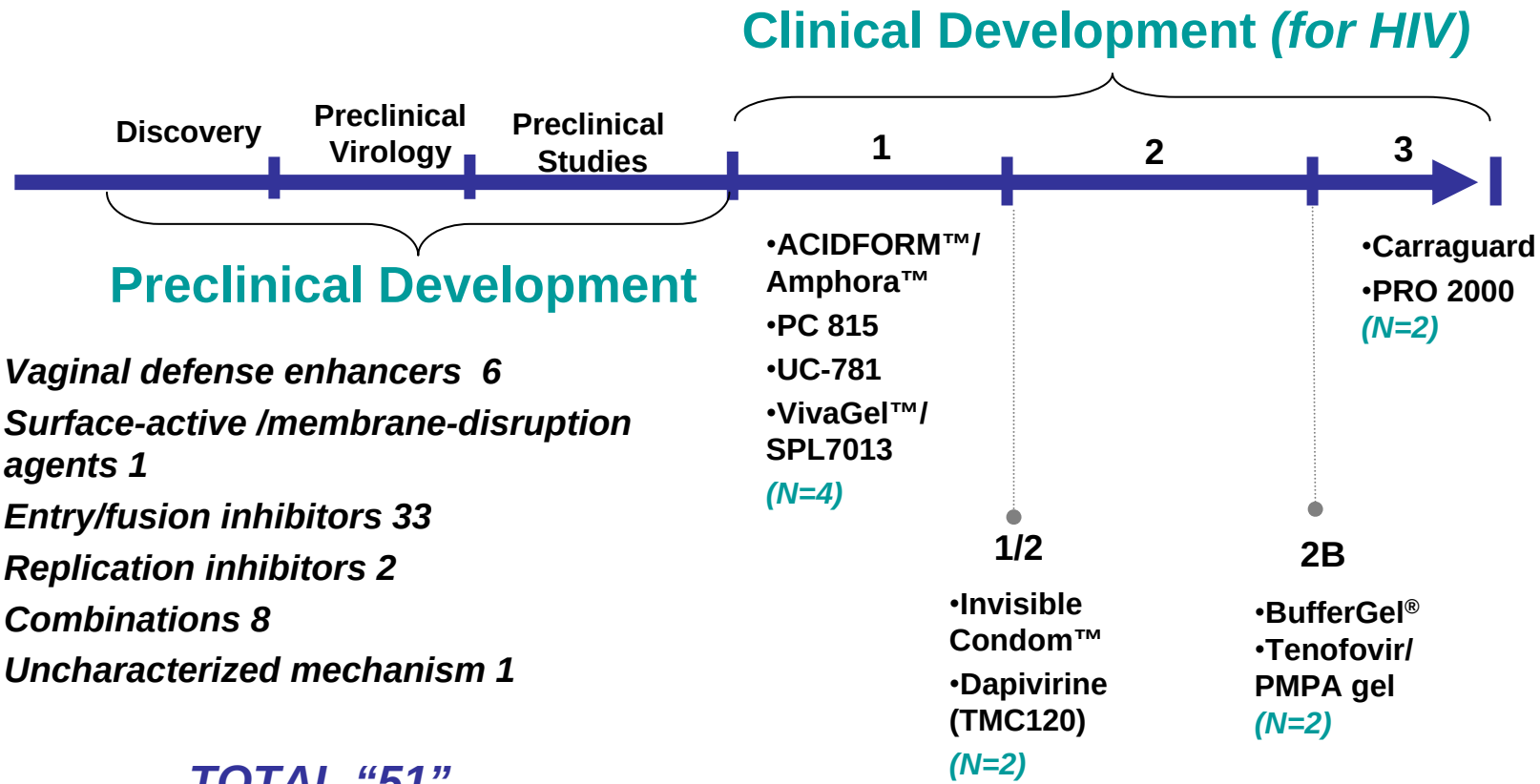
Moving Forward with ART Based Microbicides

Sharon L. Hillier, Ph.D.
University of Pittsburgh School of Medicine

OVERVIEW: The Microbicide Pipeline



- *Vaginal defense enhancers 6*
- *Surface-active /membrane-disruption agents 1*
- *Entry/fusion inhibitors 33*
- *Replication inhibitors 2*
- *Combinations 8*
- *Uncharacterized mechanism 1*

TOTAL "51"

Discovery/early preclinical "44"

Advanced preclinical "7"

Source: Alliance for Microbicide Development, 9 April 2007

MTN Portfolio Years 1and 2

Study	Products	Design
HPTN-035	PRO-2000, BufferGel	Phase 2/2B
HPTN-059	Tenofovir (PMPA gel)	Phase 2
MTN-004	VivaGel	Phase 1
MTN-001	TDF (oral), tenofovir (PMPA gel)	Phase 2
MTN-003	TDF, tenofovir gel, ± Truvada	Phase 2B
MTN-002	Tenofovir	Phase 1-pregnant women
MTN-015	Seroconverter Protocol	Observational

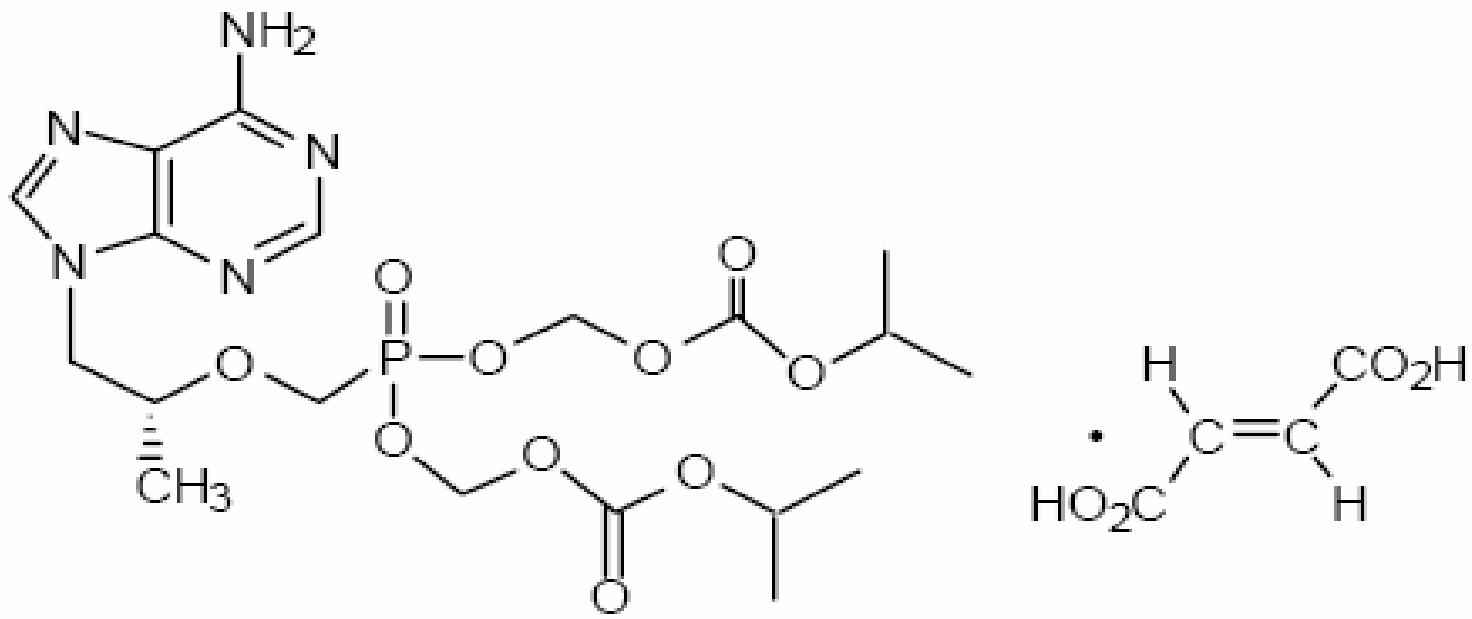
ARTs as Topical Microbicides

- TMC-120 (Dapavirine): available as gel and ring; being developed by the International partnership for microbicides
- PMPA gel (Tenofovir): available as a gel; being development by CONRAD
- MIV150: available as gel, just entering phase 1 testing; being developed by the Population Council

Redefining The Road to Success for Microbicides in 2007

- More focus on highly potent inhibitors of HIV
- Enhance assessment of safety in animal models and tissue explants
- Add more assessments of safety in new trials of microbicides
- Move toward coitally independent use of microbicides

Tenofovir



Mechanism

- Acyclic nucleoside analog of AMP.
- Requires hydrolysis to form tenofovir diphosphate.
- Tenofovir diphosphate inhibits reverse transcriptase by
  - competing with deoxyadenosine 5’-triphosphate incorporation into DNA,
  - by DNA chain termination once incorporated

- A weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA

Advantages of Tenofovir for Prevention of HIV

- Activity in target cells for HIV infection: Langerhans-dendritic cells; monocyte/macrophages, T cells of the vagina and cervix including non activated cells.
- Known activity agent for treatment of HIV
- Low frequency of local and systemic toxicity observed in Phase I for topical tenofovir
- Being evaluated as an oral agent for HIV prevention

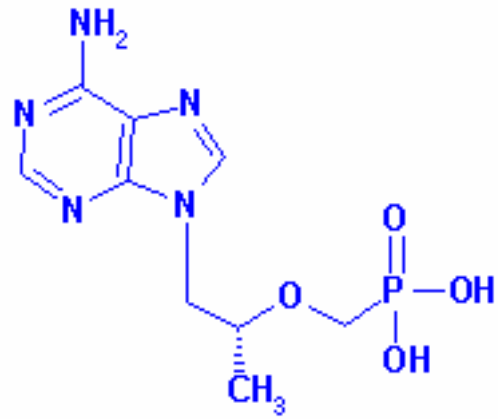
How Could Tenofovir Work Topically? Animal Model Data on Topical Tenofovir or PMPA for Prevention of SIV

- A total of 6 studies to date
- All challenges performed with SIVmac251
- Female rhesus macaques challenged intravaginally
- Various dosing regimens prior to SIV exposure evaluated

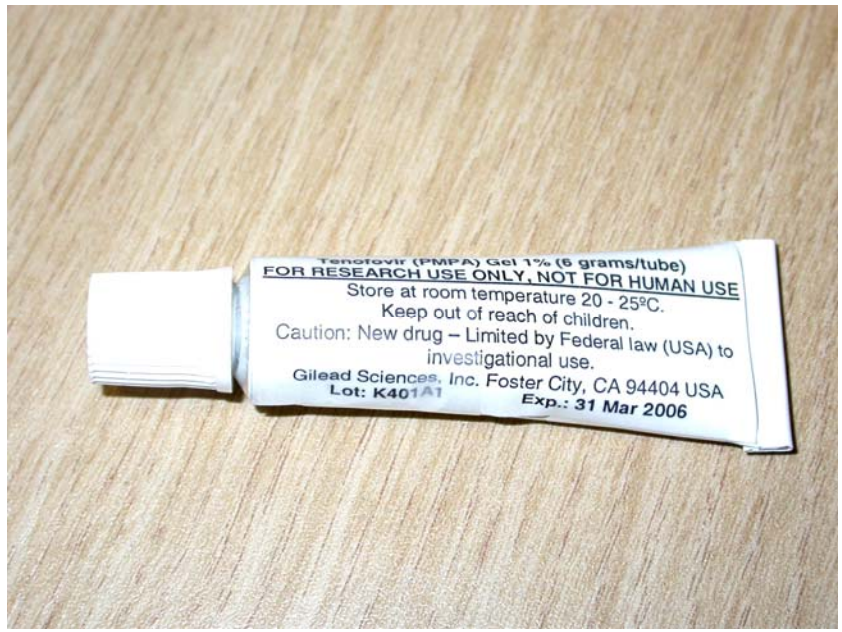
Animal Challenge Studies with Topical Tenofovir

- Administration of topical tenofovir 1% in gel form prior to SIV challenge was at least partially protective in several studies
- Because tenofovir must be converted to the active form intracellularly daily dosing rather than coitally-dependent dosing may provide the best sustained activity intracelluarly

Tenofovir 9-[2-(Phosphonomethoxy)Propyl]Adenine



Acyclic nucleoside phosphonate



1% Gel – Gilead Sciences Inc

HPTN 050

- Phase 1 safety study of PMPA gel in HIV infected and HIV un-infected women
- Women used PMPA gel daily for 7 days and then twice daily for 7 additional days
- Frequent assessment for safety to the vaginal epithelium
- Good safety profile in sexually abstinent and sexually active women

Ref: Mayer et al AIDS February 28, 2006

HPTN 059: Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel

- Study population: 200 sexually active HIV negative women with normal lower genital tract
- Women randomized to coitally dependent or daily use of placebo vs. 1% tenofovir gel
- Product to be applied at least 2 hours before each act of intercourse in the coitally dependent group
- Maximum use of gel: twice daily

HPTN 059: Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel

- Status: currently enrolling in Pune India, and Birmingham, AL and Bronx Lebanon in NY
- Recruitment finalized April 2007

Site	Date of First Enrollment	Total No. Screened	Total No. Enrolled
NARI	August 24, 2006	116	100
BLHC	August 11, 2006	115	48
UAB	August 9, 2006	71	52
Total	NA	302	200

Highlights of HPTN 059 Progress as of April, 2007

- Inappropriate enrollment: 0
- Completed visits per protocol
  - 4 week: 144/146 (97%)
  - 8 week: 117/119 (98%)
  - 12 week: 91/98 (93%)
  - 16 week: 67/72 (93%)
  - 20 week: 40/41 (98%)
  - 24 week: 11/11 (100%)

What Have We Learned From HPTN 059?

- HIV uninfected women are willing to use tenofovir gel either daily or in a coitally dependent manner
- Adherence with daily gel use has been high (>80%) and non adherence with daily gel associated primarily with menses
- Safety profile appears to be excellent; additional lab analyses ongoing

Topical Tenofovir (PMPA) Next steps for MTN

- Ongoing study of vaginal pharmacokinetics underway (CONRAD)
- Head to comparison of daily oral tenofovir vs PMPA for acceptability and pK (MTN001)
- PMPA pK in pregnant women (MTN002)
- MTN003: Oral vs topical tenofovir of prevention of HIV

MTN-001

- Randomized, controlled, Phase II trial
- Comparing adherence & pharmacokinetics of oral vs topically applied tenofovir
- Once daily vaginal PMPA 1% gel
- Once daily oral tenofovir disoproxil fumarate (TDF) 300 mg tablet
- Cross-over design

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MTN 001 Rationale

- First head-to-head comparison of oral versus vaginal prevention dosing strategies
- Inform the design of 003 Tenofovir Phase 2B study (MTN-003)
  - Adherence estimates
  - Drug level estimates
- Activate new sites

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MTN-001 Sites

- Case Western Reserve University, Cleveland, OH
- University of Pittsburgh, Pittsburgh, PA
- University of Cape Town, CapeTown, South Africa
- Makarere University, Kampala, Uganda
- Durban, South Africa
  - (2 sites)

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MTN-001

- Draft protocol available for discussion at the Regional meeting
- Hope to finalize study design while in S Africa
- Proposed submission to the PSRC at DAIDS in June 2007
- Version 1.0 available to sites for submission to the IRBs in September 2007

MTN-002 PMPA (tenofovir gel) Study in Pregnancy:Rationale

- Pregnancy high-risk for HIV acquisition
  - Gray. Lancet 2005;366
- Pregnant women:
  - Rx and OTC medications used frequently
    - Andrade. AJOG 2004;191
    - Werler. AJOG 2005;193
- Practical:
  - If microbicides available
    - Pregnant women will use
    - Will answer question regarding need to exclude pregnancy among women given access
- Role for use in HIV(+) gravidas to decrease maternal-child perinatal HIV transmission

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MTN-002 Goal/Specific Aims

- **MTN: Proactively assess formulations in pregnancy**

- **1. Assess term pregnancy maternal single-dose PK of Tenofovir/PMPA gel**
  - **? Altered/increased absorption in late pregnancy**
  - **Compare to non-pregnant recent historic controls**

  2. Assess placental transport (fetal exposure) of single-dose Tenofovir/PMPA gel

MTN-002 Proposal

- Phase I, open label, Pharmacokinetic and safety evaluation
- 10 Healthy term HIV (-) (≥ 37 gestational weeks) parturients
  - Scheduled elective cesarean sections
  - No suggestion of placental disease
    - No IUGR, DM, HTN, CTD, etc.
- Single-site in Pittsburgh-collaboration with NICHD funded pregnancy pK unit

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MTN-002

- Protocol in development for proposed submission to PSRC for review in June 2007
- Anticipate that there will be multiple questions regarding this protocol from NIH and FDA
- Hope to have protocol implementation in October 2007

Where Are We Now for PMPA Gel?

- Extended safety study (059) will be completed in October 2007
- CAPRISA 04 will evaluate effectiveness of coitally dependent 1%tenofovir gel in a phase 2B study initiated May 2007 (USAID/FHI)
- Vaginal pharmacokinetic study (CONRAD) will be completed December 2007
- Oral vs vaginal pK and acceptability study (MTN 001) will be implemented Nov-Dec 2007
- First pK data for PMPA gel in pregnancy (MTN 002) completed by June 2008

Background: Oral Tenofovir

- Monotherapy with oral tenofovir not a clinically recognized treatment strategy
  - Significant potential for development of resistant virus
  - Resulting impact on future treatment strategies

Oral Versus Vaginal Tenofovir For Pre-exposure Prophylaxis for HIV

- Several large studies are underway evaluating “a pill a day” for prevention of HIV in high risk populations
- Some studies have been stopped due to ethical concerns and community activists activity but several more are being planned or are underway
- Evaluation of oral versus topically-applied products for prevention of HIV a top priority

MTN-003

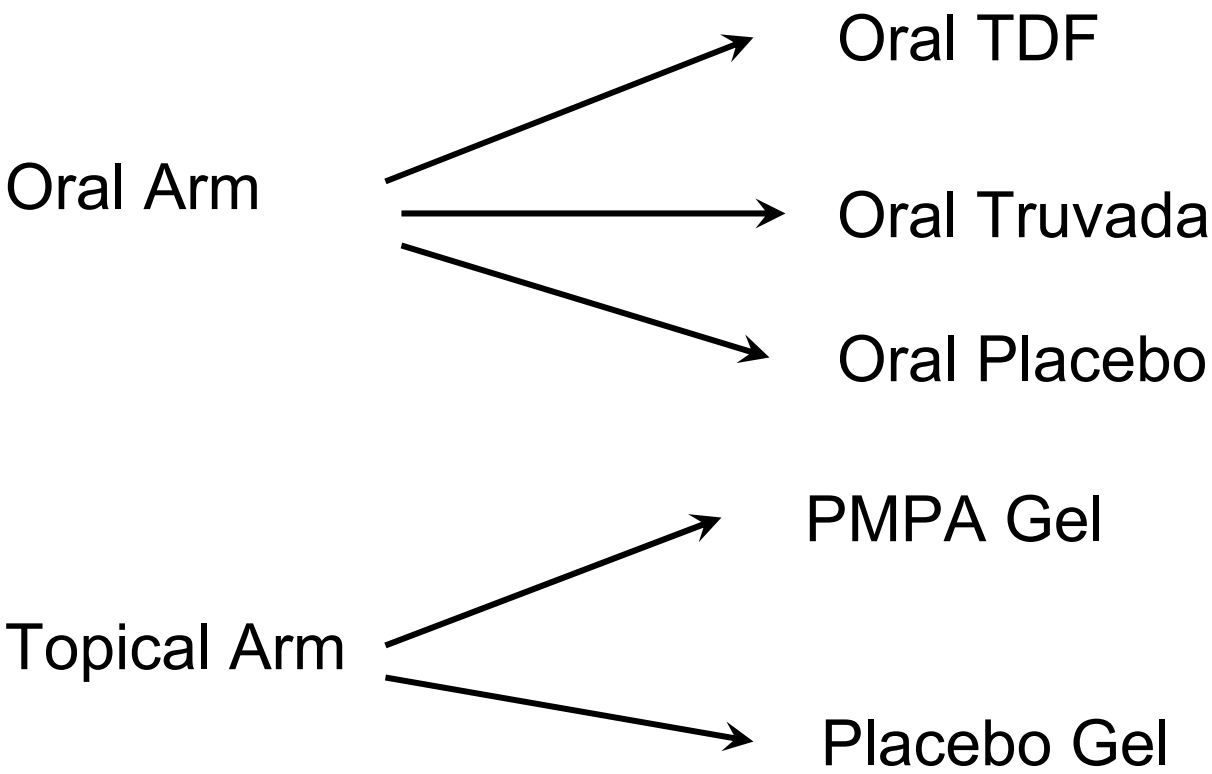
- Equipoise re: effectiveness and requirement for daily topical versus systemic administration
- Theoretical advantages for either route of delivery
  - Topical: lower systemic exposure, toxicity, resistance
  - Oral: easier administration, possible rectal protection
- Answers “cutting edge” question in prevention

Why a head to head trial?

- Each approach carries specific theoretical and operational advantages
  - vaginal use may confer less systemic toxicity
  - oral use is less closely linked to sexual practices, and can be administered by the woman without knowledge of her partner
- Theoretical reasons to favor either approach for efficacy and/or selection of resistance
- Only a head-to-head trial of these two approaches will answer this question

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 from populations having HIV seroincidence of >3% per year**

Sample size

- **Single Pivotal Trial**
- **Phase 2B Proof of concept study**
  - **1/4 to 1/3 of size of Phase III with 1.5 Strength of Evidence**
- **90% power to detect 55% effectiveness (false+ error rate 0.25%)**
- **Ruling out lower efficacy of 25%:**

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

$\Rightarrow$ 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.

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

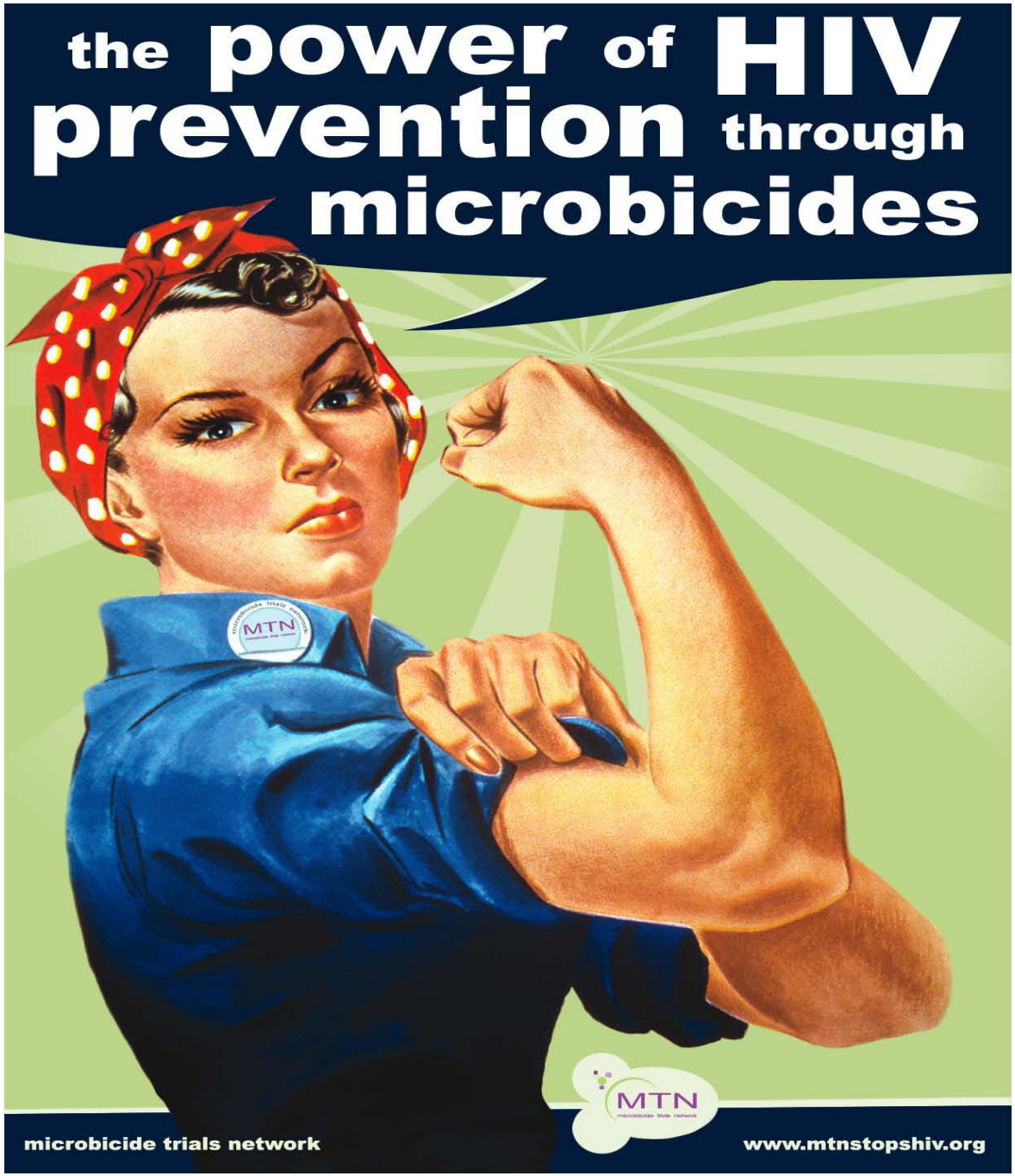
- Comparison not fully powered but will provide some evidence on the potential physical barrier/lubrication effects of placebo gel

How Will We Look For Tenofovir Resistance?

- Theoretical concern taken seriously
- Two-tiered approach
  - Standard resistance testing (detects variants comprising 30% of population)
    - Perform in real-time
  - More sensitive assays
    - Allele-specific RT-PCR detects 0.1%
    - Single genome sequencing – identifies new variants at low frequency ~ 1%

MTN-003 Proposed Design : Timeline

- Formal concept to be submitted to NIH for funding consideration in May 31, 2007
- Site and community feedback in Africa May 21-24, 2007
- Presentation of MTN-003 design to DAIDS Leadership, other network leaders and external advisors on June 27, 2007
- Develop protocol in Q3 of 2007
- Initiate community preparedness activities surrounding study of oral verses vaginal PrEP Q3 2007
- Submission for DAIDS review Q4 2007
- IRB submission and site training Q2 2008
- Initiate enrollment in Q3 of 2008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