Multipurpose Prevention Technologies *for* Reproductive Health

Accelerating Research on Multipurpose Prevention Technologies for Reproductive Health

Challenges in MPT research: limitations, gaps and opportunities

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First challenge for researchers: select appropriate MPT product for development

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- IMPT consultations on MPT Target Product Profiles and on a preliminary prioritisation of product pipeline. Considered a range of indications.

- A useful start as general guidance, but diversity of needs according varied epidemiology between different global regions - and even within countries (eg pockets of high HIV incidence in India). Cultural diversity (acceptability issues). Time to involve end-users (women and men).

- Several MPTs needed to cover these situations, and also to provide choices.

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- Against these general criteria, select products for R&D that are:

  - potentially capable of making a significant public health impact.

  - potentially achievable within an acceptable time-frame.

- Pre-clinical research (modest resource needs); clinical research (increasingly complex/costly).
- Few MPT products will reach Phase 3 trials.

Limitations to currently available products

- Wide range of drugs, devices, drug-device combinations and multipurpose RH vaccines in **early** or **later** stages of development.
- Hormonal contraceptives (HCs) for preventing unwanted pregnancy: effective and well-tried approach. Oral tablets, injectables, implants, vaginal gels or intravaginal rings.
- But associated with common undesirable side-effects.
- Debate continues about HCs and enhanced risk of acquiring HIV.
- **Non-hormonal contraceptive agents deserve further attention.**

MPT intravaginal rings (IVRs)

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CHALLENGES

- Incorporate sufficient API into ring material or into reservoirs within the IVR.
- Attain fairly constant and sufficient rate of drug elution:

  - *in vitro*.

  - *in situ,* PK/PD studies, measuring drug levels in vaginal secretions and in epithelial tissue biopsy samples.

  - methodology for biopsy studies is important and is evolving, including evaluation of inhibitory drug levels by infecting biopsy specimens with HIV. Relevant to intravaginal rings, gels and oral PrEP.

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For ring or gel containing two or more APIs, eg contraceptive and ARV agents, need to rule out:

- physico-chemical incompatibility within the ring or in the gel.

- toxicity of the drug combination.

- interference of one drug with the other in terms of elution behaviour *in vitro* and PK/PD with the ring *in situ*.

Two MPT gaps

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1. Need for non-hormonal contraceptives

- Spermicidal contraceptives used pericoitaly are particularly useful to women who:
  - have sex fairly infrequently
  - wish to avoid side-effects of HCs
  - want immediate yet quickly reversible contraception
- Unfortunately, currently available spermicides use nonoxynol-9, octoxynol-9 or benzalkonium chloride. Irritant and inflammatory properties. Nonoxynol-9 shown capable of increasing HIV risk in women.

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2. Need for agents to prevent common bacterial STIs and other RT infections

eg chlamydia, gonorrhoea, BV.

Ideally: safe, effective, affordable vaginal spermicidal/antimicrobial products, free of surfactants and hormones. Could have considerable public health benefit for India and in other regions.

Contraceptive gel, no hormones or surfactants

- **Acidform**: Low pH gel, originally formulated by TOPCAD, Rush University, Chicago, as a microbicide; further development (Amphora) by Evofem, San Diego [AS independent consultant].
- Potent spermicide *in vitro* and intravaginally.
- Phase 3 contraceptive trial in progress (2800 women): non-inferiority vs Conceptrol (4% nonoxynol-9). Currently >60% complete; open-label design, data so far indicate *at least* as safe and as effective as Conceptrol. Not a surfactant. Anticipate submit for US FDA approval end-2013. Trial in India under consideration to meet DCGI requirements.

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Stand-alone vaginal contraceptive AND as a replacement for nonoxynol-9 spermicides for use with diaphragms such as SILCS (studies required: compatibility, safety, acceptability, efficacy etc).

Antimicrobial activity

- *In vitro,* Acidform inactivates *Neisseria gonorrhoeae, Chlamydia trachomatis,* HSV-2, HIV and HPV, as well as many BV organisms. No effect on lactobacilli.

- Protects mice from genital challenge with *N. gonorrhoeae, C. trachomatis and* HSV-2.

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- Antimicrobial activity **in part** due to low pH (3.6).

- Contains **2% L-lactic** acid, a potent microbicide against genital pathogens. Richard Cone and colleagues [Microbicides 2012, Sydney]: lactic acid molecule itself, not just acidic pH, potent microbicidal effect on HIV, *N. gonorrhoeae* and many BV organisms; **not** other acids tested at same pH. L-lactic acid 20-40x more potent than D isomer.
- Harmless to lactobacilli.

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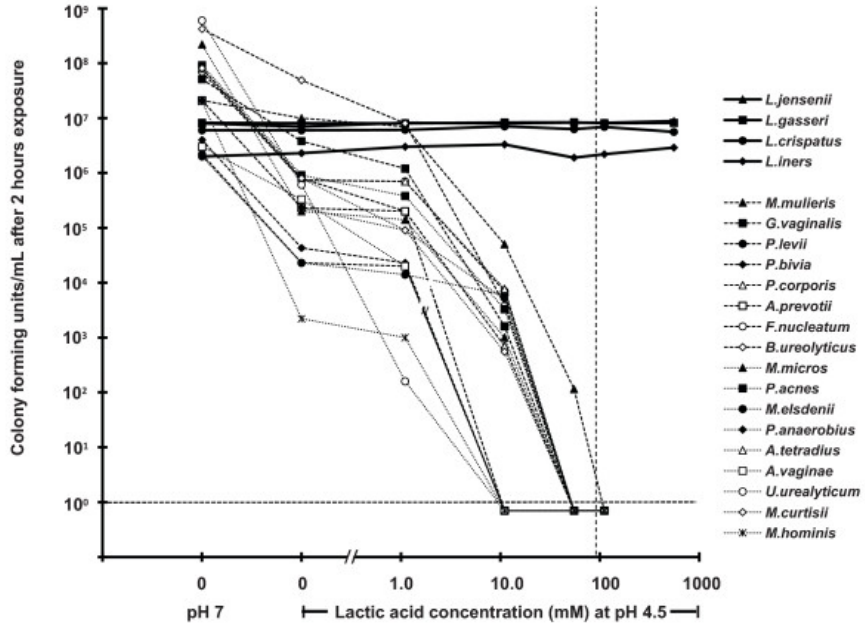
QUESTION: will at least some of these laboratory antimicrobial findings translate to the clinic? Definitive trials planned. CHALLENGES: identify populations at high-risk of STIs, define end-points, maximise adherence, access funding.

QUESTION: Will women using HCs, IUDs, sterilisation as main method of contraception - none of which protect against STIs - use antimicrobial Acidform pericoitally to protect themselves from infection?

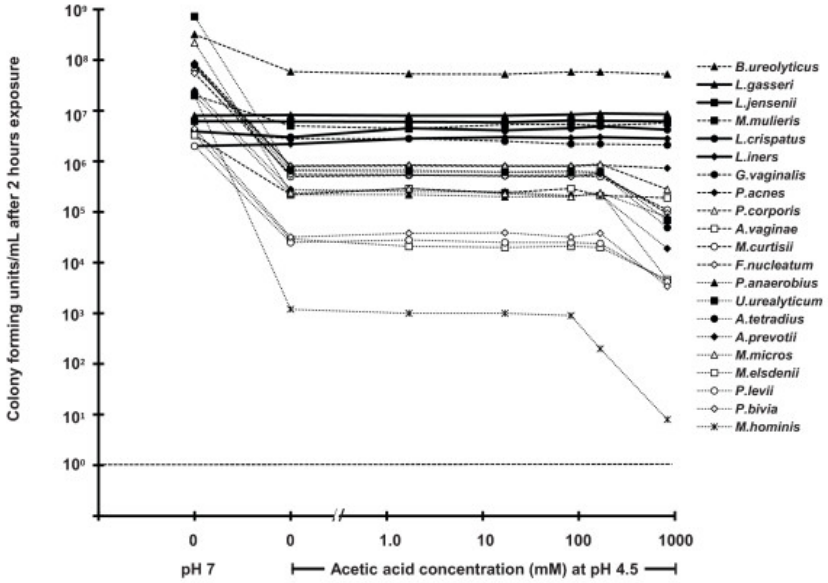
Antimicrobial activity of lactic and acetic acids at pH 4.5

From: O'Hanlon, Moench and Cone, BMC Infect Dis 2011; 11:200

Lactic acid at pH 4.5



Acetic acid at pH 4.5



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Opportunity: Acidform combined with tenofovir

Potential merits if it can be achieved: unwanted pregnancy, HIV, HSV-2, other STIs?

CHALLENGES:

1. Possible to get sufficient (1%) drug into solution at pH 3.6?
2. Will the ARV stay in solution?
3. Chemical stability of ARV in Acidform environment?
4. Will special physical characteristics of the gel be retained?
5. Shelf-life of the combination?

6. Will the ARV reach inhibitory concentrations in genital epithelia if delivered in this gel at this pH?
7. Will the ARV interfere with the spermicidal potency of the gel?
8. Safety of the combination?
9. REGULATORY: Extent to which safety data, spermicidal studies *in vitro* and *in situ,* and PK/PD studies regarding the ARV component, might contribute to the regulatory approval process for this MPT?

Achieved so far: 1-5.