

Microbicides 2002
Track B Summary
Clinical Science

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May 15, 2002

Clinical Development Pipeline for Microbicides – Stages of Development

Product	Phase I Vaginal HIV-uninfected	Phase I Vaginal HIV-infected	Phase I Penile HIV-uninfected	Phase I Penile HIV-infected	Phase I Rectal Safety	Post-Coital Activity	Phase I/II Expanded Safety	Phase II	Phase II/III HIV Prevention	Contraceptive Efficacy	Phase III HIV Prevention	Other
Acid Buffers/Enhancers of Vaginal Defenses												
BufferGel	HPTN ReProtect	HPTN ReProtect	GMP ReProtect	HPTN ReProtect	HPTN ReProtect	NICHD CONRAD ReProtect			HPTN GMP ReProtect	NICHD ReProtect		BV tx; Shedding - ReProtect
Acidform	CICCR		GMP			GMP	GMP					BV tx GMP
Lactobacil. Suppos.	DMID											BV tx - DMID
Praneem Tablet	India MRC											
Surfactants												
Savvy (C31G)	Biosyn		GMP Biosyn			GMP Biosyn	GMP Biosyn		Biosyn	NICHD Biosyn	FHI	Chlamydia prevention – Biosyn
Invisible Condom	Laval University											
Entry Inhibitors												
Dextrin Sulfate	EC ML Labs	EC ML Labs	ML Labs	ML Labs				EC ML Labs			UK MRC ML Labs	
Carraguard (PC 515)	Pop Council	Pop Council	Pop Council CDC		Pop Council		Pop Council	Pop Council CDC NIAID			Pop Council CDC	
Cellulose Sulfate (CS)	CICCR	HPTN GMP	CICCR		GMP		WHO/GMP			CONRAD CICCR	GMP CONRAD	Imaging – GMP
							GMP/FHI (2)				FHI	Imaging - GMP
Polystyrene Sulfonate (PSS)	CICCR		GMP				GMP			CONRAD CICCR	GMP	Imaging – GMP
PRO 2000	HPTN Interneuron	HPTN Interneuron	GMP	HPTN	HPTN		EC Interneuron	EC	HPTN Interneuron		UK MRC	
							HPTN					
Replication Inhibitors												
Tenofovir (PMPA)	HPTN Gilead	HPTN Gilead										
Status:	Finished		Ongoing		Planned							

Phase I Vaginal Studies

Product	Mechanism	Duration of exposure	Dose/frequency	Controls	Colposcopy	Other Measurements	Outcome
C31G	Surfactant	14 days total	3 doses/1x then 2x	3% N-9	0, 7, 14 days	absorption; microflora; cytology – All OK	0.5%; 1% low irritation 1.7%; N-9 similar
Invisible Condom	Surfactant	14 days	1x/2x	None	0, 7?, 14 days	pH; microflora – all OK	No lesions/ulceration; few mild symptoms
Praneem tablets	Polyherbal	7 days	1x	None	0, 9 days	Systemic effects; cytology – all OK	No lesions/ulceration
Dextrin sulfate	Inhibition of attachment	28 days	2x	Placebo; no treatment	7, 14, 28 days	Systemic effects microflora	No lesions/ulcerations

Determinants of Appropriate Dose/Volume

Cervicovaginal Lavage

- To measure conc of PRO 2000 after vaginal application. Use of 5ml CVL representative of post-coital volume.
 - 2 hrs post first dose of 0.5% (5.3X) and 4% (123X) min inhib conc (>25 ug/ml)
 - 12 hours post – 0.5% (5/12); 4% (10/12) exceeded mic

Spread Assessment Techniques

- Non-invasive imaging using MRI
 - Reproducibly evaluate in vivo distribution; high spatial resolution
 - Spread dependent on volume; time; ambulation; sexual activity
 - Gel moves into upper reproductive tract in 50% of subjects
- Optical device inserted vaginally
 - High spatial resolution; different gels distribute differently

Phase II Microbicide Studies

Carraguard

- Thailand: 165 women enrolled in a RCT; 12 months use of product min 3x/week
 - 83/95% follow-up; 89/91% gel use; 73/62% condom use
 - No HIV; low STDs similar in both groups; BV 23/34%; no difference in rate of genital lesions
- South Africa: 400 women enrolled in RCT; 6-12 months use of product min 3x/week
 - 66/60% gel use during >75% of sex acts; HIV/STD rates similar in both groups; high STD/HIV prevalence during screening

Clinical Safety Issues and Regulatory Perspectives

- Rationale for placebo/no treatment arms in early studies
 - Insufficient info on background rates of vaginal lesions in sexually abs/active women
- Duration of exposure – 14 days/2x per day
- Routine colposcopy in early studies
 - Issues of standardization; relevance of findings
- Measure systemic exposure
- Social harms

Male Tolerance Studies

Product	Mechanism	Duration of exposure	Dose/frequency	Controls	Measurements	Outcome
Cellulose sulfate	Inhibition of attachment	7 days	1x/day	Conceptrol (1:2 random)	Naked eye exam; urine leukocyte esterase	1/24 vs 3/12 tingling/dry skin, etc
PRO 2000	Inhibition of attachment	7 days	1x/day	placebo	Same as above; absorption	Flaking of product
Buffergel	Acid buffer	7 days	1x/day	KY Jelly	Same as above	Mild dryness, etc
C31G	Surfactant	7 days	1x/day	?	Same as above	ongoing
PRO 2000 Buffergel (HIV+ men)	See above See above	7 days cross-over design	1x/day	placebo	Same as above	Well-tolerated/ongoing
Dextrin sulfate (IV-/+ men)	Inhibition of attachment	14 days	1x/day	placebo	Same as above	No clinically signif diff.

Rectal Microbicide Studies

- Data from a number of previous cohort studies – 10% of women report engaging in anal sex in the last six months
- Rectal mucosa – easily damaged, porous columnar epithelium that heals rapidly
- Methodological challenges (NIH Rectal Microbicides Workshop)

Safety Issues in Rectal Microbicide Studies

Safety issues

- Clinical (eg anoscopy) and pathology (biopsies/lavage) assessment in real time pre/post exposure
- Evaluate effect on rectal inflammation and HIV shedding for both ART treated and untreated HIV-infected men.
- Pap smears and rectal biopsies may provide complementary information about inflammation and epithelial disruption.

Physical Barriers

The role of the cervix

- Unique susceptibility of columnar epithelium—fragile like rectal tissue
- Portal to upper reproductive tract
- Uterine uptake of vaginal fluids

Diaphragm

- Dual protection mechanical and microbicidal when used with an effective microbicide – retrospective cc studies
- Allergy to latex; UTIs, toxic shock
- Pilot study in Kenya of acceptability in preparation for STD RCT efficacy study (on-going)

Phase III Trial Design

RCTs

- The gold standard for microbicide phase III trials
- Community-level randomization
- Intent-to-treat
- Compliance subgroup analyses
 - error-prone compliance data
- Generalizability of results/multiple sites and popul.
- Run-ins; multiple control groups; LARGE trials

STI outcomes

- Effects of products on STD detection assays

Phase III Implementation

Minimizing loss-to-follow-up

- Build trust
- User-friendly environment
- Home visits
- Group appointments
- Committed staff

Lessons from the past

- Political support (health authorities, policy makers)
- Ethical reviews
- Community collaborations; Participant/community education; informed consent; access to care
- Cohort studies; phase I's
- Laboratory – communications/couriers

Clinical Effectiveness: The Regulatory Perspective

The “Perfect” Study

- Appropriately designed; adequate randomization and blinding
- Tight confidence intervals
- Multiple sites/populations with internal consistency; bridging populations
- HIGH follow-up
- Good Clinical Practices

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Summary of the Summary

- High quality clinical microbicide trials can be done – with the right preparation and resources
- The Science is Easy!! - setting up the programs for access is the hard part.
- Need to build it TODAY – the perfect segue into Track C