HIV Prevention Trials Network

ACTG AIDS CLINICAL TRIALS GROUP

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

HPTN 069 / ACTG A5305

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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)*:

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

*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)

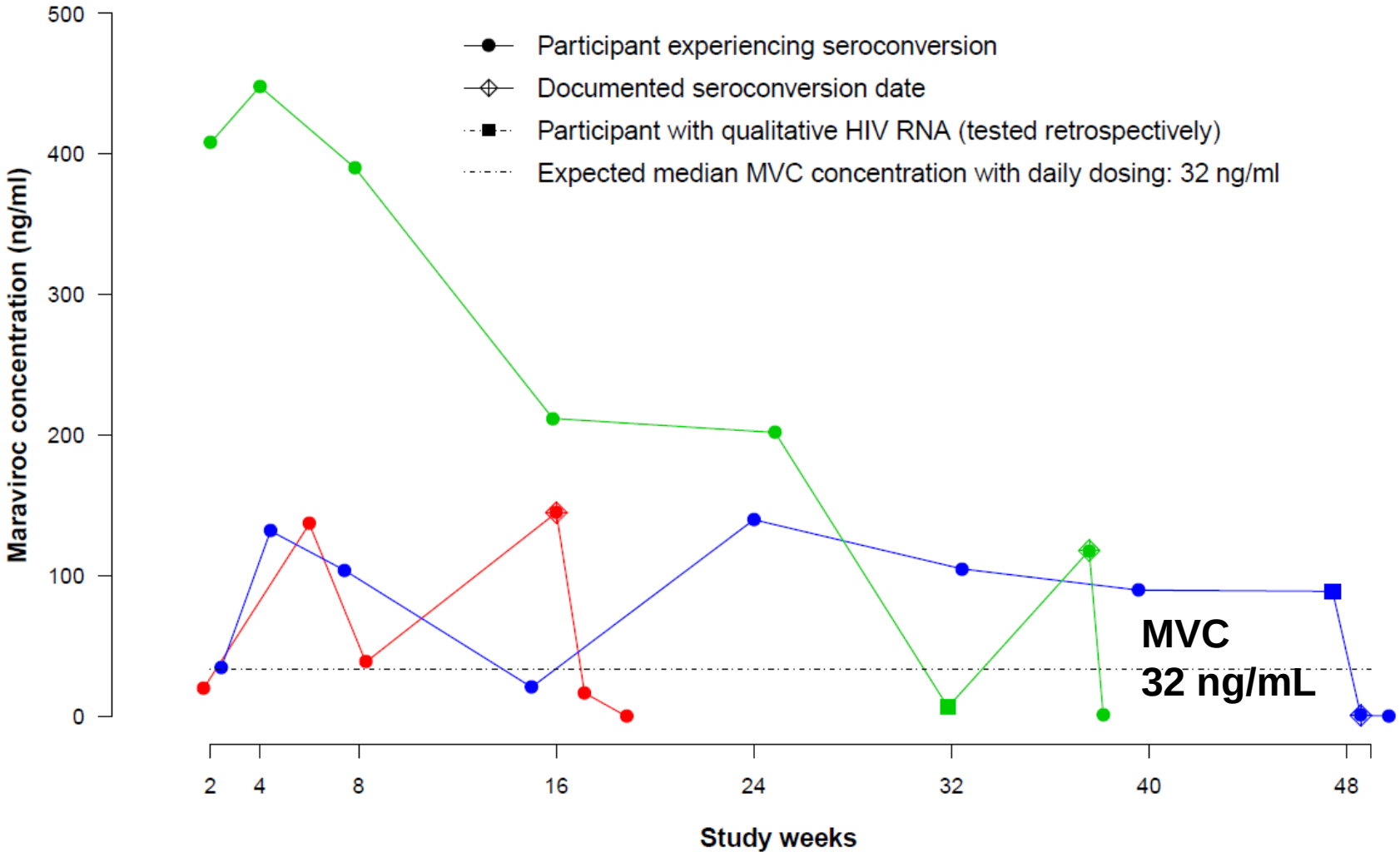
HPTN 069 / A5305: HIV Infections

#	Demos. (age, race/ ethnicity, HIV risk)	Study arm	First reactive HIV+ test (week)	HIV RNA (cps/mL)	HIV trop-ism	Geno-typic drug resis-tance	CD4 cells (/mm^3)	Plasma drug conc. at serocon-version visit (ng/mL)*
1	**20, black MSM**	MVC+ TDF	4	122,150	R5	none	357	MVC=0† TFV=0
2	**61, Asian MSM**	MVC alone	16	981	R5	none	294	MVC=145
3	**21, mixed MSM**	MVC alone	24	106,240	R5	none	325	MVC=0†
4	**35, white MSM**	MVC alone	32	13,626	R5	none	828	MVC=6.7
5	**36, black MSM**	MVC alone	48	52,191	R5	none	804	MVC=0.7

* 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

HPTN 069 / ACTG A5305 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:

  Rivet Amico, Adriana Andrade, Todd Brown, Sally Hodder, Raphy Landovitz, Joe Margolick, Ian McGowan, Bruce Schackman

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  DAIDS: Wairimu Chege, Karin Klingman, Fulvia Veronese, Usha Sharma

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- HPTN 069/A5305 Protocol Team (continued)

  Protocol Specialists: Phil Andrew and Marybeth McCauley

  Data Manager: Leslie Cottle

  Field Representative: Cheryl Marcus

  Community Program Manager: Jonathan Lucas

  DAIDS pharmacists: Ana Martinez and Bijal Patal

  Pharmaceutical Co-sponsors:

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- HPTN Laboratory Center: Johns Hopkins

- HIV Prevention Trials Network (HPTN)
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH

- Study Volunteers!