HPTN 069 / ACTG A5305 Phase II Study of Maraviroc (MVC)-Containing Regimens for HIV PrEP in Men Who Have Sex With Men (MSM)
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Reported by Jules Levin

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HPTN 069 / A5305: Conclusions

• MVC-containing regimens were comparably safe and well-tolerated to TDF+FTC when used over 48 weeks as HIV PrEP.
• Comparable specific GI and renal toxicities.
• No drug-drug interactions with MVC, FTC, TDF.
• ~80% of pts. had detectable plasma drug conc.
• 5 new HIV infections (incidence 1.4%)
  – all R5 virus without drug resistance
  – plasma drug concs. were absent, low, or variable
• MVC-containing regimens should be considered for testing in clinical efficacy trials.
HPTN 069 / A5305: Coming

- Men’s Tissue Substudy
- Behavioral and Quality of Life Data

- Women’s Cohort (n=188)
- Women’s Tissue Substudy (n=42)

- Combined Men and Women’s Bone Mineral Density Data (n=594)
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HPTN 069 / ACTG A5305: Background

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

- Maraviroc (MVC)
  - CCR5 antagonist with activity against R5 virus
  - approved + well-tolerated in HIV+ individuals
  - concentrates in the genital tract / rectum
  - not used commonly for HIV treatment
  - selects drug resistance uncommonly
  - can be given orally once-daily

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 \{ standard doses 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 the safety and tolerability of MVC, MVC +FTC, MVC+TDF, and TDF+FTC over 48 wks
  - Safety: grade 3 or higher adverse events
  - Tolerability: rate/time to permanent study drug d/c

- SECONDARY:
  - safety: grade 2 events; 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 use Kaplan-Meyer survival analysis and comparisons between study arms use chi-square, t-test or log-rank testing

- P-values are two-sided

- Powered to estimate safety and tolerability, not efficacy.

- 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 (participants could report more than one)
- 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)

• 37 (9%) discontinued study treatment (rx) early
  – 26 d/c rx and continued f/u; 11 d/c both rx and f/u

• No differences 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

- There were 67 grade 3-4 AEs
  - No differences in occurrence or rate among the 4 study arms (p>0.05 in pairwise comparisons)

- Grade 2 or higher AE occurring in >5%:
  - hypophosphatemia (17%) and URI (11%)

- Selected GI and renal AE (grades 2-4) – ALL grade 2

<table>
<thead>
<tr>
<th></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>increased creatinine</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0.25%</td>
</tr>
</tbody>
</table>

- 90 (22%) had 115 STI diagnosed during study f/u
HPTN 069 / A5305: Pharmacology

• ART Drug Interactions: MVC, FTC, TFV
  – First 72 consenting participants (18/arm) at wk 2
  – Compared concentrations of MVC alone vs. MVC +FTC and MVC+TDF
    • No significant difference in MVC plasma 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)
    • No differences between the study arms (p>0.3)
**HPTN 069 / A5305: HIV Infections**

- 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

<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>CD4 cells (cells/mm³)</th>
<th>HIV tropism</th>
<th>Genotypic drug resistance</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>357</td>
<td>R5</td>
<td>none</td>
<td>MVC = 0†&lt;br&gt;TFV = 0</td>
</tr>
<tr>
<td>2</td>
<td>61, Asian MSM</td>
<td>MVC alone</td>
<td>16</td>
<td>981</td>
<td>294</td>
<td>R5</td>
<td>none</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>325</td>
<td>R5</td>
<td>none</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>828</td>
<td>R5</td>
<td>none</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>804</td>
<td>R5</td>
<td>none</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
HPTN 069 / A5305: Study Drug Concns. in New HIV Infections

Note: 2 others with new HIV infection had undetectable study drug at every visit.
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Acknowledgements (1)

* HPTN 069/A5305 Protocol Team
  Chair: Trip Gulick
  Co-Chairs: Ken Mayer and Tim Wilkin
  Statisticians: Ying Chen and Alicia Young
  Co-investigators:
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  Data Manager: Leslie Cottle
  Field Representative: Cheryl Marcus
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  Pharmaceutical representatives: Alex Rinehart (ViiV), Jim Rooney (Gilead)
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• Study Volunteers!