HPTN 069/ACTG 5305
NEXT-PREP: Novel Exploration of Therapeutics for PREP

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HPTN 069 Protocol Team Meeting, June 7, 2011
HPTN Annual Meeting, Washington, DC
Ideal PrEP Criteria

- Safe
- Penetrates target tissues
- Protects against HIV infection in tissues
- Long-lasting activity for convenient dosing
- Unique resistance profile or high barrier to resistance
- No significant drug-drug interactions
- Possibly, not a part of current rx regimens
- Affordable, easy to use and implement

DAIDS Working Group Report 4/09
DHHS Preferred Starting Regimens

- **NNRTI-based**
  - TDF/FTC + EFV
- **PI-based**
  - TDF/FTC + ATV/r
  - TDF/FTC + DRV/r
- **INSTI-based**
  - TDF/FTC + RAL

DHHS Guidelines, 1/10/11
MVC for PREP: Advantages

- Maraviroc (MVC) acts early in the HIV life cycle (HIV entry)
- MVC safety established over 5 years
- MVC achieves high tissue levels
  - Higher levels in vaginal secretions than blood (Dumond JAIDS 2009)
  - Higher in rectal tissue than blood (Brown JID 2011)
- MVC prevented HIV infections in animal model (Neff PLoS One 2010)
MVC for PREP: Advantages (2)

- MVC drug resistance is uncommon
- MVC used uncommonly for HIV treatment
- MVC once-daily dosing possible
  (Rosario Brit J Clin Pharm 2008)
### MVC for PREP: Disadvantages

- Limited safety data in HIV-uninfected individuals
- Increased pathogenicity of some viral infections (e.g., West Nile virus)
- Other theoretical safety risks
- Not active against X4 virus
- Not labeled for once-daily dosing
- Some potential for drug-drug interactions
<table>
<thead>
<tr>
<th>Rank</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MVC monotherapy</td>
</tr>
<tr>
<td>2</td>
<td>MVC + FTC</td>
</tr>
<tr>
<td>3</td>
<td>MVC + 3TC</td>
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<tr>
<td>4</td>
<td>MVC + TDF/FTC</td>
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<tr>
<td>5</td>
<td>MVC + TDF</td>
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<tr>
<td>6</td>
<td>RAL + FTC</td>
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<tr>
<td>7</td>
<td>MVC + RAL</td>
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<tr>
<td>8</td>
<td>RAL + 3TC</td>
</tr>
<tr>
<td>9</td>
<td>RAL + TDF/FTC</td>
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</tbody>
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HPTN 069 Design

- Safety and Tolerability of PrEP regimens to prevent HIV transmission in at-risk men who have sex with men (MSM)

- Study Design
  - Phase II
  - Double-blind
  - Randomized
  - 4 arm/multi-site (12 sites – US only)
  - 400 participants to be enrolled
Study Arms

• There are 3 active products
  – maraviroc (MVC)
  – emtricitibine (FTC)
  – tenofovir (TDF)

• Regimens being tested are:
  – maraviroc + FTC placebo + TDF placebo
  – maraviroc + emtricitibine + TDF placebo
  – maraviroc + tenofovir + FTC placebo
  – emtricitibine + tenofovir + MVC placebo
Subset Investigations

- **Drug Interaction Subset**
  - PK on first 72 enrolled participants who consent (18 ppts/arm)
  - Evaluate MVC/FTC and MVC/TFV interactions
  - Analysis to shed light on whether these drugs can be used in combination or not

- **Tissue Subset**
  - 60 participants who consent to further testing (15 ppts/arm)
  - Subset looks at concentration of drugs in plasma, PBMCs, rectal tissue, rectal fluid and hair samples (hair will possibly be tested in future analysis)
  - If multi-compartment model can be built from results, then it can be used for future efficacy studies
Protocol Arm Schematic

Screening

Enrollment and Randomization
N = 400

Arm 1, N=100
MVC (active) + FTC (placebo) + TDF (placebo)
Tissue Subset N = 15
Drug Interaction Subset N = 18

Arm 2, N=100
MVC (active) + FTC (active) + TDF (placebo)
Tissue Subset N = 15
Drug Interaction Subset N = 18

Arm 3, N=100
MVC (active) + FTC (placebo) + TDF (active)
Tissue Subset N = 15
Drug Interaction Subset N = 18

Arm 4, N=100
MVC (placebo) + FTC (active) + TDF (active)
Tissue Subset N = 15
Drug Interaction Subset N = 18
Beyond Safety & Tolerability

Other objectives of the study include:

- Changes in lipids
- Changes in bone mineral density (BMD)
- Drug Interaction between the MVC, FTC and TDF – Drug Interaction Subset
- Tissue concentrations (MVC, FTC, TFV, FTC-TP, TFV-DP) – Tissue Subset
- Adherence – CASI, EDM, and drug concentrations
- Sexual behavior using CASI, SMS
- QOL assessments
Core Protocol Team

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