Phase II Study of Maraviroc (MVC)-Containing Regimens for HIV PrEP in Men Who Have Sex With Men (MSM)

HPTN 069 / ACTG A5305

Roy M. Gulick, MD, MPH
Professor of Medicine
Weill Medical College of Cornell University
for the HPTN 069/ACTG A5305 Team
Disclosure

I have no financial relationships with commercial entities.
HPTN 069 / ACTG A5305: Background

- Tenofovir/emtricitabine (TDF/FTC)
  - only approved drug for HIV PrEP
  - associated with GI, renal, and bone effects
  - used commonly for HIV treatment
  - may select drug resistance

- Maraviroc (MVC)
  - HIV entry inhibitor active against R5 virus
  - well-tolerated in HIV+ individuals
  - concentrates in the genital tract / rectum
  - can be given orally once-daily
  - not used commonly for HIV treatment
  - selects drug resistance uncommonly
HPTN 069 / ACTG A5305: Hypothesis

• MVC-containing regimens will be generally safe and well-tolerated when compared with TDF/FTC given as HIV PrEP in at-risk individuals
HPTN 069 / ACTG A5305: Study Design

• Study population
  – HIV-1-uninfected adults (≥18 yo); born male
  – History of condomless anal intercourse with at least one HIV+ or unknown sero-status man in the prior 90 days
  – No injection drug use
  – Adequate safety labs; est. CrCl ≥70 mL/minute; HBsAg (-)

• Randomized, double-blind, placebo-controlled study of U.S. sites of the HPTN + ACTG:
  – MVC alone
  – MVC + FTC
  – MVC + TDF
  – TDF + FTC

  } daily dosing with matching placebos

• Study regimen: 3 pills (w/ placebos) orally once daily
• Visits: BL, wks 2, 4, 8, then every 8 wks to wk 48, 49
HPTN 069 / ACTG A5305: Objectives

• PRIMARY: To assess safety/tolerability of MVC, MVC+FTC, MVC+TDF, and TDF+FTC over 48 wks
  – Safety: Occurrence of grade 3 and higher adverse events
  – Tolerability: Rate and time to permanent discontinuation

• SECONDARY:
  – safety: grade 2 or grade 1 events resulting in study drug discontinuation, lipid changes, bone mineral density
  – drug interactions, drug concentrations, adherence, sexual behavior, quality of life

• EXPLORATORY:
  – characterize participants with new HIV infection
    • drug concentrations, HIV RNA, drug resistance and viral tropism
HPTN 069 / A5305 : Statistical Methods

- All analyses are intent-to-treat

- Primary analyses used Kaplan-Meyer survival analysis and comparisons between study arms used chi-square, t-test or log-rank testing

- P-values are two-sided

- Reviewed at least biannually by the HPTN Study Monitoring Committee (SMC) for safety
HPTN 069 / ACTG A5305: Participants

- **N = 406** individuals enrolled
- 100% male at birth; 7 (2%) transgender
- Median age 30 (range 18, 70)
- 28% black, 22% Latino, 62% white, 10% other
- 71% single, 28% with a primary partner
- 52% full-time employed, 23% part-time, 25% unemployed
- 20% high school education or less, 67% some college or more, 13% advanced degrees
- 31 (8%) had 34 STIs during study screening:
  - 15 (4%) chlamydia, 5 (1%) gonorrhea, 14 (3%) syphilis
HPTN 069 / A5305: Disposition

- 406 randomized; 404 started study drugs
  - 340 (84%) completed the study
- 29 (7%) prematurely discontinued study f/u
- 37 (9%) lost to follow-up
- 1 death (automobile accident)
- 404 (99%) started randomized study rx
  - 37 (9%) discontinued study rx early
    - 26 completed follow-up off study meds; 11 d/c study

**No difference by study arm in:**
- proportion who discontinued study drugs (p=0.6)
- time to permanent study drug discontinuation (p=0.6)
HPTN 069 / A5305: Adverse Events

- 306 (75%) pts experienced 988 grade 2-4 AEs
- No differences in occurrence or rates of grade 2-4 AEs among the 4 study arms (p<0.05 in pairwise comparisons)
- Selected adverse events (grades 2-4)*:

<table>
<thead>
<tr>
<th>Event</th>
<th>MVC (n=101)</th>
<th>MVC+FTC (n=106)</th>
<th>MVC+TDF (n=99)</th>
<th>TDF+FTC (n=100)</th>
<th>Total (N=406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>diarrhea</td>
<td>2%</td>
<td>8%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>nausea</td>
<td>0%</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>vomiting</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>unintentional weight loss</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>hypophosphatemia</td>
<td>18%</td>
<td>10%</td>
<td>16%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0.25%</td>
</tr>
</tbody>
</table>

*all grade 2 events, except hypophosphatemia which included 2% grade 3 events
HPTN 069 / A5305: Pharmacology

- **Drug Interactions:** MVC, TFV, FTC
  - First 72 consenting participants (18/arm) at wk 2
  - Compared MVC alone vs. when given with FTC or TDF
    - No significant difference in MVC concentrations (p>0.05 with Bonferroni correction)

- **Plasma Drug Concentrations:**
  - Random subset across 4 study arms (n=160)
  - All study drugs in regimen detectable in 83% (week 24) and 77% (week 48)
**HPTN 069 / A5305: HIV Infections**

<table>
<thead>
<tr>
<th>#</th>
<th>Demos. (age, race/ethnicity, HIV risk)</th>
<th>Study arm</th>
<th>First reactive HIV+ test (week)</th>
<th>HIV RNA (cps/mL)</th>
<th>HIV trop-ism</th>
<th>Genotypic drug resistance</th>
<th>CD4 cells (/mm³)</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20, black MSM</td>
<td>MVC+ TDF</td>
<td>4</td>
<td>122,150</td>
<td>R5</td>
<td>none</td>
<td>357</td>
<td>MVC=0† TFV=0</td>
</tr>
<tr>
<td>2</td>
<td>61, Asian MSM</td>
<td>MVC alone</td>
<td>16</td>
<td>981</td>
<td>R5</td>
<td>none</td>
<td>294</td>
<td>MVC=145</td>
</tr>
<tr>
<td>3</td>
<td>21, mixed MSM</td>
<td>MVC alone</td>
<td>24</td>
<td>106,240</td>
<td>R5</td>
<td>none</td>
<td>325</td>
<td>MVC=0†</td>
</tr>
<tr>
<td>4</td>
<td>35, white MSM</td>
<td>MVC alone</td>
<td>32</td>
<td>13,626</td>
<td>R5</td>
<td>none</td>
<td>828</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>5</td>
<td>36, black MSM</td>
<td>MVC alone</td>
<td>48</td>
<td>52,191</td>
<td>R5</td>
<td>none</td>
<td>804</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml
† undetectable plasma drug concentrations at every study visit
HPTN069 / A5305: Drug Concs in New HIV Infections

Note: 2 other participants acquired HIV infection with undetectable study drug concentrations at every study visit.
HPTN 069 / A5305: Conclusions

- MVC-containing regimens were comparably safe and well-tolerated to TDF/FTC when used over 48 weeks as HIV PrEP.
- No differences in specific toxicities (↓ power).
- No drug-drug interactions with MVC, FTC, TDF.
- ~80% of pts. had detectable plasma drug conc.
- 5 new HIV infections, all with R5 virus without drug resistance; study drug plasma concentrations absent, low or variable.
- MVC-containing regimens could be tested for efficacy in clinical trials.
HPTN 069 / A5305: Future Plans

- Men’s Tissue Substudy (n=55)
- Women’s Cohort (n=188)
- Women’s Tissue Substudy (n=42)
- Behavioral and Quality of Life Data
- Men and Women’s Bone Mineral Density Data (n=594)
- MVC Hair Levels
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Acknowledgements (1)

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  Chair: Trip Gulick
  Co-Chairs: Ken Mayer and Tim Wilkin
  Statisticians: Ying Chen and Alicia Young
  Co-investigators:
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- Study Volunteers!