Session 3: Considerations for Planning Future Prevention Trials

PREP:
DOES FORMULATION IMPACT DRUG CONCENTRATIONS IN DIFFERENT COMPARTMENTS?
IMPLICATIONS FOR PREVENTING HIV INFECTION

Angela DM Kashuba
UNC Center for AIDS Research
Eshelman School of Pharmacy
UNC Chapel Hill
Concentration Matters

- Drug Concentration
- Formulation
- PrEP EFFICACY

Inset graph: Vaginal Lymphocyte TNF-α Concentration vs. Time After Gel Insertion (HIV Transmission Workshop, July 2010)
Tenofovir in Vaginal Tissue (topical vs oral)

- Tenofovir (TFV) 1% gel
- Tenofovir Disoproxil Fumarate (TDF) 300mg orally

Schwartz et al IAS 2009
Patterson et al WAC 2010

2 log (100-fold) difference
Tenofovir-DP in Vaginal Tissue (topical vs oral)

Schwartz et al IAS 2009

TDF 300mg PO

Patterson et al WAC 2010

TFV 1% GEL

2 log (100-fold) difference
TFV-DP Correlates with TFV in Vaginal and Cervical Tissues

- Vaginal Tissue ($r^2 = 0.9; p<0.05$)
- Cervical Tissue ($r^2 = 0.8; p<0.05$)

median (range) days post-gel: 24 (15-155)
median (range) days post-infection: 37 (17-350)
PK/PD of TFV 1% Gel In the Female Genital Tract

Derived from CVF in CAPRISA 004

Abdool-Karim et al Lancet in press 2011
Tenofovir in Rectal Tissue (topical vs oral)

Anton et al CROI 2011
TFV 1% GEL
Patterson et al WAC 2010
TDF 300mg PO

0 difference at 24h
Tenovir-DP in Rectal Tissue
(topical vs oral)

Anton et al CROI 2011

Patterson et al WAC 2010
Anton et al CROI 2011

0 difference at 24h
TFV-DP Correlates with TFV in Colorectal Tissue

TOPICAL

ORAL

Anton et al CROI 2011

Patterson et al WAC 2010
PK/PD of TFV in Colorectal Tissue (topical vs oral)

Anton et al CROI 2011
Does Formulation Impact Tissue Concentrations?

- **NO**
  - Rectal Tissue for TFV and TFV DP
  - TDF PO = TFV 1% GEL

- **YES**
  - Vaginal Tissue for TFV and TFV DP
  - TDF PO \( \equiv 1\% \) of TFV 1% GEL

Current evidence suggests that \(~100 – 1000\) fmol /mg TFV-DP required for partial protection against HIV
Implications for Future Prevention Strategies

- PO drugs may differentially penetrate mucosal tissues (vaginal vs rectal; 2 logs for TFV-DP, 1 log for FTC-TP)
- Due to varying surface area, topical products may also penetrate differentially in tissues
- To inform dose selection and dosing strategies
  - Dose-ranging tissue PK should be performed in early phase studies
  - PK-PD relationships should be identified preclinically and in early phase clinical studies