2007;34

Lagakos. National Academies Press,2008.



# Requirements for Microbicide Use in Pregnancy

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- Segment I, II, III studies done
  - Designed to determine drugs ability to interfere with reproductive health, fetal development and early development
    - Seg I: General fertility and reproductive performance
    - Seg II: Teratology
    - Seg III: Perinatal and Postnatal development
- Genotoxicity studies
- General toxicology
- Carcinogenicity studies

# Challenges with Pregnancy Considerations: Safety



- Safety #1
  - FDA categories not always satisfactory (A,B,C,D,X)
  - Little/no human data
    - Sometimes oral human data (TFV, 3TC)
      - ? Analogous to human levels
    - ? Absorption in pregnant genital tissues
    - Direct absorption through cervical canal to uterus
      - Uterine 1<sup>st</sup> pass affect

# Challenges with Pregnancy

## Considerations: Safety – cont'd

- Conventional approach for studying therapeutics in pregnancy: Avoid exposure if unsure safety profile....Catch 22
  - Preclude pregnant women from participation – very little data
  - Remove from trial asap with + preg test
    - Still have exposures based on frequency of testing
    - 1<sup>st</sup> trimester critical time period for organogenesis (2-8 wks)
    - ? Will encourage induced abortion by participants to get back on trial

# Challenges with Pregnancy

## Considerations: Safety – cont'd

- FDA recommends effective contraception be used if safety not established
- Alternative approach:
  - With sufficient pre-clinical data without red flags...trial participants make their own choice to participate
    - Reasonable if all pre-clinical data suggest safety
    - Ethical foundation: autonomy
    - Provides invaluable information – widespread use after licensure during pregnancy
    - Requires up front discussion and consensus on what data deemed “safe” to proceed

# Challenges with Pregnancy Considerations: Early Pregnancy

- Chemical pregnancy
  - Detectable urine hCG + no symptoms of pregnancy – never transition into sustained gestation
    - Approximately 1/3 pregnancies end before out of 1<sup>st</sup> trimester (SAB's, EAB's, etc.)
  - Detection inevitable given sensitivity of modern hCG assays
  - How to handle...may disrupt planning, stats, enrollment, etc. of microbicide/PrEP trials



# Challenges with Pregnancy

## Considerations: Statistical

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- Statistical considerations:
  - Pregnant participants overall use less study product...but remain in the analysis
    - Decrease powered expected effectiveness
    - Enroll more women
  - Potential problem:
    - 2 study groups have different pregnancy rates
    - ? Differential susceptibility to HIV in pregnancy
      - Could alter HIV incidence either way and change data from reality
      - Hard to manage/control for



# Challenges with Pregnancy Considerations: Contraception

- Optimal way to prevent pregnancy safety concerns
  - IUD's, Injections, TL >>> OC's, rings, patches
- Problems:
  - Not always accessible in certain locations
  - If provide for trial...hard to abruptly stop provision
    - Some locations logistically difficult
  - Side effects → ? Decrease enrollment
  - ? Alter vaginal environment and change susceptibility to HIV

# Challenges with Pregnancy: Ethical Paradigms

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- 1<sup>st</sup> Do no harm
  - If unsure....exclude pregnant women
  - Catch 22...when and how to be no longer unsure?
- Autonomy
  - Allow pt to decide
- Ethically inappropriate to exclude pregnant women
  - Small controlled study vs. study while new on market: larger overall exposure
- If pregnant women exposed:
  - Obligation to follow and refer

# Various Approaches

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- Depends on location, size of study, endpoint of study, resources, etc.
  - Exclude pregnant women
  - Exclude women who want to conceive
  - Predictive models → ? validity
  - Exclude recently pregnant women
  - Mandate effective contraception for study participants
  - Regular uHCG testing (q month) vs. await clinical s/s pregnancy
  - Direct small-scale controlled study
  - Passive epidemiological surveillance of pregnancy exposures

# Rationale for Directed Investigation

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- Microbicides developed to:
  - Prevent HIV/STI transmission
  - Intended for sexually-active women
  - Planned widespread availability - OTC
- Pregnancy common among:
  - Young sexually-active women
  - Cohort matches eventual users
- Sexual activity common in pregnancy/early PP – multiple partners not unusual
  - Solberg. NEJM 1973:288
  - Klebanoff. Lancet 1984
  - Read. AJOG 1993;168
  - Rowland. Can Fam Phys 2005;51

# Rationale – cont'd

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- Pregnancy high-risk condition: HIV acquisition
  - Gray. Lancet 2005;366
- Pregnant women:
  - Rx and OTC medications used frequently
    - Andrade. AJOG 2004;191
    - Werler. AJOG 2005;193
- Practical:
  - If microbicides/prevention agents available
    - Pregnant women will use
    - (?)... Need for pregnancy test to use them
- Role for use in HIV(+) gravidas to decrease Maternal-Child perinatal HIV transmission

# Pregnancy-specific Physiological Alterations

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- Blood volume expansion – 40-50%
- Fetal compartment for drug deposition
  - Above combined give large  $V_d$
- Decreased plasma protein [ ]– alterations in drug binding
- Increased GFR/RPF  $\geq 50\%$
- Vaginal Hyperemia - ? Affect on local drug absorption

# MTN Approach

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- **MTN: Proactively test microbicides and other prevention tools in pregnancy**
  
- MTN-002:
  - Phase I, open label, Pharmacokinetic, Placental transfer and safety evaluation – Single Site (MWH)\
  - Enroll 16 term Gravidas
  
- MTN-016 – HIV Prevention Agent Pregnancy Exposure Registry
  - Protocol development in progress

# MTN-002: Goal/Specific Aims

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## □ **Primary:**

- Assess term pregnancy maternal single-dose PK of Tenofovir/PMPA gel

## □ **Secondary:**

- Assess amniotic fluid, cord blood, endometrial tissue and placental tissue levels following single-dose tenofovir 1% vaginal gel
- Characterize the systemic safety profile of single-dose tenofovir 1% vaginal gel in term gravidas
- Compare 3rd trimester absorption of tenofovir 1% vaginal gel to absorption in non-pregnant recent historic controls



# MTN-002 Protocol

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## □ Regimen:

- Screening visit  $\leq$  4 weeks prior to scheduled CS
  - Demographic data, confirm eligibility criteria, undergo informed consent
  - Targeted pelvic: Trich Cx, GC/CT SDA
  - Blood:
    - Serum creatinine
    - AST and ALT
    - Rapid HIV test with pre- and post-test counseling
    - \*Confirmatory Testing for HIV, \*HBsAg, \*RPR, \*Confirmatory Testing for Syphilis
      - \* Prn and/or not in prenatal records
- Single-dose Tenofovir (TFV) gel (40 mg)
  - Placed vaginally in CS Pre-operative holding area

# MTN-002 Protocol - cont'd

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- Maternal PK
  - Baseline, 1 hour, 2, 4, 6, 8, 12, and 24 hour
  - @ 24 hour follow-up/PK specimen:
    - record review/collect ?side effects, plan 2 week phone call
  - Maternal endometrial biopsy:
    - Evaluate uterine first pass effect
- Fetal TFV concentration assessment at time of CS
  - Amniotic Fluid
  - Cord Blood
  - Placental biopsy
- 2 week phone call
  - Query adverse events

# MTN-002 Protocol - cont'd

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- Major Endpoints:
  - Maternal 3rd trimester pharmacokinetic measures (AUC, C<sub>max</sub>,)
  - Placental transfer:
    - cord blood tenofovir levels, placental tissue tenofovir levels, amniotic fluid tenofovir levels
  - Endometrial tenofovir levels
  - Other Analysis:
    - Compare 3<sup>rd</sup> trimester single-dose absorption to non-pregnant absorption TFV gel PK (Mayer et al. AIDS 2006;20)

# MTN-016

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## □ **Pregnancy Exposure Registry**

- Prospective observational cohort:
  - inadvertent exposures to microbicides and/or PrEP agents early pregnancy
  - Planned exposures late in gestations (MTN-002 etc.)

### ■ **In protocol development phase**

#### **Primary Objectives:**

- Evaluate the safety and teratogenic risks of exposure in pregnancy to: Microbicides, oral PrEP, other HIV prevention measures.
- To evaluate the prevalence of structural abnormalities identified in fetuses or infants (in the first year of life) of mothers exposed to an active study agent during pregnancy as compared to those of mothers not exposed to an active study agent during pregnancy.

# MTN-016 – cont'd

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## Secondary Objectives

- Monitor for select risks of prevention agents identified during pre-clinical reproductive toxicology studies by trimester(s) of exposures
- Monitor for select laboratory, clinical, and developmental abnormalities in the first year of life among infants born to study participants
- Provide margins of reassurance for lack of risk from prevention agent exposures in pregnancy.

# MTN Future Directions

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- Pending favorable PK/safety data in 002
  - Phase I-II, Placebo-controlled, multi-dose PK, tolerability, safety study of candidate microbicide
  - Step-wise approach to moving earlier in pregnancy
    - 36-38 weeks
    - 34-36 weeks,
    - 32-34 weeks, etc.
- Ongoing: MTN-016 until goal reached

# Summary

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- Pregnancy poses unique and unavoidable challenges in the design & conduct of HIV prevention trials
- The MTN has taken a combination approach to achieve robust safety, PK and efficacy data that will eventually support use of prevention agents in pregnancy
  - HIV prevention for maternal & neonatal benefit
- Implications of proposed research for the study of prevention drugs in pregnancy is far-reaching → beyond HIV prevention

# Acknowledgements

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- MTN is funded by NIAID (5U01AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health