Microbicides

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Women as the Face of AIDS
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What is a Topical Microbicide?

An active agent or cocktail of active agents that prevents or reduces transmission of HIV and/or other Sexually Transmitted Infections when applied vaginally and/or rectally

How would a Topical Microbicide be used?

Delivery could be in the form of a:

- gel
- film
- sponge
- intravaginal ring or diaphragm
- bio-engineered naturally-occurring vaginal bacterial species

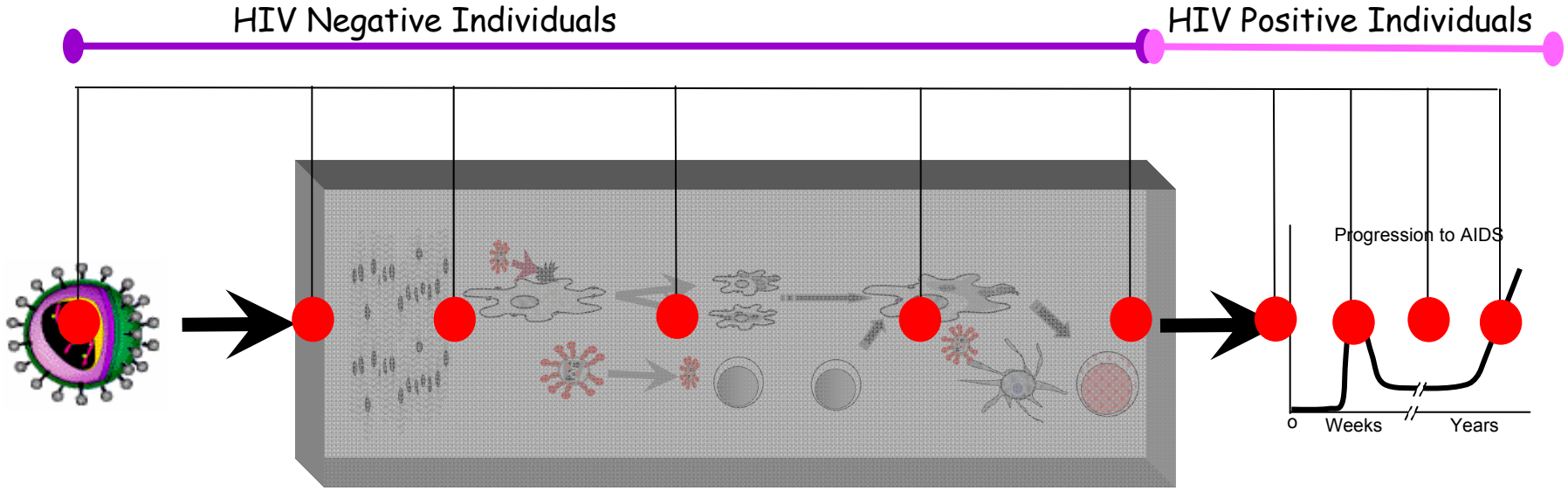
Coitally associated or independent

NIAID Topical Microbicide Program

Ultimate Goal

To identify and support/facilitate development of safe, effective and acceptable topical microbicides to prevent HIV/AIDS and other STIs

Intervention Points for Microbicides in HIV Infection and Disease



Characteristics of an Ideal Microbicide

- Safe, even with frequent use
- Effective
- Acceptable to target populations
- Widely available (OTC), inexpensive
- Easy to use, store
- Stable
- Broad activity (HIV and STDs)
- Independent of coitus
- Contraceptive or non-contraceptive

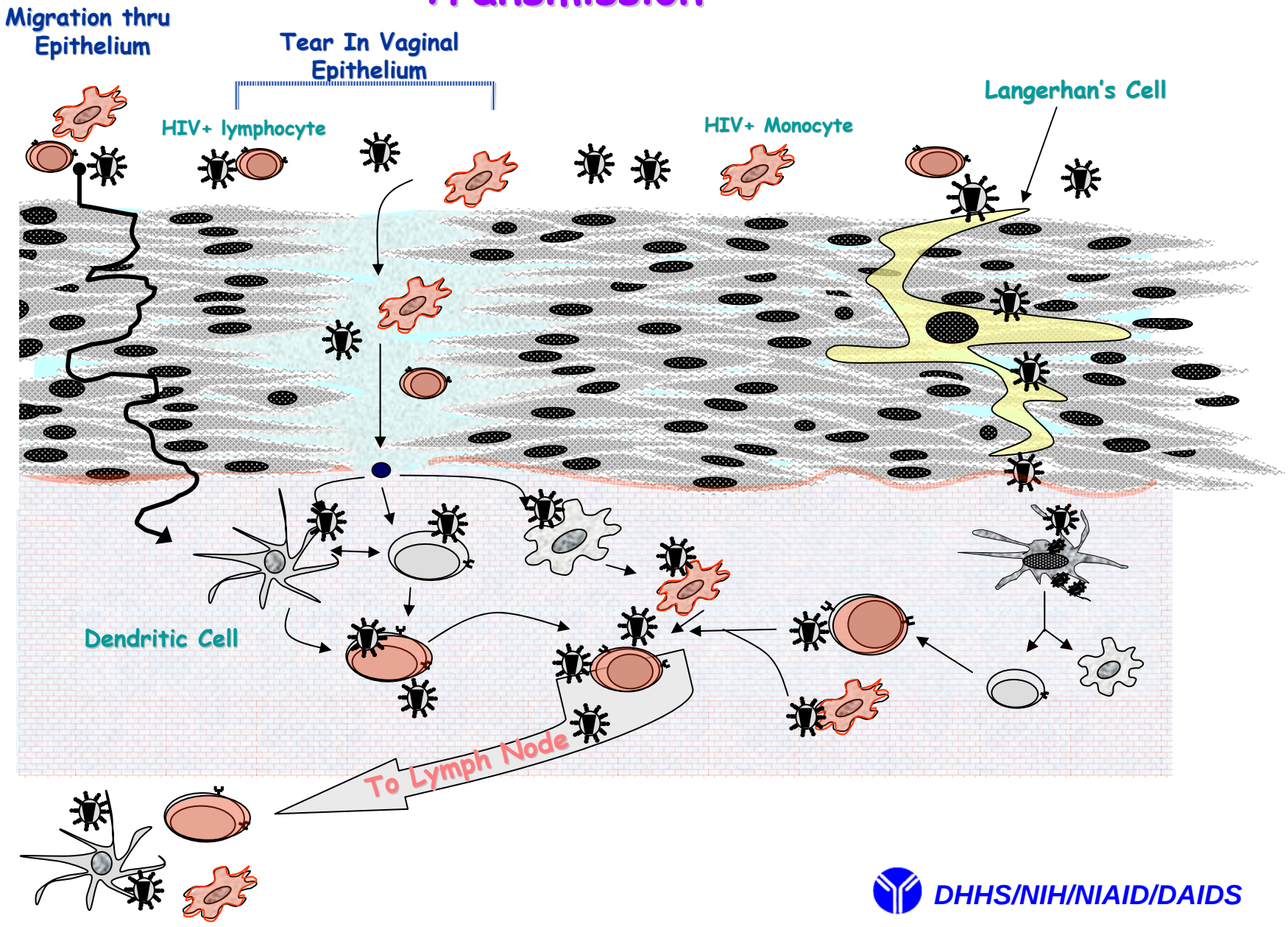
Products: Purposes and Indications

Singular indication product, e.g., HIV microbicide

Combination sexual health product, e.g., HIV microbicide + contraceptive

Combination disease prevention product, e.g., HIV + HSV microbicide

Proposed Mechanisms for Cervicovaginal HIV Transmission



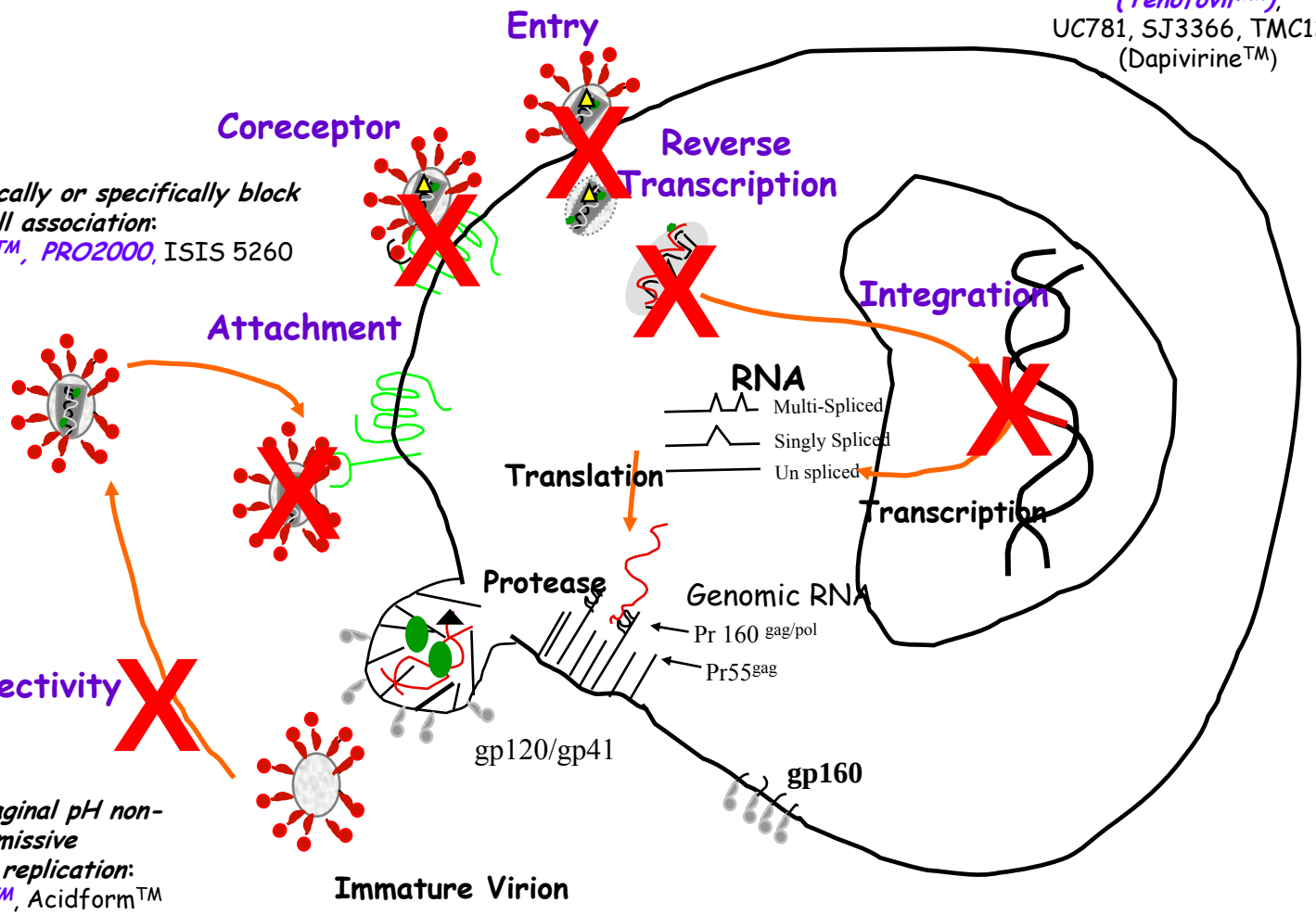
Possible Actions of Vaginally Administered Topical Microbicides

- Gel/cream lubricate and create a physical barrier
- Maintain normal microflora
- Prevent other STDs
- Viral inactivation or neutralization
- Inhibition of binding and fusion
- Inhibition of reverse transcriptase
- Inhibition of HIV-1 uptake by or infection of dendritic cells

What are the Potential Targets in the HIV Replication Cycle?

Block virus/cell gp120/CD4, gp41 and Coreceptor interactions:
SAMMA, PSC-RANTES, SCH-C, monoclonal antibodies, cyanovirin-N, *SPL7013*, T20, Griffithsin, CMPD-167, BMS-806

RT Inhibitors: ***Block reverse transcriptase enzyme***: *PMPA (Tenofovir™)*, UC781, SJ3366, TMC120 (Dapivirine™)

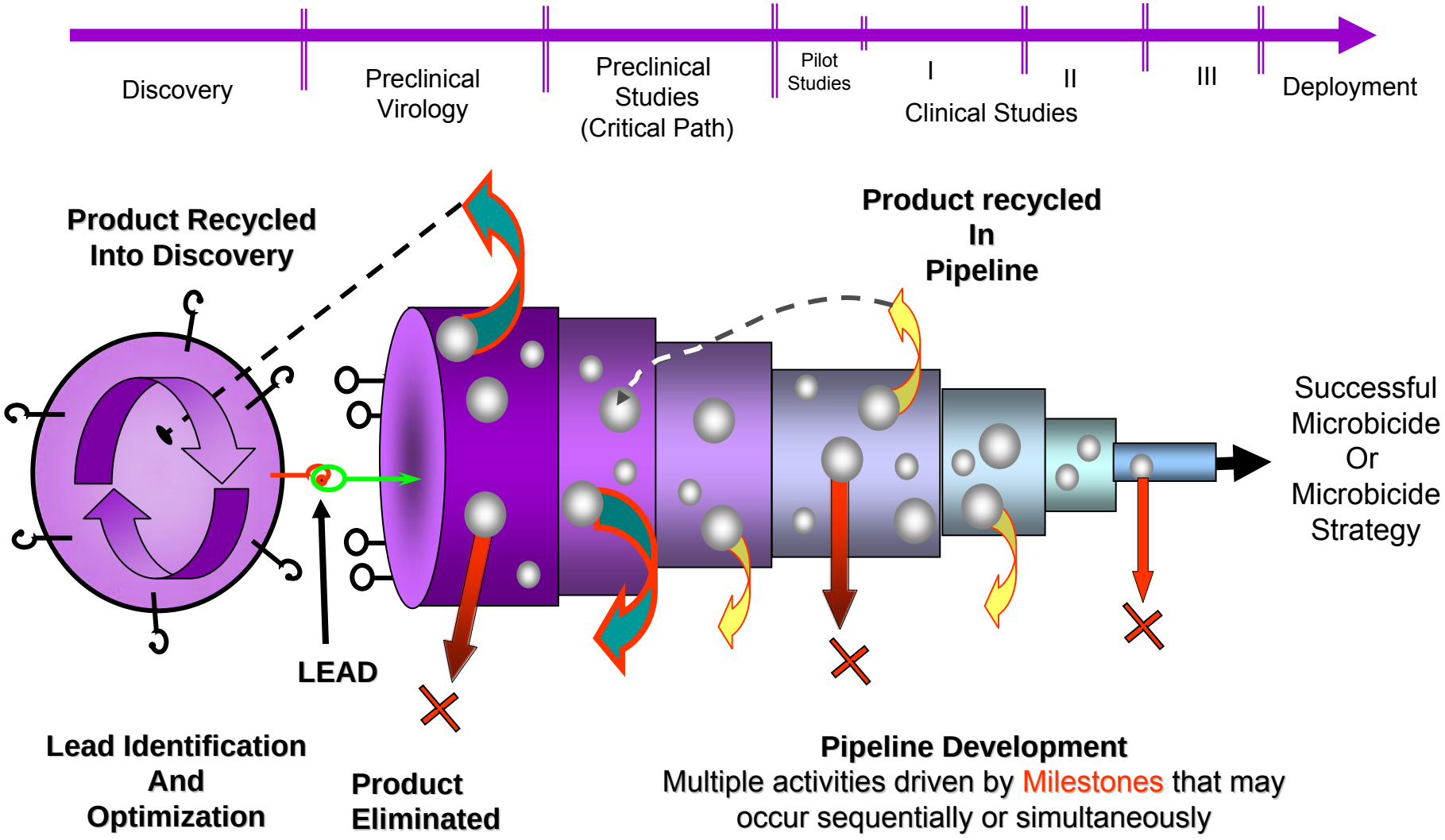


Non-specifically or specifically block virus-cell association:
Carraguard™, PRO2000, ISIS 5260

Reduced vaginal pH non-permissive for HIV replication:
BufferGel™, Acidform™

Virus Inactivation: Nucleocapsid p7 Inhibitors

The Microbicide Development Pipeline



What is needed for the Translation from Preclinical to Clinical?

Preclinical Virology — **Preclinical Studies** — "Critical Path"

General Preclinical Virology

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

Preformulation

↓GLP

Formulation

- Stability
- Sterility
- Homogeneity
- Purity

Microbicide Specific

Lab

- Condom Compatibility **GLP**
- Effect on Lactobacilli
- Effect of Matrices
  - –Seminal Plasma
  - –Cervical fluid
  - –Mucin
- Other STIs
- Cervical Explants
- NHP iVag transmission

Animal

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

PK and Toxicology GLP

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

Chemistry Manufacturing and Control (CMC) GMP

Unformulated	Formulated
Drug Product	gel

Stability, Sterility, Packaging, Storage

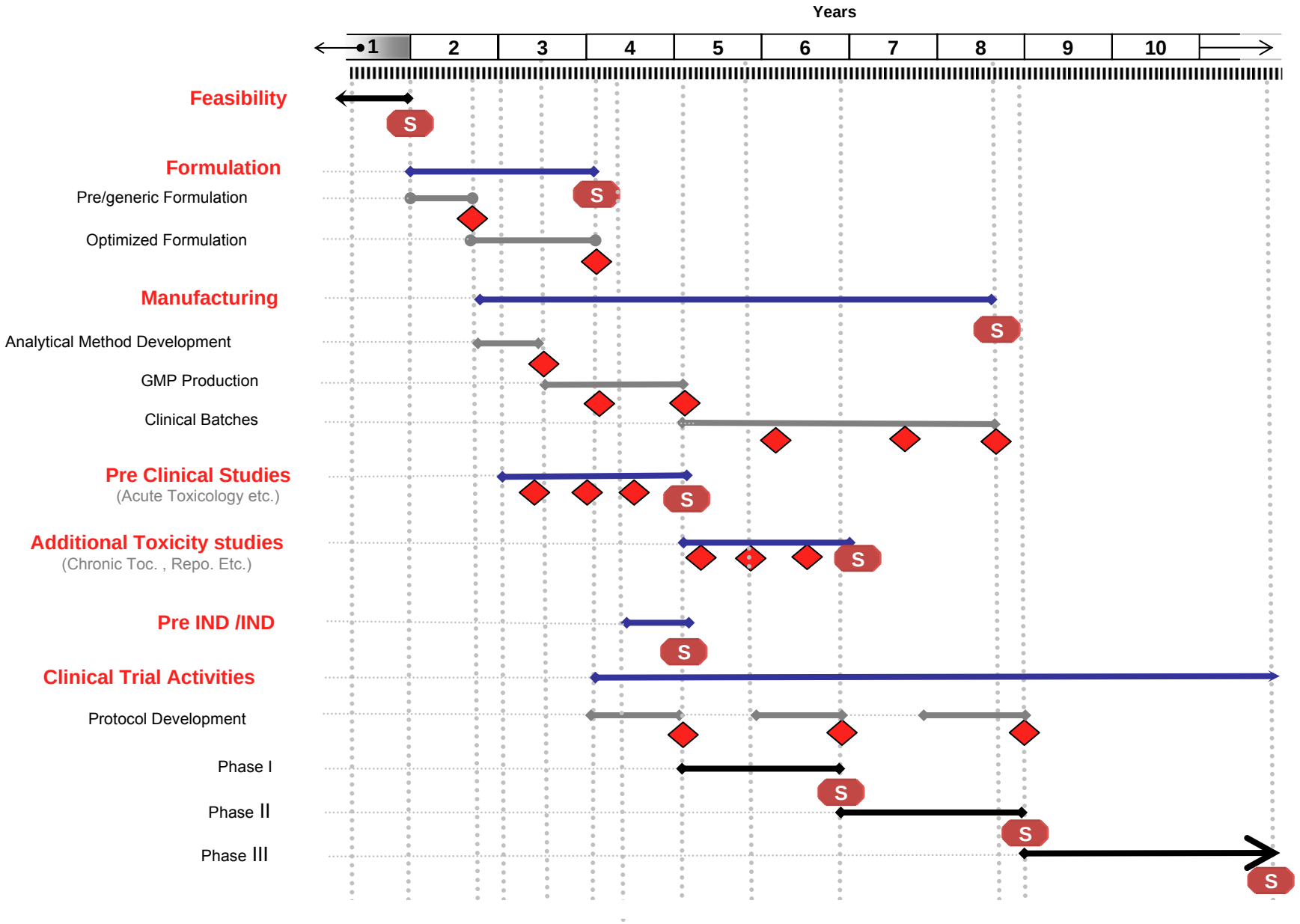
Applicator GMP

Selection Labeling
Acceptability Filling

Must be carried out in accordance with the CFR for GLP and GMP studies

DHHS/NIH/NIAID

Generalized GANTT Chart for Microbicide Product Development

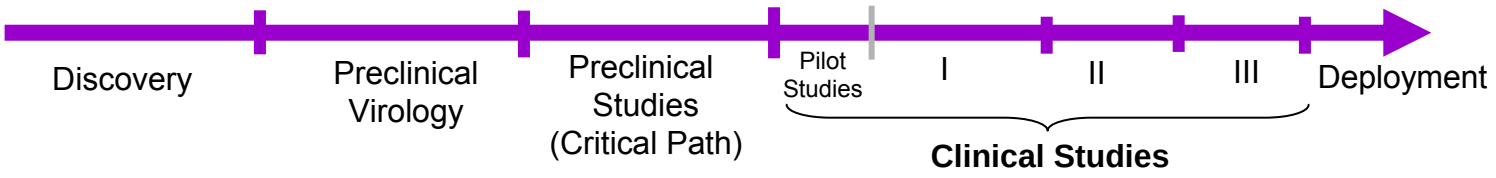


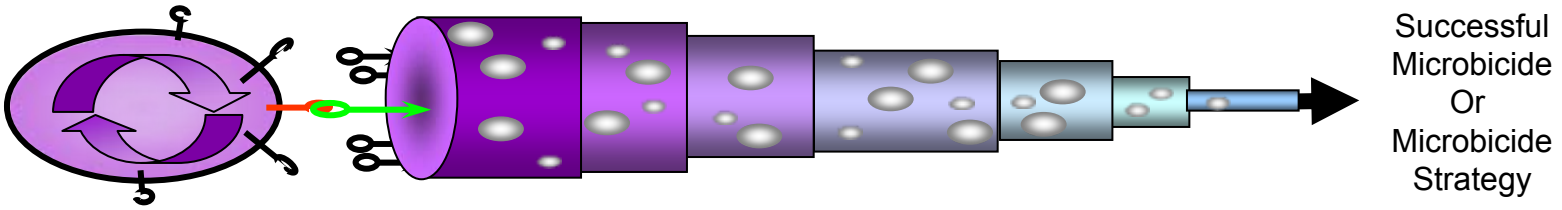
DHHS/NIH/NIAID/DAIDS

Microbicides: Where Are We?

No Proof-of-Concept for Microbicide Safety, Efficacy and Acceptability

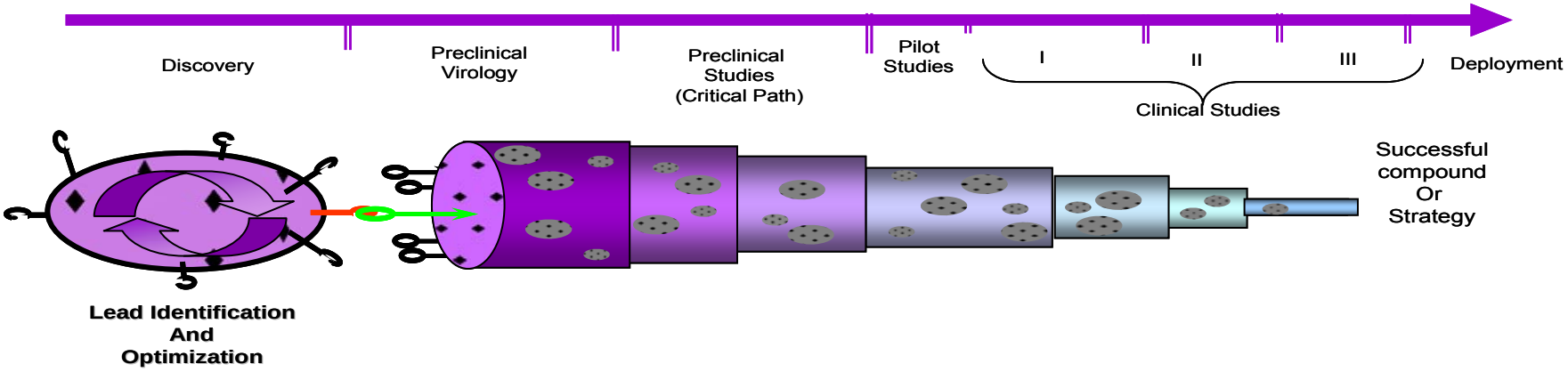
Scenario building while waiting for data





Phase	Number	Candidates
Preclinical	Multitudes	ZFI, Entry inhibitor, NNRTI, Nucleosides, Engineered Lactobacilli, Etc.
1	5	Vivagel ™ /SPl7013; TMC120 gel; UC-781; Tenofovir Gel (1%); Ethanol
1-2	3	Invisible Condom™; TMC120 gel; TMC120 vaginal ring
2	1	Tenofovir Gel (1%)
2/2B	2	Tenofovir gel and PRO2000 (0.5%); BufferGel™ and PRO2000 (0.5%)
3	1	PRO2000 (0.5%)

NIAID Topical Microbicide Program



- Basic biomedical research
  - Foster basic science and preclinical pipeline studies
- Nonclinical product development
  - Identify and advance the most promising approaches to clinical testing
- Clinical evaluation
  - Evaluate safety, efficacy and acceptability in populations most in need

Gaps in Knowledge for Microbicide Development

- Mechanism of mucosal infection by HIV--what are the cellular targets and their distribution?
- What are the infectious, physiologic and ecologic cofactors that influence HIV infection?
- How can we optimize the physical properties of a microbicide formulation to maximize safety, efficacy and acceptability?
- How does the immune or inflammatory responses triggered by a microbicide effect the safety of the product?
- What are the potential surrogate markers or safety and efficacy that can be validated by clinical evaluation?
- How should HIV resistance to ARVs influence microbicide candidate selection?
- What is the role for combinations of actives as a microbicide strategy?

NIAID: Microbicide Research Program

Basic Research → Preclinical Development → Clinical Trials

Basic Microbicide Research Support

- Unsolicited R21, R01 and SBIR grants, CFAR
- Microbicide Innovation Program — NIAID, NIMH

Microbicide Specific Development Support

- STI and Topical Microbicide Cooperative Research Centers — DMID
- Partnerships for Microbicide Development — DMID
- Integrated Preclinical-Clinical Program-HTM — DAIDS
- HIV Microbicide Design and Development Teams — DAIDS

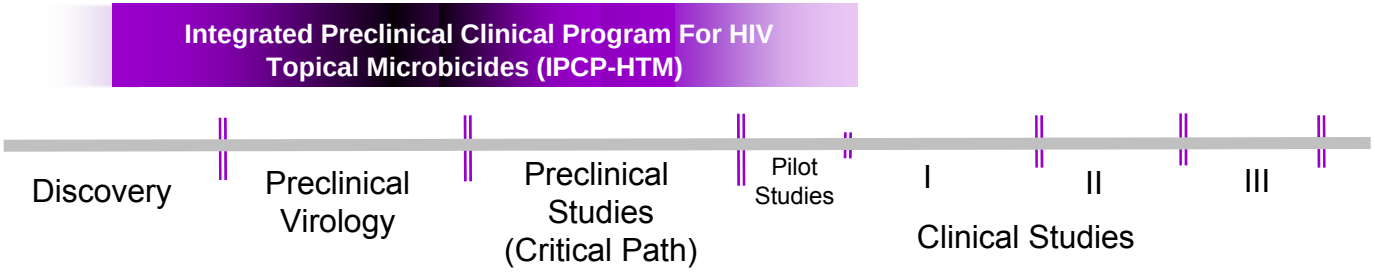
Microbicide Clinical Trial Support

- Microbicide Trials Network (MTN) — DAIDS
- STI Clinical Trials Group — DMID
- HIV Prevention Trials Network — DAIDS

Microbicide Development Contract Support

- In Vitro Evaluation Support — DAIDS
- Development Support — DAIDS, DMID
- Model Development & Evaluation Support, Safety and Efficacy — DAIDS, DMID
- Preclinical Master Contract — DAIDS

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



Integrated multi-project programs in collaboration with industry partners to create "mini-pipelines" for development

- ✓Stimulate and support a diverse preclinical base of single and combination microbicides for vaginal and/or rectal use
- ✓Support translation of new microbicides and microbicide strategies from preclinical studies to pre-Phase I clinical trials,
- ✓Facilitate entry of new methods and expertise for determining microbicide safety, efficacy and acceptability into microbicide development

IPCP-HTM Scientific Profile

Microbicide Targets

- ✓ CD4
- ✓ gp120
- ✓ gp120/CD4 interaction
- ✓ gp41
- ✓ Coreceptor
- ✓ NNRTI
- ✓ HIV p7 nucleocapsid Inhibitor

New Concepts/Strategies

- ✓ Combinations
  - Dual
  - Triple
  - Multi-mechanism inhibitors
- ✓ Lactobacilli delivery of microbicides
- ✓ siRNA –*virus and cell targets*
- ✓ Integration of formulation and acceptability
- ✓ Biomarkers and coital effects on microbicide efficacy
- ✓ Rectal microbicide development
  - Establishment of preclinical algorithm
  - Vaginal formulation delivered rectally
  - Specific rectal formulation
- ✓ New imaging modalities for safety assessment:
  Optical Coherence Tomography
- ✓ Coital disassociated microbicide delivery
  - Vaginal rings
  - Smart gels

- **Mission:** Reduce HIV transmission through development and evaluation of topically applied microbicides
- **Goal:** Conduct scientifically rigorous and ethically sound efficacy trials to support licensure of microbicide products

✓**Pharmaceutical model---Advances microbicides with an existing IND.**
✓**Implement standardized preclinical criteria for the rational selection of microbicide products to advance**
✓**Rapidly implement emerging safety assessment tools into phase 1 & 2 trials**
✓**Behavioral Research Committee – to develop the scientific agenda and priorities**

Microbicide Evolution

1st Generation — Nonoxynol-9 →

2nd Generation — Nonspecific inhibitors →

3rd Generation — HIV specific inhibitors →

- ✓NRT
- ✓NNRT
- ✓CCR5

4th Generation — Combination Inhibitors →

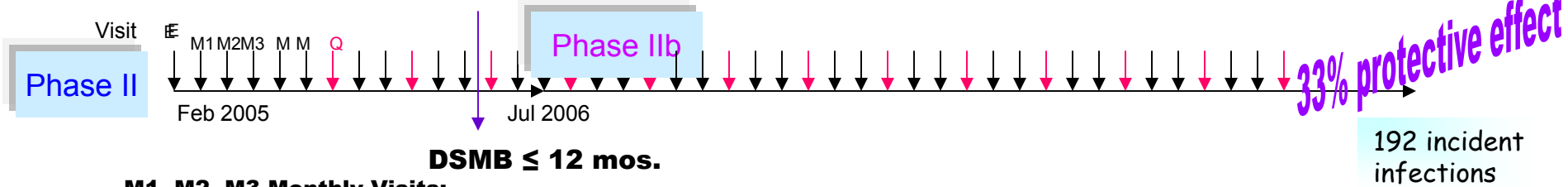
Results: 1st and 2nd Generation of Microbicides

N-9 Gel (52.5 mg)	Trial completed, evidence of harm
N-9 Film (70 mg)	Trial completed, no evidence of harm or benefit
Savvy (C31G)- Nigeria	Trial stopped due to futility; trend toward harm
Savvy (C31G) - Ghana	Trial stopped due to futility, increased reproductive tract AEs

Results and Update: 2nd Generation of Microbicides

Cellulose Sulfate – CONRAD	Trial stopped, trend toward harm
Cellulose Sulfate - Family Health International	Trial stopped, no harm
Carraguard® - Population Council	Trial completed, no evidence of harm or benefit
0.5% PRO2000 Gel/P- Microbicides Development Programme	Ongoing
0.5% PRO2000 Gel/P and BufferGel	Enrollment complete, participants exiting, results expected Q1/2009

HPTN 035: Phase II/IIb Trial of Vaginal Microbicides for the Prevention of HIV Infection in Women



DSMB ≤ 12 mos.

M1, M2, M3 Monthly Visits:
Pelvic exam, safety labs with pregnancy and HIV tests (colposcopy for subset)

Quarterly Visits: Pelvic exams and HIV tests
MonthlyVisits: Pregnancy test

N = 200/~605
BufferGel

N = 200/~605
0.5% PRO2000 Gel

N = 200/~605
Placebo

N = 200/~605
No treatment

N = 100

N = 700

Philadelphia, PA

Durban & Hlabisa, SA
Lilongwe, Malawi
Harare, Zimbabwe
Blantyre, Malawi
Lusaka, Zambia

N ≈ 220

N ≈ 2200

Primary endpoints:
Safety
HIV infection

Secondary endpoints:
BV
Chlamydia infection
Genital ulcer disease
Gonorrhea infection
HSV-2 infection
Pregnancy
Syphilis infection
Trichomoniasis

Treatment regimen: Apply a single dose of the product intravaginally up to 60 mins before each act of vaginal intercourse

Participant follow-up: 12-30 mos.

3rd Generation Microbicide Update

1. Tenofovir Gel (1%) - Dosed prior to and after intercourse – within 24 hour time frame
2. Tenofovir Gel (1%); Viread; Truvada – Dosed daily

1. Ongoing in South Africa
2. Expected to start Q4 2008/Q1 2009 at multiple sites in Africa

MTN-003:The VOICE Study

Vaginal and Oral Interventions

to Control the Epidemic

Phase 2B, Safety and Effectiveness Study

1% Tenofovir (PMPA) Gel

Tenofovir DF (TDF) Tablet

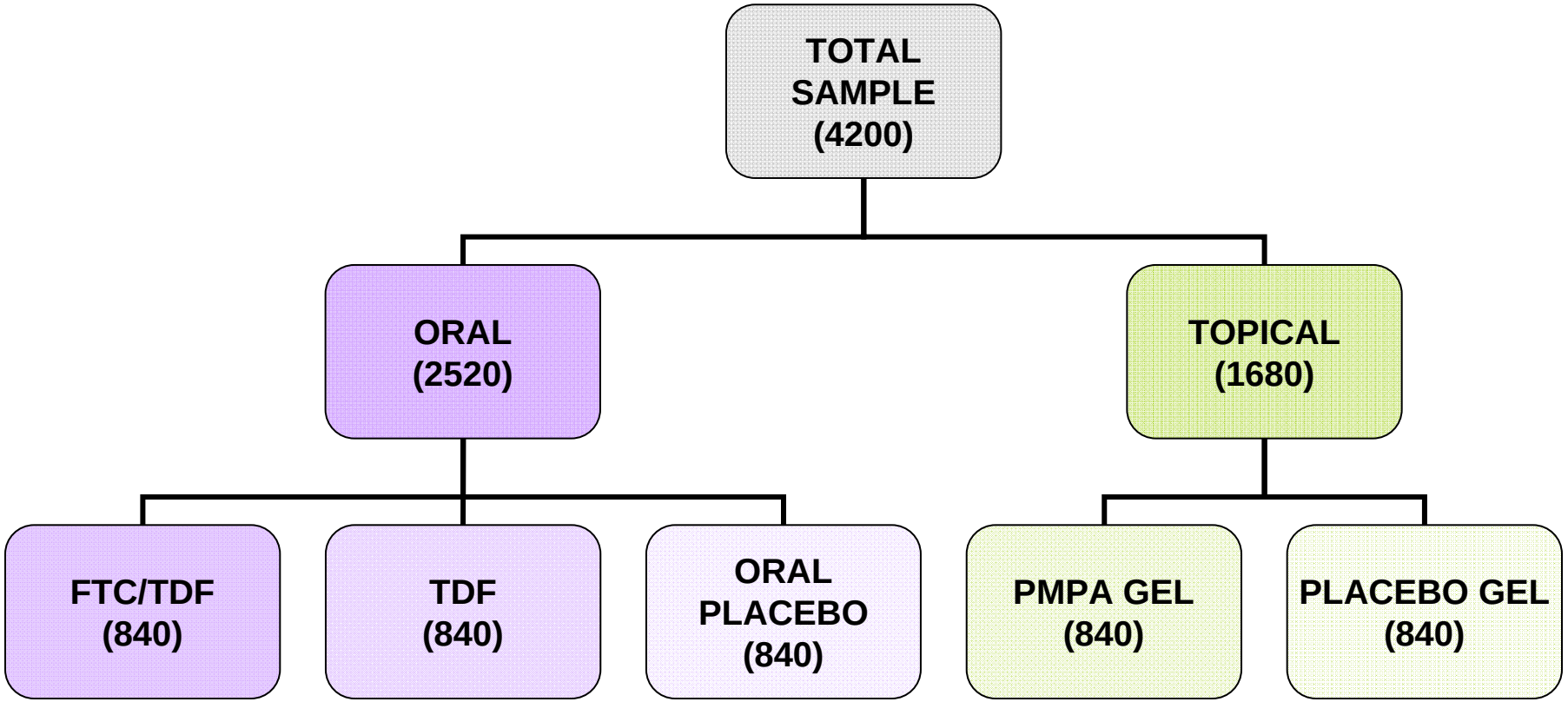
TDF/FTC (emtricitabine) Tablet

MTN
microbicide trials network

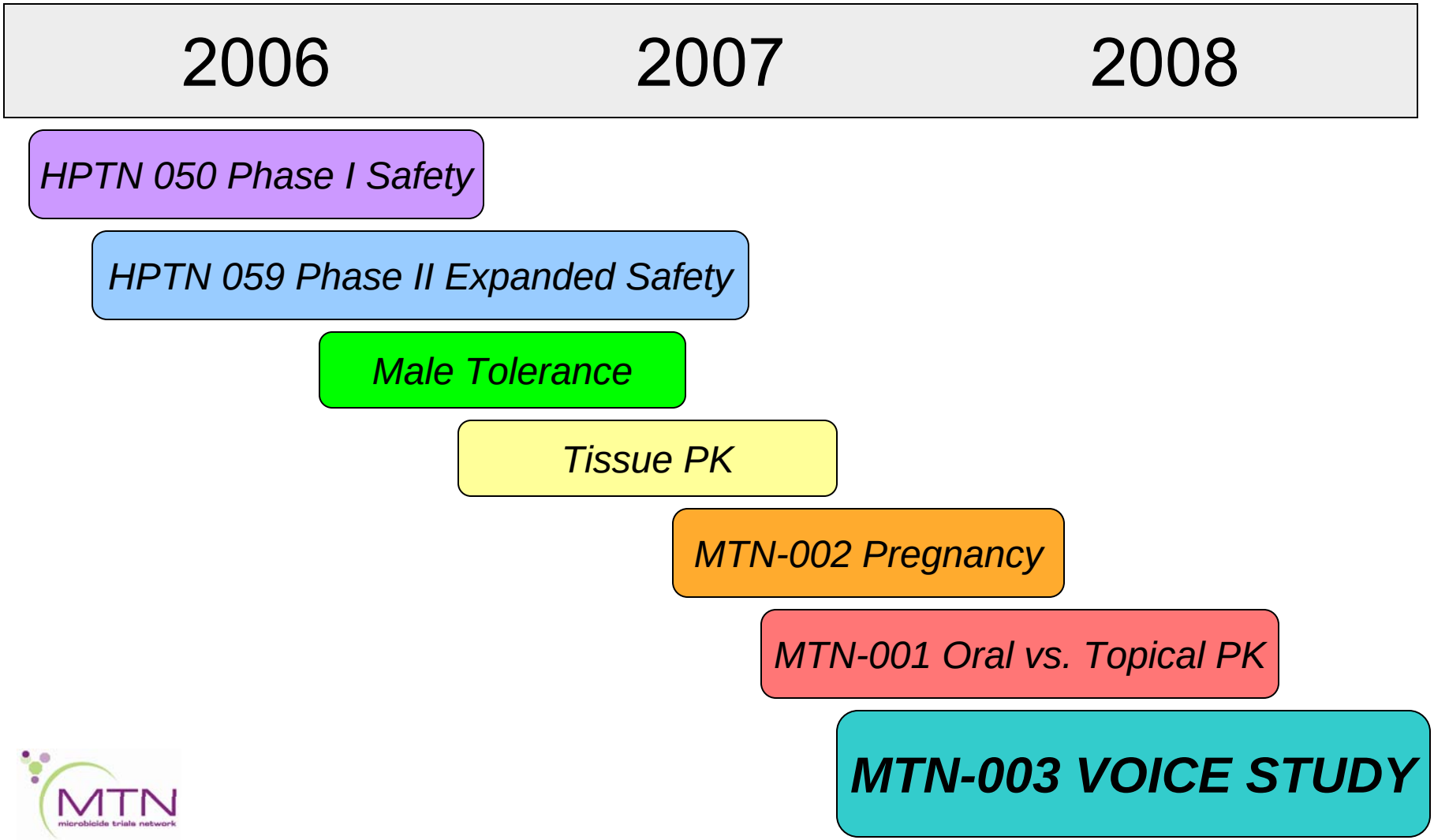
General Rationale

- Safe and effective PrEP is essential
- Strong opinions about….
  - Topical vs. Oral
  - Single Drug vs. Combinations
  - Safety
  - Acceptability/Adherence
  - Effectiveness
  - Consequences of Resistance
  - Overall Risk/Benefit
- **No human data!**

MTN-003: The VOICE Study



PMPA Gel: Following a Classic Drug Development Paradigm



Why a Head-to-Head Trial?

- Theoretical reasons to favor either approach for safety, acceptability, efficacy and/or selection of resistance
  - vaginal use may confer less systemic toxicity and less resistance
  - vaginal use may be more culturally acceptable
  - oral use is less closely linked to sexual practices, and can be administered by the woman without knowledge of her partner
  - NO HUMAN DATA

- **Only head-to-head trial will answer questions**

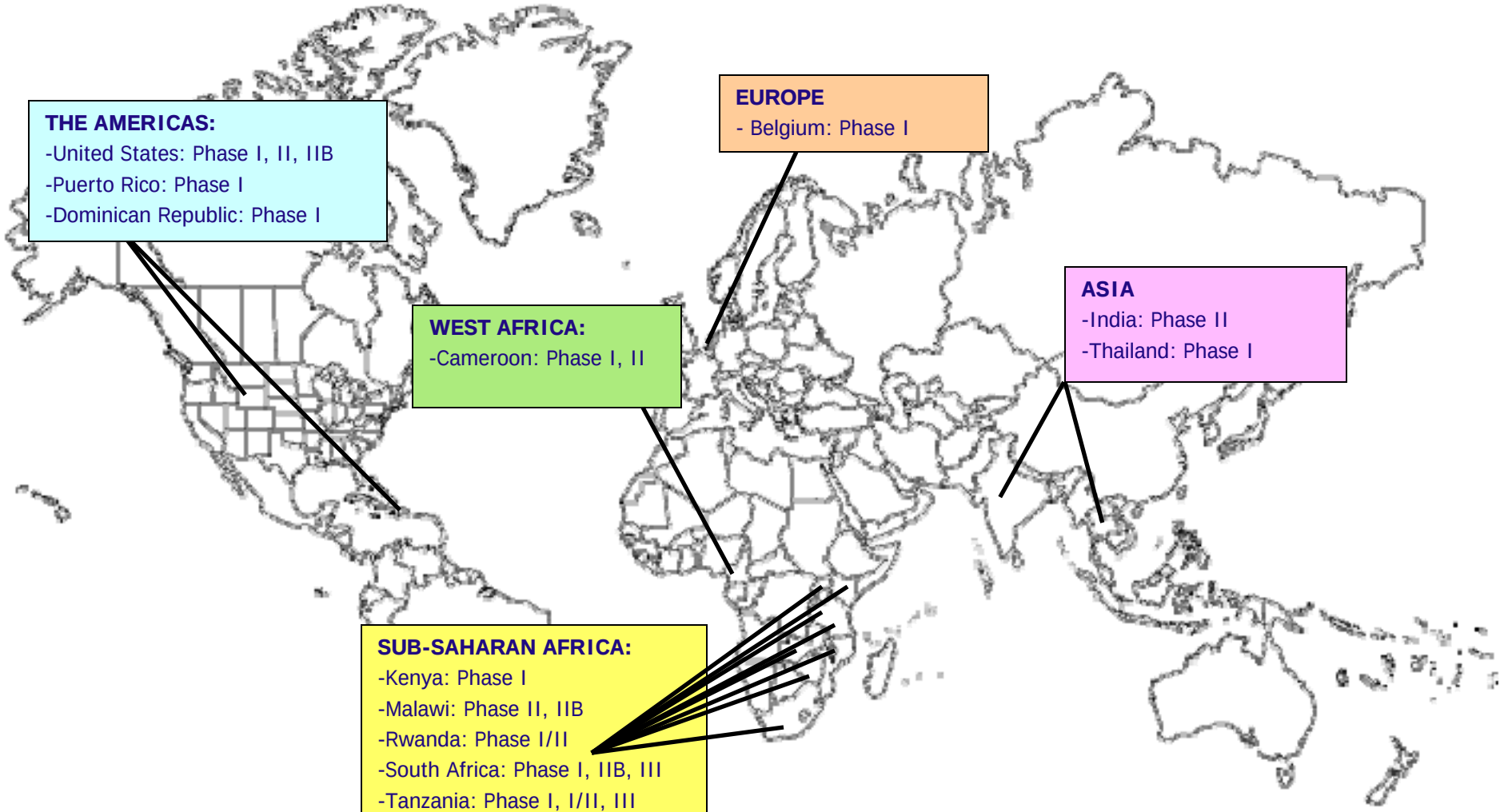
Study Objectives

- Primary Objectives
  - Estimate effectiveness of 1% tenofovir gel, oral TDF, and oral FTC/TDF in preventing HIV infection among at-risk women.
  - Evaluate extended safety of daily 1% tenofovir gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection.

Challenges

- Development of optimal formulations
- Assessment of safety
  - Preclinical
  - Clinical
- Biomarkers/Surrogate markers
  - Safety
  - Efficacy
- Clinical trial implementation
  - Incidence
  - Risk reduction counseling

Clinical Trial Sites in 2008



THE AMERICAS:
-United States: Phase I, II, IIB
-Puerto Rico: Phase I
-Dominican Republic: Phase I

EUROPE
- Belgium: Phase I

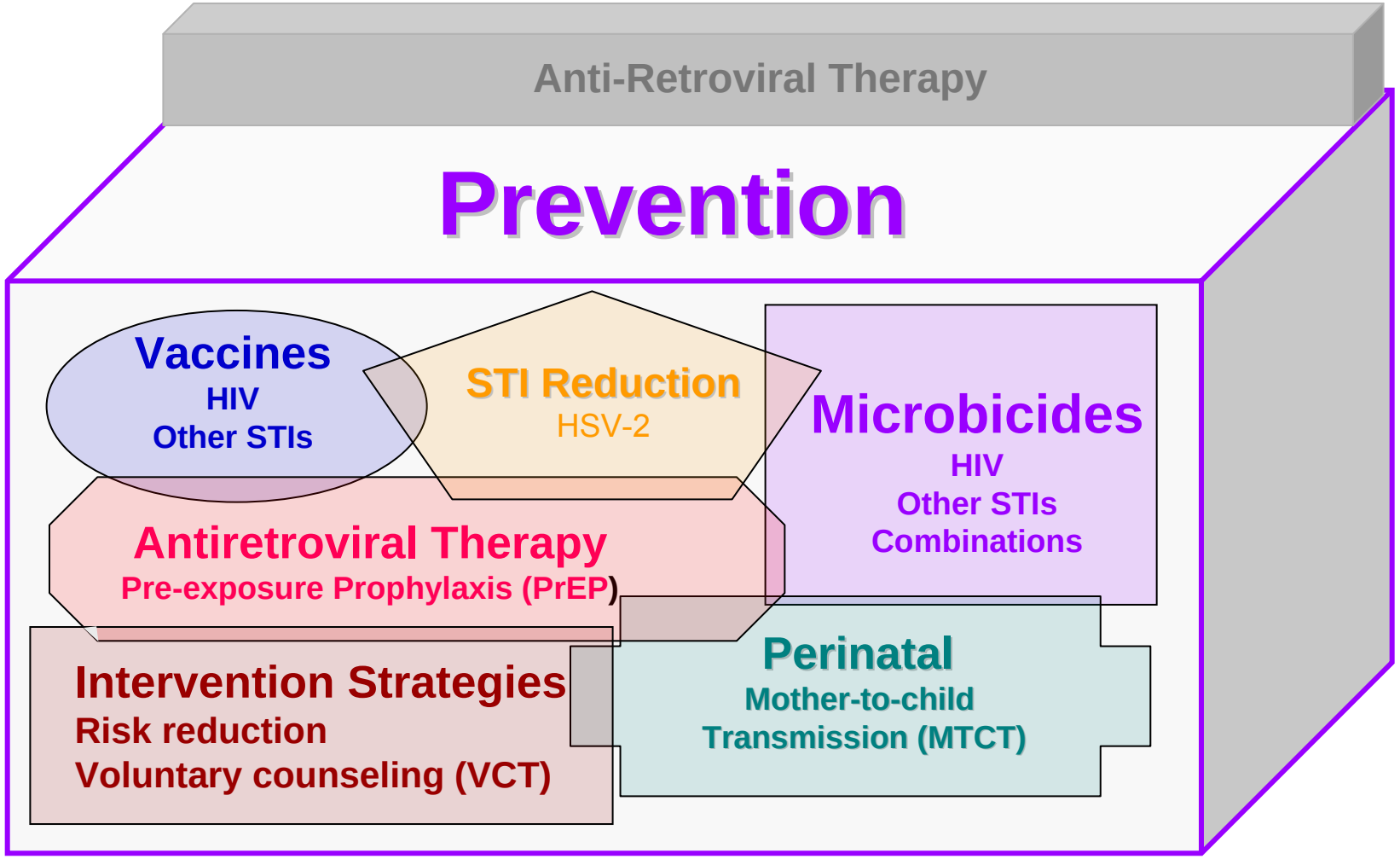
WEST AFRICA:
-Cameroon: Phase I, II

ASIA
-India: Phase II
-Thailand: Phase I

SUB-SAHARAN AFRICA:
-Kenya: Phase I
-Malawi: Phase II, IIB
-Rwanda: Phase I/II
-South Africa: Phase I, IIB, III
-Tanzania: Phase I, I/II, III
-Uganda: Phase III
-Zambia: Phase IIB, III
-Zimbabwe: Phase I, II, IIB

Source: Alliance for Microbicide Development

Controlling the Pandemic



Ultimate Goal:

Multi-Component Prevention Strategy