Protocol Update: MTN-003

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Agenda of February 12, 2007: MTN-003 Planning Meeting

- Meeting was held in MTN Core Pittsburgh to discuss PrEP studies involving Oral Tenofovir, Oral Truvada*, and Tenofovir 1% vaginal gel (PMPA)
  - Review of animal model studies of PMPA gel, Oral TDF, Oral Truvada
  - Review of human studies of PMPA gel, Oral TDF, Oral Truvada
  - Perform 'Gap Analysis': What we will know and won't know after current studies are completed?
- Meeting was attended by Sponsors, MTN Leadership, Gilead, CONRAD, and MTN SDMC biostatisticians.

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*Truvada combines emtricitabine and tenofovir

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Some Outcomes of February 12, 2007: MTN-003 Planning Meeting

- Phase II PMPA gel study (HPTN 059) will be completed by the end of the year (2007). If (expanded) safety profile of PMPA gel is confirmed, PMPA gel is ready to move into efficacy evaluation.
- Limitations of some of the current PrEP studies on oral TDF and oral Truvada
  - Most are powered to detect large effectiveness

Oral PrEP	**>65% (65%-80%)**
Microbicide:	30-50% effectiveness
IDU substitution tx:	50% effectiveness
HIV Vaccine:	60% vs. 30%
HSV2 tx:	50% effectiveness
Circumcision	50% effectiveness

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Some Outcomes of February 12, 2007: MTN-003 Planning Meeting

- Current PrEP studies of oral TDF and oral Truvada are unlikely to provide a definitive answer: a proof of concept
  - Lower bound of 95% CI on effectiveness will likely be close to 0%
    - ⇒Difficult to ascertain the effectiveness at the population level
    - ⇒For example, what is the next step for an observed effectiveness, say of 53% with 95% CI [14%;74%] (assuming a 50 events trial)
    - ⇒Math modeling exercises have shown:
      - ⇒HIV vaccine might need to have >30% efficacy in order to offset the possible increase in HIV risk behaviors (sexual disinhibition)
      - ⇒Abbas et al, CROI 2007 suggests >50% for PrEP
    - ⇒Potential for increase in HIV risk behaviors if PrEP effective
  - Conducted in several different populations (MSM, IDU, Heterosexual Men and Women)
    - ⇒Will be difficult to 'combine' results of several studies

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Other Discussion Points: Combination of Prevention Methods?

Oral TDF : once a day pill
Oral Truvada: once a day pill
PMPA gel: once daily application

- Is it plausible that the effects of gel plus oral are additive or multiplicative?

Oral TDF/Truvada	:	60% efficacy alone
PMPA gel	:	40% efficacy alone
Oral TDF/Truvada + PMPA gel	:	??? 80% ???

- Most felt that women would *not* take a daily pill **and** use a gel daily
  - Reduces the usefulness of 'double-dummy type' trials

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Other Discussion Points:
Head-to-Head Comparison of Prevention Methods?

- Is Oral Truvada or Oral TDF superior to PMPA gel or vice versa?
  - This question will be asked … if at some point oral and topical are both effective
  - Group felt that the trial to answer this question with appropriate statistical power would be too large … but it would be important to provide some evidence

Other Discussion Points:
What should be the control intervention?

- This is more of an issue for topical gel than for oral prevention interventions

  ⇒ Placebo control only: Oral/Topical placebo gel
  ⇒ Placebo control and No-placebo control (e.g., condom only arm)

- Felt that HPTN 035 will answer the question:

  – Does the placebo gel have an effect?
  – If it does, we still need to prove that a microbicide gel provides a 'antimicrobial' effect for licensure. FDA might be less concerned about the placebo gel effect with the HPTN 035 data available.

Other Discussion Points:
Product Development/Licensing Strategy

If effective:

=> Oral Tenofivir/Truvada: Possible change of labeling

=> PMPA gel: License product

- What should be the next step after a Phase II?
  - Phase IIb, intermediate size/screening trial (e.g., HPTN 035)
  - Fully powered Phase III
    - No efficacy 'signal' in humans obtained from Phase II … a big step

- The "Single Pivotal Trial" road

  Trial with: 1.0 Strength of Evidence

  1.5 Strength of Evidence ← **HPTN 035**

  2.0 Strength of Evidence

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End of the Day on Feb. 12, 2007

- Need to evaluate efficacy of PMPA gel
- Further efficacy evaluation of oral PrEP is likely to be needed
- Once daily pill and once daily gel use : Not viable
- No formal fully powered head-to-head comparison of oral versus topical
- Placebo control only trial (no “condom only” arm)
- Product development strategy :
  - For PMPA gel, single pivotal trial, Phase IIB with 1.5 strength of evidence
- Need to be able to ‘rule-out’ lower efficacy :
  - Lower bound of 95% CI needs to be substantially higher than 0%

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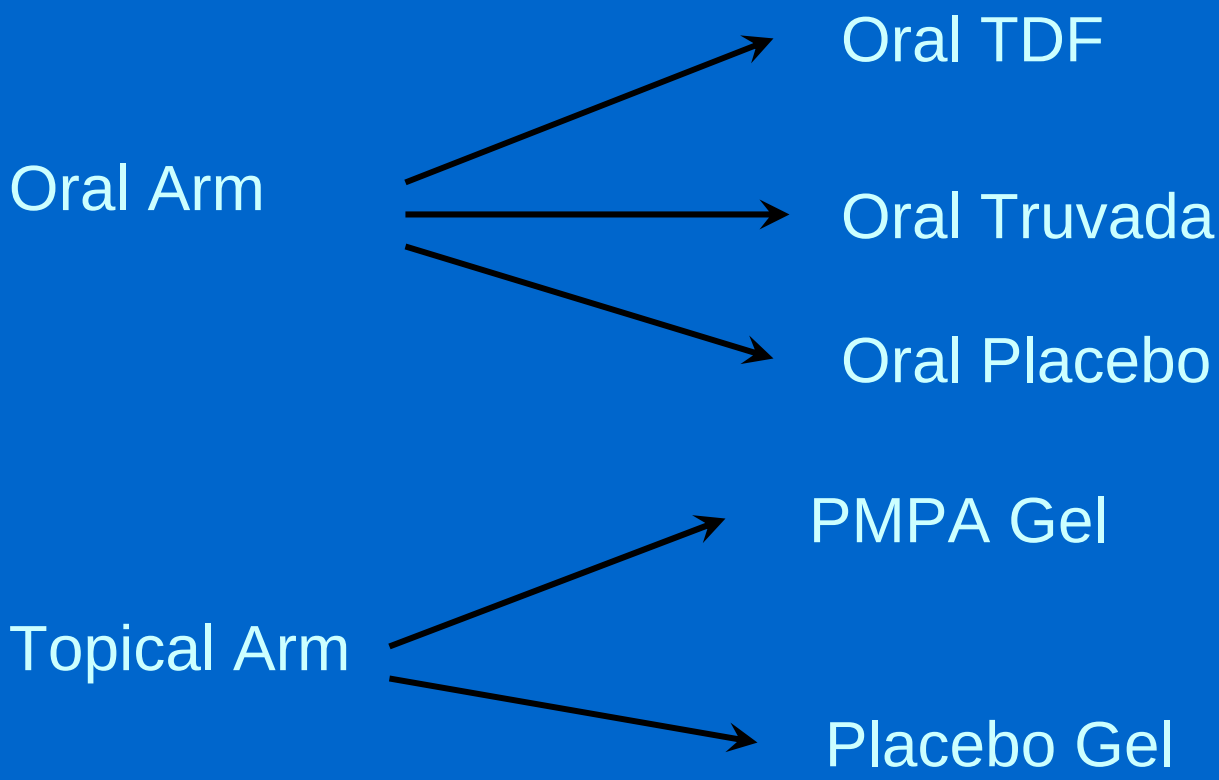
MTN-003 Proposed Design

5 arms: First, randomize woman to Oral Arm or Topical Arm



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MTN-003 Proposed Design

- Population
  - Sexually active women
- Sites
  - MTN sites with HIV incidence > 3% per year
- Sample size
  - Single Pivotal Trial
  - Phase IIB
    - 1/4 to 1/3 of size of Phase III with 1.5 Strength of Evidence (1.5 SOE)
  - 90% power to detect 55% effectiveness (false+ error rate 0.25%)
  - Ruling out lower efficacy of 25%: **H_0: Effectiveness ≤ 25%**

    H_1: Effectiveness > 25%

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MTN-003 Sample Size

- 65-86 events needed per pairwise-comparison
  - 65-86 events for the placebo gel vs PMPA gel comparison
  - 100-130 events for both the oral placebo vs oral TDF and for the oral placebo vs oral Truvada comparisons

⇒ Total of 165-216 events

(3800 to 5000 person-years)

As a comparison, HPTN 035 is a 192 event trial with a projected 4340 person-years.

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MTN-003 Proposed Design : Highlights

1- Evaluate superiority of PMPA gel over placebo gel

2- Evaluate superiority of Oral TDF over oral placebo

3- Evaluate superiority of Oral Truvada over oral placebo

4- Allow comparisons of Oral TDF and Oral Truvada

- Comparison not fully powered but will provide some evidence

5- Allow comparisons of PMPA gel vs Oral PrEP

- Comparison not fully powered but will provide some evidence

6- Allow comparisons of placebo gel vs oral placebo gel

- Comparison not fully powered but will provide some evidence on the potential physical barrier/lubrication effects of placebo gel

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MTN-003 Proposed Design : Timeline

- Formal concept to be submitted to NIH for funding consideration in April 2007
- Presentation of MTN-003 design to DAIDS Leadership, other network leaders and external advisors on June 27-28, 2007
- If approved develop protocol in Q3 of 2007
- Initial community preparedness activities surrounding study of oral verses vaginal PrEP
- Submission to PSRC Q4 2007
- IRB submission and site training Q2 2008
- Start enrolling in Q3 of 2008

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