Beyond Daily TDF/FTC as PrEP: Exploring new drugs and regimens for PrEP

AVAC
Global Advocacy for HIV Prevention

October 3, 2012

HPTN 067/ADAPT Introduction

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October 2012

National Institute of Allergy and Infectious Diseases

NIMH National Institute of Mental Health

National Institutes of Health

U.S. Department of Health and Human Services
NATIONAL INSTITUTES OF HEALTH
NIDA National Institute on Drug Abuse

HPTN HIV Prevention Trials Network

Study Title

- HPTN 067
- The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)
- **A**lternative
- **D**osing
- to **A**ugment PrEP
- **P**ill
- **T**aking

= ADAPT

Study Design: 3 arms

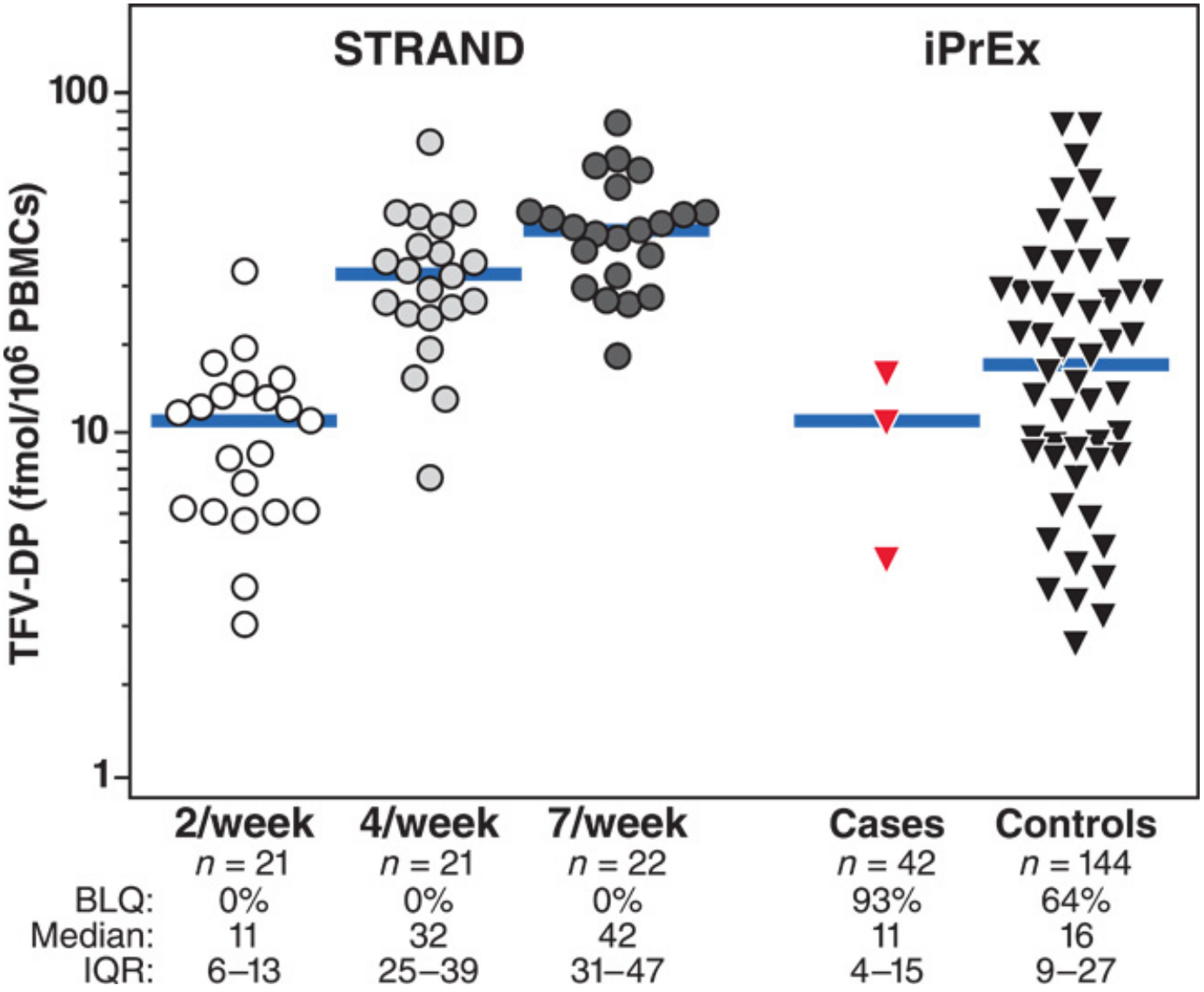
- **Daily**:
- One tablet of FTC/TDF once a day regardless of sexual activity
- **Time Driven**:
- One tablet of FTC/TDF 2 days/week and a post-exposure booster dose within 2 hours after sexual intercourse
- **Event Driven**:
- One tablet of FTC/TDF prior to sexual intercourse & a post-exposure booster dose within 2 hours of sexual intercourse

Study Sites

- Emavundleni Centre, in Cape Town, South Africa
  - Activated: 29 August 2011
  - Current enrollment: ~180 women
- Silom Community Clinic in Bangkok, Thailand
  - Enrolling MSM and Trans Women (goal 180)
- Harlem Hospital Affiliate, NYC, USA
  - Planning to enroll MSM and Trans Women (goal 180)

- Study Duration
- 6 weeks of weekly Directly Observed Therapy
- 24 weeks of Self Administered Therapy

Drug-Protection Relationship in MSM



Anderson et al, Science Translational Medicine 2012 4;151:151ra125

Conclusions

- ADAPT study is progressing well
- Will evaluate the behavioral feasibility and acceptability of regimens requiring post-exposure and/or pre-exposure dosing
- Pathways to efficacy evaluation are unclear
  - No need to evaluate efficacy of unpopular regimens
  - Surrogate markers are needed
    - One estimate available for MSM

IPERGAY
Study Design

IPERGAY un essai ANRS Intervention Préventive de l'Exposition aux Risques avec et pour les GAYS

Effectiveness of "on demand" PrEP
Randomized placebo-controlled trial

- High risk MSM
- Condomless anal sex with ≥ 2 partners

→ **Full prevention services* TDF/ FTC before and after sex (n=950)**

→ **Full prevention services* placebo before and after sex (n=950)**

- Counseling, testing for STI, condoms, vaccination, PEP
- Primary endpoint : HIV infection, 64 events expected
- Incidence of HIV-infection: 3%PY, ~ 2000 pts

www.Ipergay.fr

Study Rationale

- Data from animal models support this strategy
- A more convenient treatment strategy
- Better adherence possible with a potentially better efficacy/safety ratio
- Intermittent use of TDF gel effective in Caprisa 004 whereas daily TDF gel ineffective in VOICE
- Could be more cost-effective
- Sexual activity is not permanent, and is usually concentrated during week-ends and pre-planned

Why Such a Design?

- A trial comparing daily to intermittent PrEP
    - Seems unrealistic since 20.000 participants required
    - Could lead to behavioral changes
    - Results difficult to interpret in an open-label design
- A placebo-controlled trial remains the “best” way to assess intermittent PrEP
- 2,000 participants is an achievable goal
- Participants will not know if they are receiving an active drug and there will therefore be less risk of sexual disinhibition / pill sharing than in an open-label trial

Timelines

- Pilot phase in 3 sites in France
- First patient randomized early March 2012
- 117 patients screened and 102 randomized with a prevalence of HIV-infected at 5%
- Canada has received IRB approval and is about to start
- Consultation ongoing with IRB, DSMB and CAB about continuation of the trial following FDA approval in the US
- Trial extension in different European countries under discussion

PROUD

Advocates call

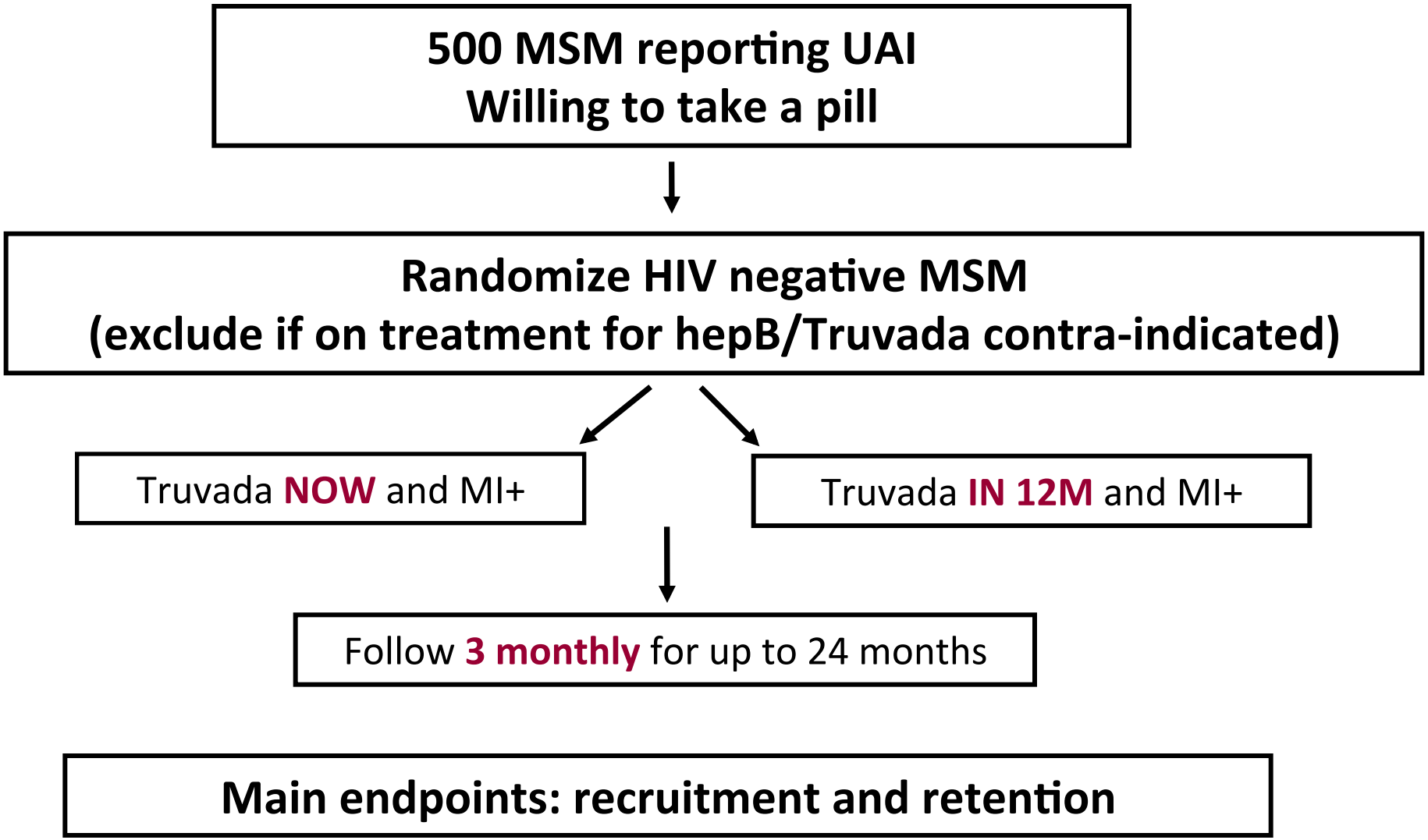
3rd October 2012

Background to Pilot: the PrEP eGroup

- April 2011: PrEP eGroup launched to achieve consensus for UK
  - Health care workers
  - Community organisations
  - Commissioners
  - Researchers
- May 2011: eGroup became a forum for discussing clinical research programme
  - Integration of PrEP in risk reduction package and intensify efforts
  - Need to collect evidence of 'real life' effect in clinical research programme
- July 2011: application for RCT randomising ~5,000 gay men to have access to Truvada as part of the package immediately or after 12m follow-up
  - Dec 2011 rejected
- March 2012: funding secured for a pilot study

International Journal of STD & AIDS 2012; 23: 1-4

PROUD Pilot


500 MSM reporting UAI
Willing to take a pill
Randomize HIV negative MSM
(exclude if on treatment for hepB/Truvada contra-indicated)
Truvada NOW and MI+
Truvada IN 12M and MI+
Follow 3 monthly for up to 24 months
Main endpoints: recruitment and retention

Visit schedule

- Every 3 months from enrolment
  - HIV testing
  - STI testing at 6, 12, 18 and 24, and extra if indicated
  - Creatinine 0, 12, 24 for immediate and 12, 24 for deferred
  - Dispensing when on drug
- Visit 1 month after starting Truvada to check how everything is going
- Self-reported behaviour
  - Monthly short and Annual long questionnaires
  - Diaries
- Detectable drug reported back to a subset of ppts
- In depth interviews in a subset of ppts selected according to a risk matrix

Pilot Outcomes

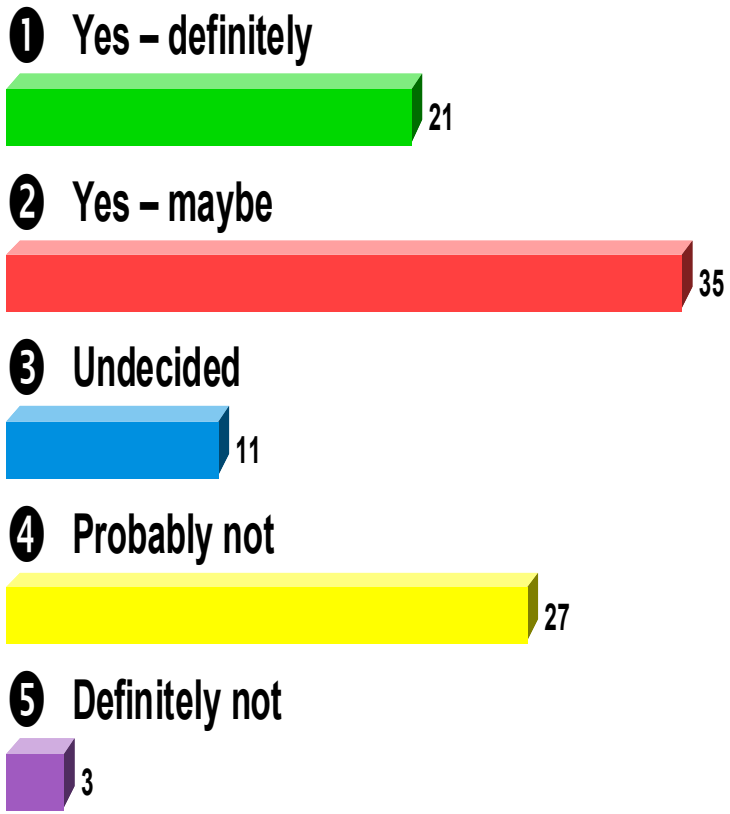
- Whether or not a large trial is feasible
  - Level of interest in PrEP in clinic populations
  - Acceptability of randomisation
- Who takes up offer of PrEP
- Risk behaviour over time (self-report, STIs)
- Change in risk following behavioural interventions
- Adherence behaviour over time (self-report, pill count, and real time PK in a sub-set)
- Facilitators and barriers to reducing risk and adhering to a daily pill

Next steps: trial feasible

- Supported by
  - Clinics achieving their targets in a timely manner
  - Majority of men attend 6m follow-up visit in both groups

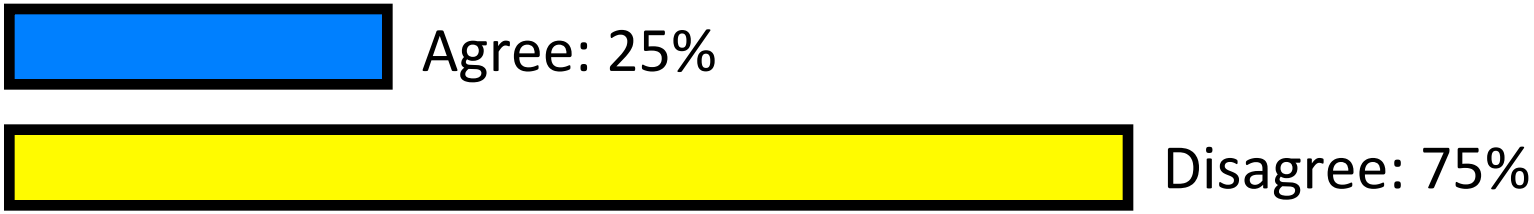
- Aim to decide in April 2013 whether or not to apply again for full trial
  - Ideal to continue seamlessly (would require accelerated review in UK system)

Question to BASHH Jan2012: PreP availability will increase risk behaviour?



BASH/ASTDA Debate Jun2012:
PrEP should never be prescribed on the NHS

- Before



- After

THE FENWAY INSTITUTE

NextPrEP:
HPTN 069/ ACTG 5305:Update

Kenneth H. Mayer, M.D. for the Protocol Team

R. Gulick, Chair

Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

Maraviroc for PREP: Advantages

- Entry inhibitor
- MVC safety profile X 5 years Gulick IAS 2012
- MVC achieves high tissue levels
  - 3X ↑ in vaginal secretions Dumond JAIDS 2009
  - 8-26X ↑ in rectal tissue Brown JID 2011
- MVC prevented HIV infections in animal model Neff PLoS One 2010
- MVC drug resistance is uncommon
- MVC once-daily dosing possible Rosario Brit J Clin Pharm 2008
- MVC used uncommonly for HIV treatment

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 labeled for once-daily dosing
- Some potential for drug-drug interactions
- Not active against X4 virus

HPTN 069/ACTG 5305 Design

- Primary objective: Assess safety and tolerability of new PrEP regimens to prevent HIV transmission in at-risk persons
- Study Design
  - Phase II, double-blind, randomized
  - 4 arm/multi-site (12 sites – US only)
  - 400 MSM and 200 women at risk for HIV

Study Arms

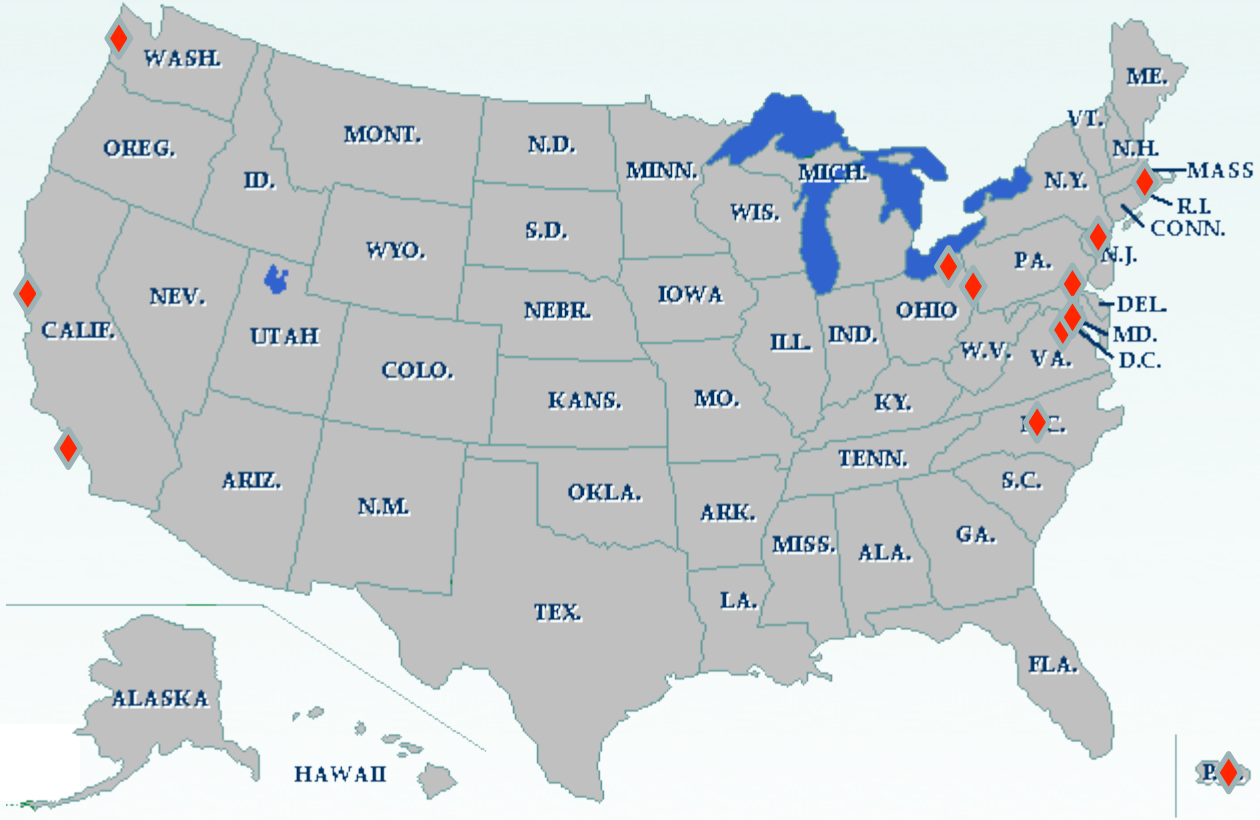
- There are 3 active study drugs
  - maraviroc (MVC)
  - emtricitabine (FTC)
  - tenofovir (TDF)

- Regimens being tested are:
  - maraviroc + FTC placebo + TDF placebo
  - maraviroc + FTC + TDF placebo
  - maraviroc + tenofovir + FTC placebo
  - tenofovir + FTC + MVC placebo

Secondary Objectives

- Changes in lipids
- Changes in bone mineral density (BMD)
- Drug Interaction between the MVC, FTC and TDF – Drug Interaction Subset (n=72)
- Tissue concentrations (MVC, FTC, TFV, FTC-TP, TFV-DP) – Tissue Subset (n=60)
  - Immune activation; HIV infectivity
- Adherence – CASI, EDM, and drug concentrations
- Sexual behavior using CASI, SMS
- QOL assessments

HPTN 069/ACTG 5305 Sites



Fenway
Cornell
UMDNJ
U Penn
Hopkins**
GW
UNC
UPR
Pitt**
Case
Western
U Wash
SF DOH
UCLA**

** = tissue substudy site

ACTG
AIDS CLINICAL TRIALS GROUP

HPTN
HIV Prevention Trials Network

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Q&A

Thank you for joining today's webinar. To ask a question you can:

- Email your question to avac@avac.org
- Ask your question in the chatbox on the web interface if you're listening online
- Once the facilitator has opened the line for questions, press *7 to unmute yourself