MTN Protocol 002 Proposal:

Maternal Pharmacokinetics and Placental Perfusion of Tenofovir/PMPA Gel

Richard H. Beigi, MD, MSc.

Assistant Professor

Division of Reproductive Infectious Diseases,

Department of OB/GYN/RS

Magee-Womens Hospital of UPMC

Rationale

- 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

MTN microbicide trials network

Rationale - cont'd

- 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 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

MTN microbicide trials network

Goal/Specific Aims

- **MTN: Proactively assess formulations in pregnancy**

1. Assess term pregnancy maternal single-dose PK of Tenofovir/PMPA gel
   - ? Altered/increased absorption in late pregnancy
   - Compare to non-pregnant recent historic controls
2. Assess placental transport (fetal exposure) of single-dose Tenofovir/PMPA gel

Proposal

- Phase I, open label, Pharmacokinetic and safety evaluation
- 10 Healthy term HIV (-) (≥ 37 gestational weeks) parturients
  - Scheduled elective cesarean sections
  - No suggestion of placental disease
    - No IUGR, DM, HTN, CTD, etc.
- Single-site – MWH in PGH

Proposal Cont'd

- Regimen:
  - Single-dose Tenofovir (TFV) gel (40 mg)
  - Placed vaginally in CS Pre-operative holding area
  - Maternal PK
    - Baseline, 1 hour, 2 hour, 4 hour, 8 hour, 12 hour, and 24 hour
  - Fetal TFV concentration assessment at time of CS
    - Amniotic Fluid
    - Cord Blood

Proposal cont'd

- Endpoints:
  - Detectable maternal plasma TFV
    - HPLC assay
  - Detectable fetal cord blood &/or Amniotic Fluid TFV levels
    - HPLC assay
- Other Analysis:
  - Compare 3rd trimester single-dose absorption to non-pregnant absorption
    - Recent TFV gel PK (Mayer et al. AIDS 2006;20)

Future Directions

- Pending favorable PK/safety data in initial pregnant Phase I
  - Phase I, Placebo-controlled, multi-dose PK, tolerability, safety & placental perfusion study:
    - late 3rd trimester healthy gravidas scheduled for upcoming term CS