Beyond Daily TDF/FTC as PrEP: Exploring new drugs and regimens for PrEP
HPTN 067/ADAPT Introduction


October 2012
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)
- Alternative
- Dosing
- to Augment PrEP = ADAPT
- Pill
- Taking
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

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
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?

1. Yes – definitely: 21
2. Yes – maybe: 35
3. Undecided: 11
4. Probably not: 27
5. Definitely not: 3
BASH/ASTDA Debate Jun2012: PrEP should never be prescribed on the NHS

• Before
  Agree: 25%
  Disagree: 75%

• After
  Agree: 46%
  Disagree: 54%
NextPrEP:
HPTN 069/ ACTG 5305: Update

Kenneth H. Mayer, M.D. for the Protocol Team
R. Gulick, Chair
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
  • maraviro (MVC)
  • emtricitabine (FTC)
  • tenofovir (TDF)

• Regimens being tested are:
  • maraviro + FTC placebo + TDF placebo
  • maraviro + FTC + TDF placebo
  • maraviro + 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
- UNC
- UPR
- Pitt**
- Case
- Western
- U Wash
- SF DOH
- UCLA**

** = tissue substudy site
Core Protocol Team

Protocol Chair/Co-Chairs:
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HPTN Network Lab:
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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