

Community trials of vaginal microbicides

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Introduction

- Phase III RCTs of candidate microbicide products are necessary
- To measure effectiveness and safety of product in target populations
- General principles of RCTs are well known
- Some specific issues need to be considered in microbicide trials

Outline of talk

- Choice of study populations
- Inclusion/exclusion criteria
- Generalisability of results
- Primary and secondary endpoints
- More complex designs

Study populations for Phase III trials

- High HIV incidence
- Low HIV prevalence at baseline
- High follow-up rate
- High compliance with product use
- Acceptability of voluntary counselling and testing for HIV

Number required per arm for 90% power

	Efficacy 50%		Efficacy 75%	
Control incid.	0% loss	20% loss	0% loss	20% loss
1%	6299	7874	2333	2916
2%	3149	3936	1166	1457
5%	1260	1575	467	584
10%	630	787	233	292

Study populations for Phase III trials

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Inclusion criteria: Age

- Legal age of informed consent \Rightarrow minimum age
- HIV incidence may decrease in older women
- Generalisability \Rightarrow avoid limits that are too restrictive

Inclusion criteria: Coital frequency

- High frequency of product use may result in adverse effects
- Limits will depend on findings from Phase I/II trials
- May be handled via choice of population rather than explicit inclusion criteria

Inclusion criteria: HIV status (1)

Option 1: Only recruit women testing HIV-negative

- Maximises study power for measuring effect on HIV acquisition
- Avoids ethical issues over notification of HIV test results
- May be difficult in populations where acceptability of VCT is low

Inclusion criteria: HIV status (2)

Option 2: Recruit women irrespective of HIV status with optional VCT service

- Need larger sample size for main endpoint of HIV incidence
- More feasible where VCT acceptability is low
- Avoids stigmatisation of HIV-positives

Inclusion criteria: HIV status (3)

Option 2: Recruit women irrespective of HIV status with optional VCT service

- Allows measurement of effects in HIV positive women:
 - Safety
 - STDs
 - HIV infectivity?

Inclusion criteria: Fertility intentions

- Issue: Product use may be contraindicated in pregnancy
- Should women intending to become pregnant be excluded?
 - Over what period?
 - Reliability of reporting
 - Alternative: Frequent follow-up and exclusion of women who become pregnant

Inclusion criteria: Vaginal douching

- Widespread in some populations
- Likely to reduce effectiveness of product depending on timing
- Alternatives:
 - Exclude women who report regular douching
 - Include but counsel to avoid douching during product use

Inclusion criteria: Anal sex

- Efficacy of vaginal use will be reduced if women engage in anal intercourse
- *Problem:* May be difficult to obtain reliable information from individuals on practice/frequency of anal sex
- May seek to avoid study populations in which anal sex thought to be common

Inclusion criteria: Endnote

- *Comparability* of effects over populations may be enhanced by adopting stringent inclusion criteria
- However this approach may reduce the *applicability* of the results to a low level in any particular population

Efficacy or effectiveness?

$$\text{Product efficacy or effectiveness} = 100 \times (1 - \text{RR}) \%$$

- *Efficacy* refers to effect when used under “optimal conditions”
- *Effectiveness* refers to effect under “routine implementation”
- Phase III aim to measure *efficacy* but use is always likely to be sub-optimal

Generalisability of results (1)

Measured efficacy may vary between populations due to multiple factors:

- Compliance:
 - Frequency and correctness of product use (with infected partners)
 - How measured?
 - Questionnaires? – Coital logs?
 - Product counts?

Generalisability of results (2)

- Frequency of condom use
 - Efficacy likely to be different when used together with male or female condom
 - Same measurement issues apply

Generalisability of results (3)

- Frequency of sex
 - Frequent product use may lead to toxicity and increased transmission
- Frequency and timing of vaginal douching

Generalisability of results (4)

- Prevalence of STDs
 - Effect on HIV incidence may be enhanced if microbicide also protects against STDs
 - Or reduced if product less effective in presence of genital lesions

Generalisability: Endnote

- Limited generalisability argues for *multiple* trials in different populations
- Factors modifying effect should be *measured* and taken into account when comparing trial results
- Some argue for *multi-centre* trials to obtain “average” effect over a range of populations

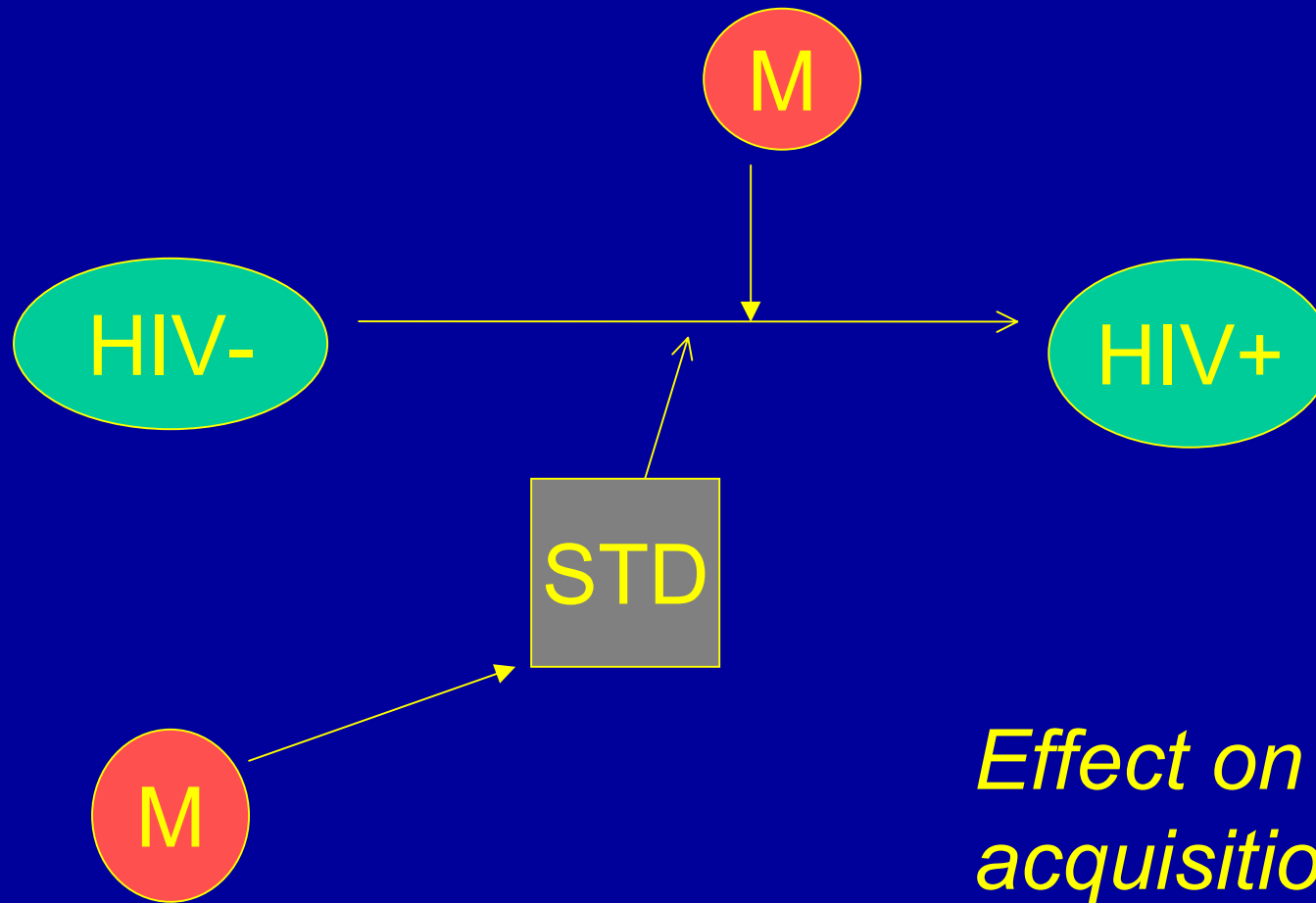
Primary endpoint

- HIV incidence

Secondary endpoints (1)

- Prevalence and incidence of STDs

Mechanisms of action



Effect on HIV acquisition

Secondary endpoints (1)

- Prevalence and incidence of STDs
 - Self-reported STD syndromes?
 - Cervical swabs for NG/CT
 - Vaginal swabs for TV/BV
 - Clinical exam for GUD plus multiplex PCR for HD, TP and HSV2
 - HSV2 or TP seroconversion

Secondary endpoints (2)

- Adverse effects (on sub-sample?)
 - Questionnaire
 - Speculum examination
 - Colposcopy

Secondary endpoints (3)

- Changes in risk behaviour (*risk compensation*)
 - Number of sexual partners
 - Frequency of condom use
 - Difficult to measure in placebo-controlled trial
 - Compare with pre-recruitment?
 - Three-arm trial with non-placebo controls?

More complex designs

- Standard Phase II trial in HIV-negative women measures efficacy against HIV acquisition
- May wish to assess:
 - Efficacy against HIV transmission
 - Community-level efficacy

Effects on HIV transmission

- Could assess in Phase III trial by:
 - Randomising HIV-positive as well as HIV-negative women
 - Measuring HIV viral shedding in genital secretions
 - Recruiting HIV-negative male partners (*discordant partners study*)

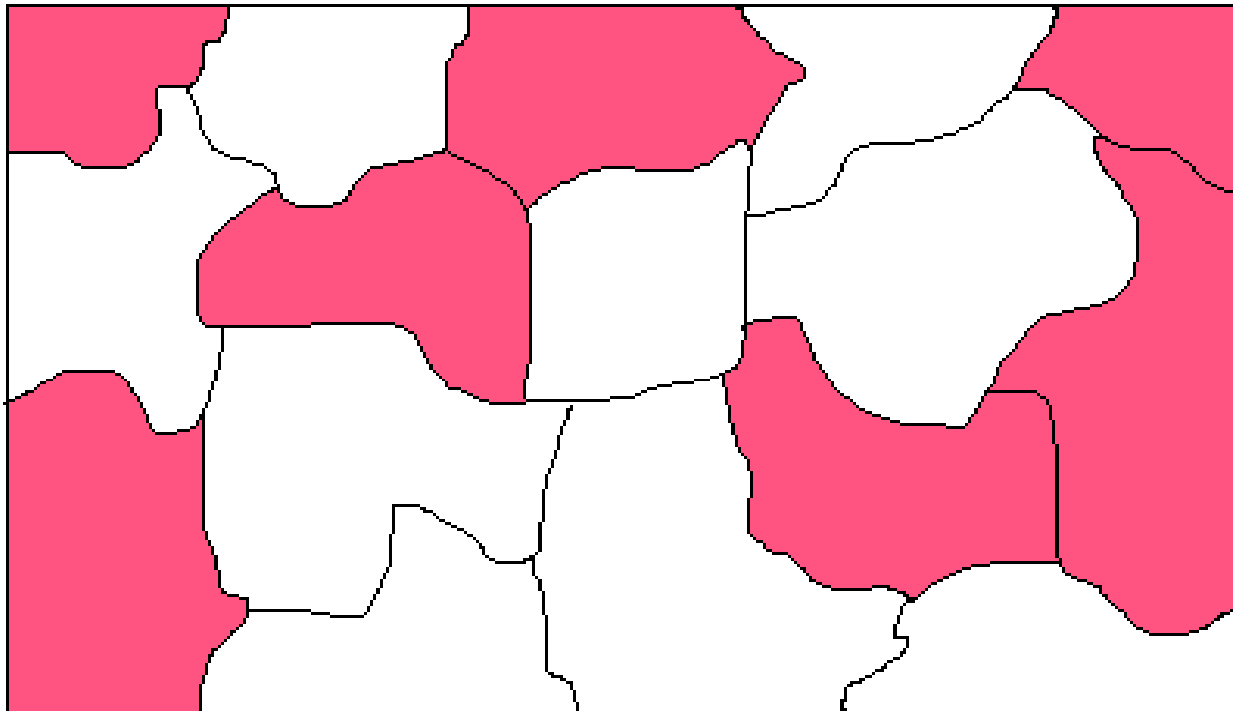
Community level effects (1)

- Modelling suggests population level effects of microbicide use at plausible levels of efficacy and use may be substantial
- May wish to measure community level impact of programme to promote microbicide use among at-risk women in general population

Community level effects (2)

- Randomise communities to intervention and comparison arms
- Capture overall effect of microbicide use:
 - Effect on HIV acquisition
 - Effect on HIV transmission
 - Herd effects (on HIV *and/or* STDs)
 - Behaviour change (positive or negative)

Example of community randomised trial design



Community level effects (3)

- Likely rationale of CRT is to measure *effectiveness* of sustainable programme to promote microbicide use
- Might follow on from Phase III *efficacy* trial
- Phased introduction of intervention: eg. *stepped wedge* design

Endnote

- Phase III trials raise a number of special issues not usually encountered in standard RCTs
- We will continue to learn how to do these trials as the microbicide initiative expands
- Importance of exchange of experience between trial groups