The NIH Pre-Clinical Pipeline: The Role of the IPCP-HTM Program in Clinical Advancement of Candidates

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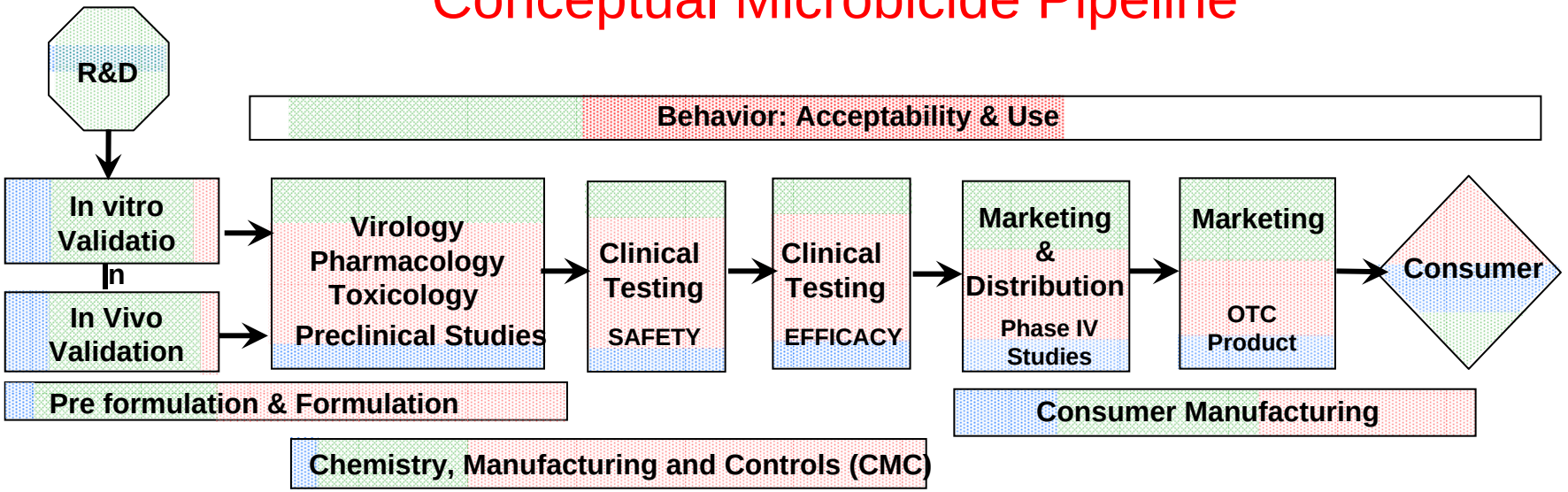
What is Really Needed to Advance a Microbicide to Clinical Testing?

Conceptual Microbicide Pipeline



- Federal, Local and State Regulations
- Product Specific
- FDA requirements

A little Closer look!

Preclinical

General Preclinical Virology

- Antiviral activity
- Toxicity Cell lines/Primary cells
- Range of Action--Subtypes
- Mechanism of Action
- Resistance
- Combination
- Relevant Matrices

Preformulation ↓ Formulation

- Stability
- Sterility
- Homogeneity
- Purity

Microbicide Specific

Lab

- Condom Compatibility
- Effect on Lactobacilli
- Effect of Matrices
  - –Seminal Plasma
  - –Cervical fluid
  - –Mucin
- Other STIs
- Cervical Explants
- Murine, NHP safety and efficacy

Animal

- 10-14 day Rabbit Vaginal Irritation (RVI)
- Systemic Absorption by iVag
- Penile Irritation

Chemistry Manufacturing and Control (CMC)

Unformulated
Drug Product

Formulated
gel

Stability, Sterility, Packaging, Storage

PK and Toxicology

Systemic Absorbance following iVag admin.

Yes
iVag AND systemic

No
iVag, +/- Systemic

- Maximum tolerated dose (MTD)
- Acute Toxicity
- Chronic Toxicity, 90+ days
- PK and Metabolites (ADME)
- General Genotoxicity
- Carcinogenesis
- Reproductive toxicology
  - –Seg. I Reproductive performance
  - –Seg. II Teratology
  - –Seg. III Perinatal/Post natal
- Dermal/systemic Hypersensitivity
- Dermal/ systemic Photosensitivity

Applicator

Selection **Labeling**
Acceptability **Filling**

We Have More Questions Than Answers

What is required to identify a safe, efficacious and acceptable microbicide in the absence of the "proof-of-concept" in humans that a microbicide can prevent HIV transmission?

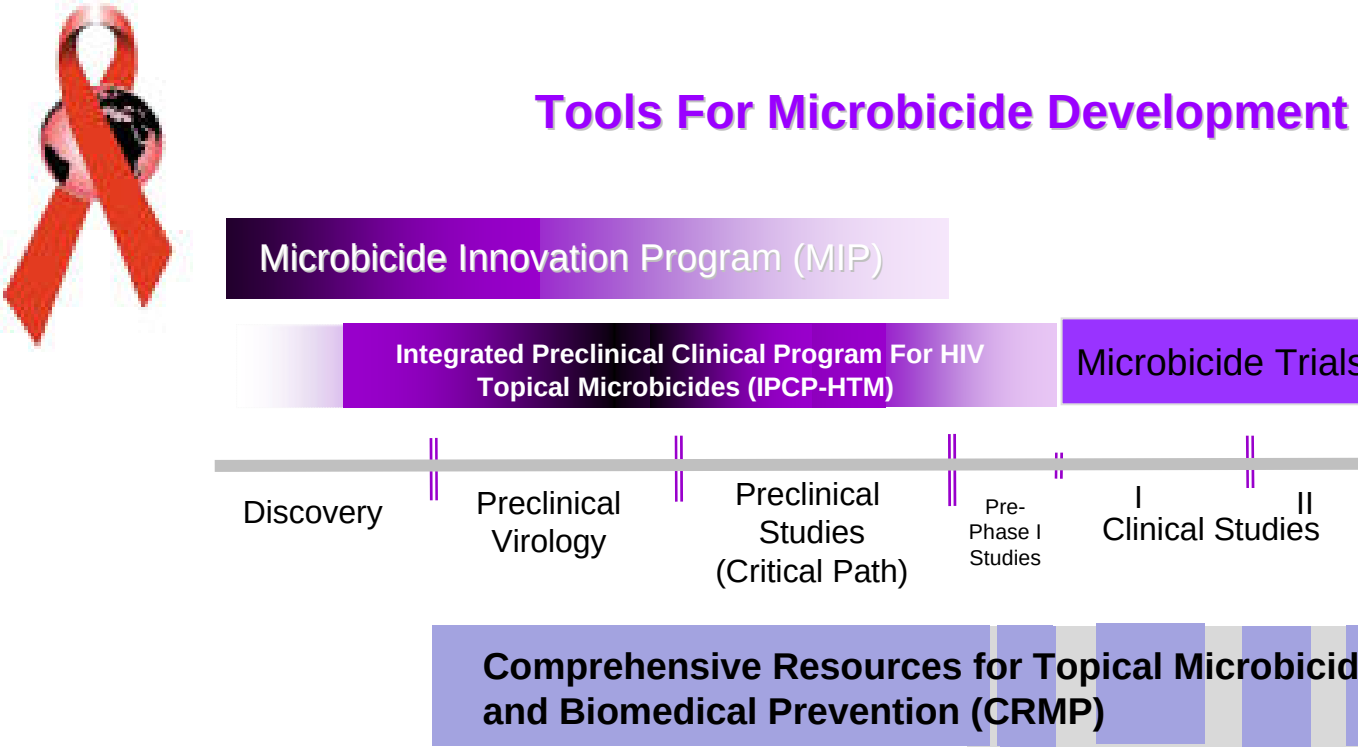
1. How do we measure safety, efficacy and acceptability?
   - Biomarkers
   - Acceptability tools
   - Tools to measure microbicides impact on the mucosal environment
2. What are the requirements for "protection"
   - Distribution
   - Microbicide properties
3. When do we need the microbicide–Coital, Pericoital, sustained protection

How is NIAID Addressing These Many Issues?

Targeted funding to:

- Support the preclinical development of promising candidates
- Support transition of candidates through critical path/preclinical development to create IND-enabled clinical candidates
- Support the development of basic and preclinical science required to enable microbicide development and clinical trials

Tools For Microbicide Development



Each Component Serves a Function

Microbicide Innovation Program (MIP) "**Engine for Innovation"**

IPCP-HTM : **"Engine for Development" = Mini-Pipelines**

MTN: "**Engine for licensure**"

Contracts: Sponsor Assistance Mechanism --Gap-filling

Integration of Components = Microbicide Pipeline

Why have the IPCP-HTM?

Enabling a microbicide for clinical testing requires meeting FDA and/or other regulatory agency (European, country specific), requirements are a complex and costly activity---Must minimally:

•Establish toxicology and pharmacology in animal models

•Ensure purity and stability of the Microbicide and its delivery system

Burdened by the fact that most of our tools to enable clinical testing must be adapted from oral or systemic drug requirements

The microbicide field is rapidly evolving and thus needs:

- New candidates
- Delivery systems ---Rings and films
- Technologies to:
  - Address safety issues as they arise
  - More efficiently select candidates for clinical testing
  - Study new delivery systems as they are developed:
    - Rings
    - Films
    - Novel gels ---smart gels, nano-gels

The Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM)

The Nutshell View

Multi-Project and -Core grant that requires an industry partner.
IPCP-HTM program may include Pre-phase 1 clinical trials

First awards in 2001---continuous (except for 2007)

- 27 awards
- >200 investigators involved
- >100 Peer reviewed publications
- >500 Presentations and abstracts at more than 20 national and international conferences, including CROI, Microbicides and IAS
- Developed Gels, Films and Intra-vaginal rings
- Has conducted 31 clinical trials

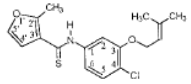
Small (Pre-Phase 1) trials designed to prioritize candidates or address pertinent scientific questions that advance microbicide clinical science

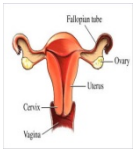
IPCP-HTM Program: 2010

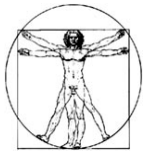
Overarching Objective: Support the Microbicide Pipeline

Currently 11 Awards in the IPCP-HTM Program

Inhibitors	Delivery Strategies	Approaches
1. Entry inhibitors ❖ Small molecule ❖ Large molecule 2. ART-based 3. Alternative strategies ❖ siRNA ❖ Protein ❖ Oligomers	1. Combination 2. Coital/non-Coital ❖ Gel ❖ Ring ❖ Film ❖ Lactobacillus	1. Vaginal 2. Rectal







The IPCP-HTM Contributions to the Clinical Pipeline

Select a "Best" formulation

Formulations

Rheological Properties
- **Viscosity**
- **pH**
- **Etc.**

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- **Preformulation**
- **Stability**
- **Formulation**

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Virology Activity in:
- **Primary cells**
- **Explants**
- **Etc.**

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Clinical Trials

- Vaginal/GI spread
  - Sitting ,standing, simulated coitus
- Semen simulant and virus surrogate
- Effect in Uterus

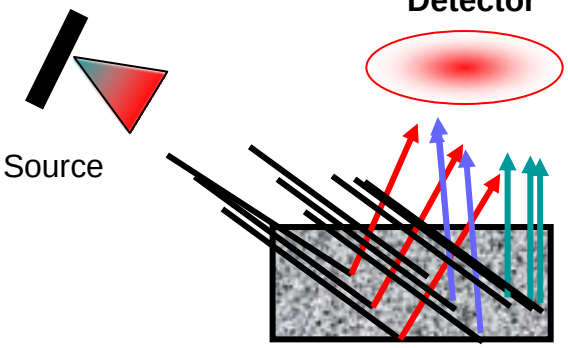
Other Clinical Trials

- New methods for detection of gels
- Optimizing detection methods
- Imaging to model GI or vaginal events

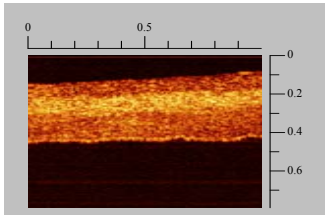
→ **Optimal Gel for a Clinical Trial**

Biosyn, Inc.: U19 AI051650
Anton: U19 AI060615
McGowan: U19 AI082637

New Safety Measures



Computerized Image



In Vivo Tissue Imaging
Develop scoring system

Rambouillet sheep

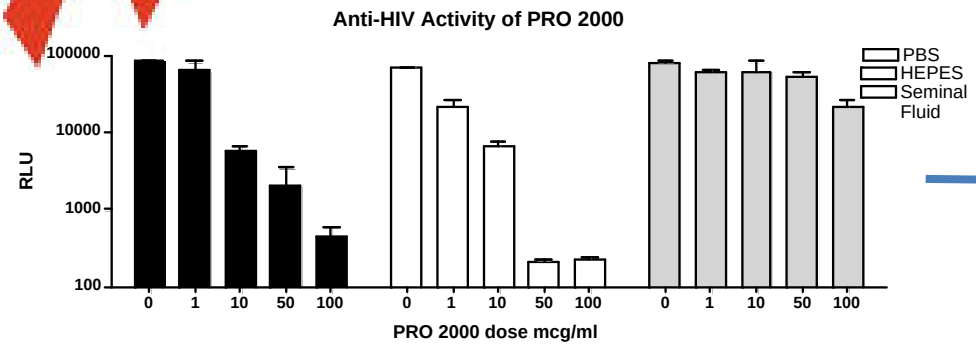
Clinical Trial

Evaluation of Optical Coherence Tomography (OCT) as a Safety Tool for Assessment of Vaginal Products

Women N=18
5.5 days 2 x day Conceptrol: Placebo
OCT pre-, last gel use and 7 days post
Acceptability and impact of OCT

Effect of Semen/Ejaculate on Microbicide Activity

IN VITRO



IN VIVO

Clinical Trial

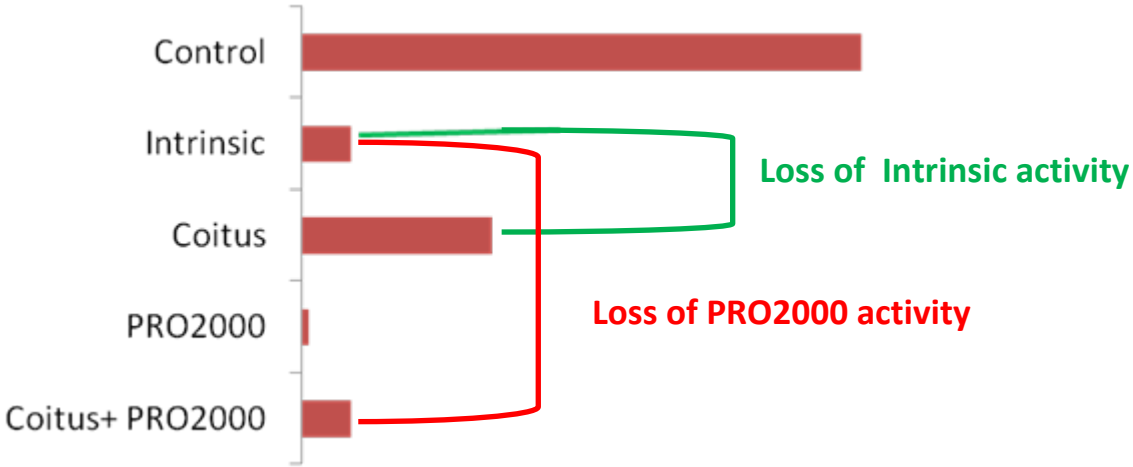
0.5% PRO2000, N=24, Measure vaginal response to PRO2000

No proinflammatory response

Decrease in hBD2, SLPI, IL-1RA, IgA

Does PRO2000 lose activity in vivo following sexual intercourse?

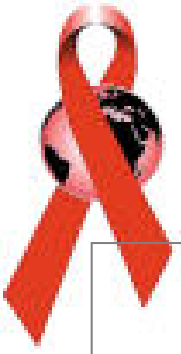
N=10 couples



Herold U19 AI077549
Keller U19 AI069551

Keller etal. AIDS 2007, 21:467
Patel et al. J,. Inf. Dis. 2007, 196:1394
Keller et al. PLoS One. 2010,5:e8781

Can Formulation Properties be Correlated with Acceptability?



Formulation

- Viscosity
- Osmolarity
- Shearing
- Stickiness
- Mixing /miscibility
- Color
- Spreading
- Coating
- Adhesion to surfaces

Link
Biophysical
with
Women's perception

Acceptability
Gels and Rings

- Leakage
- moisture
- Sexual pleasure
- Sexual comfort
- Removal &disposal
- Long residence
- Application

Focus group
in mano

Clinical experience

Identify specific formulation characteristic that yield specific women responses

Develop new tools to measure topical microbicide acceptability

Rectal Microbicide Program

Behavioral

Formulation /PK/PD

Safety

Distribution

Simulated Coitus
Semen and Virus Surrogates

UC781

First rectal use of vaginal formulation

Biopsy Challenge

Anal Health and Behavior Survey

Signs and Symptoms

Enemas

Safety

Vehicles

Aqueous and Lipid Formulations

Dose Form

RMP-02/MTN006

TNV oral and rectal gel

Acceptability

Delivery format:
Enema
Suppository
Applicator

Rectal Specific Formulations

Tenofovir, UC781, Combination

Rectal Microbicides

Microbicide Development Program

Behavioral component
Signs symptoms delivery format

Formulation and deployment
Osmolarity gel type

Rectal use of Vaginal gels
UC781 (RMP01)
Tenofovir (RMP02/MTN006)

- Safety
- Acceptability
- Trial Methods
- Surrogate markers

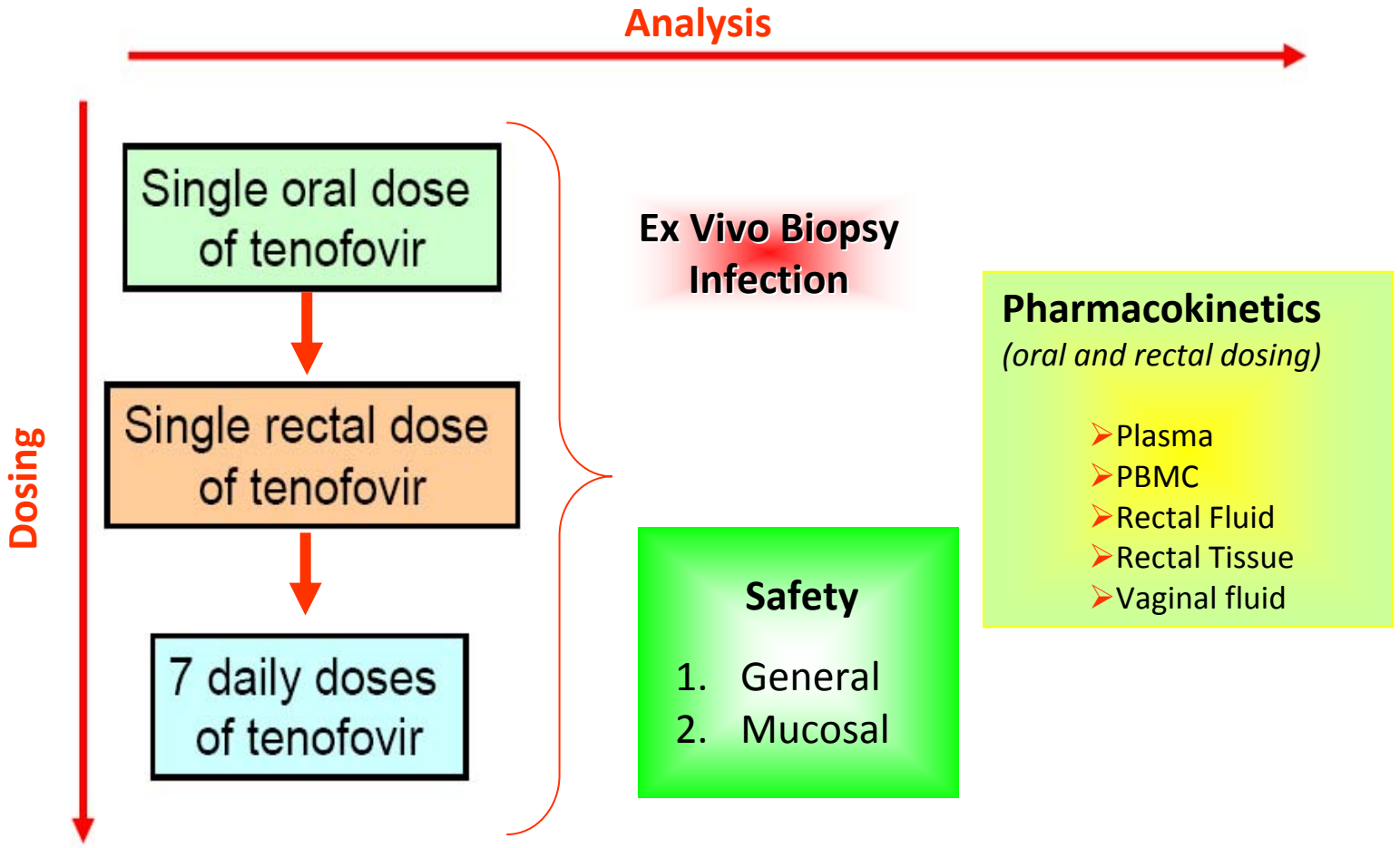
MTN007
Rectal 1% TNV gel

Combination HIV antiviral Rectal Microbicide program (CHARM)

Rectal specific Formulation
- Tenofovir
- UC781
- Combination

Anton U19 AI060615,
McGowan U19 AI082637

RMP-002/ MTN-006-A Unique Hybrid Trial by the MTN and the IPCP-HTM Program



Courtesy of Ian McGowan

IPCP-HTM and Rectal Microbicides

Creation of a pipeline

Preclinical Development

In vitro assays → Explants → NHP/BLT mice

Formulation and Deployment

Study 1 (N=9)
Hyper- iso- and hypo-osmolar
Acceptability, PK and safety (cytokines, explant challenge, permeability)

Study 2a (N=8)
Distribution of Possible Rectal gels
Water soluble
Lipid Soluble

Study 2b
Autologous semen
Simulated coitus

Behavior and Acceptability

Study 1
+/- RAI, HIV+, HIV- n=448 ♀, ♂
STI, RAI Symptoms, Anoscopy
Self-report Behaviors

Study 2
+/- RAI, HIV+, HIV- n=80 ♀, ♂
Rectal Microbicide Acceptability
OTC: Gel, foam, gel applicator, suppository, enema

Candidate selection

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Optimal distribution and gel characteristics

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Factors Impacting potential Rectal microbicide use

Wrap -Up

The IPCP–HTM has provided support for exploratory studies that are helping to:

1. Select candidates
2. Understand the interaction of microbicides with genital mucosa
3. Develop new approaches to measure safety, efficacy and acceptability
4. Creating a rectal microbicide pipeline