

Microbicides

Ian McGowan MD PhD FRCP

Consultation on the Inclusion of Adolescents in HIV
Prevention Clinical Trials

Washington DC

June, 2009







Overview

- Microbicide development
 - Preclinical
 - Clinical
- The microbicide pipeline
- Inclusion of adolescents in microbicide trials
 - MTN-004
 - NIH R01

Microbicide Development

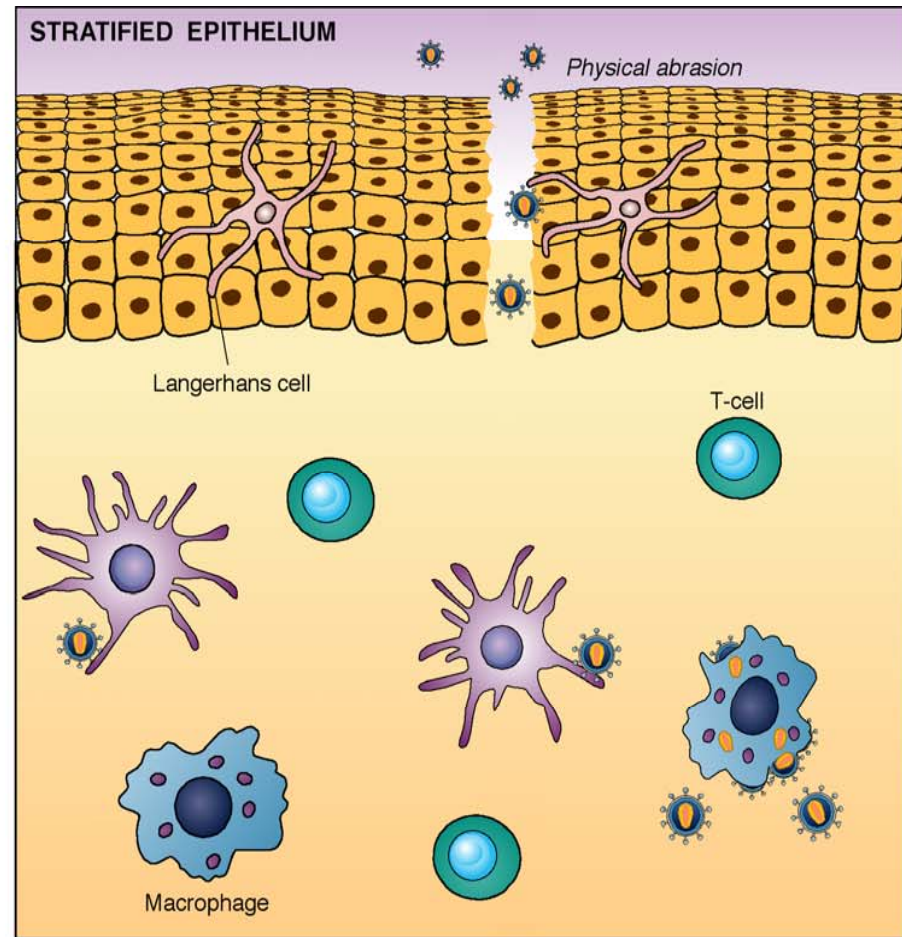
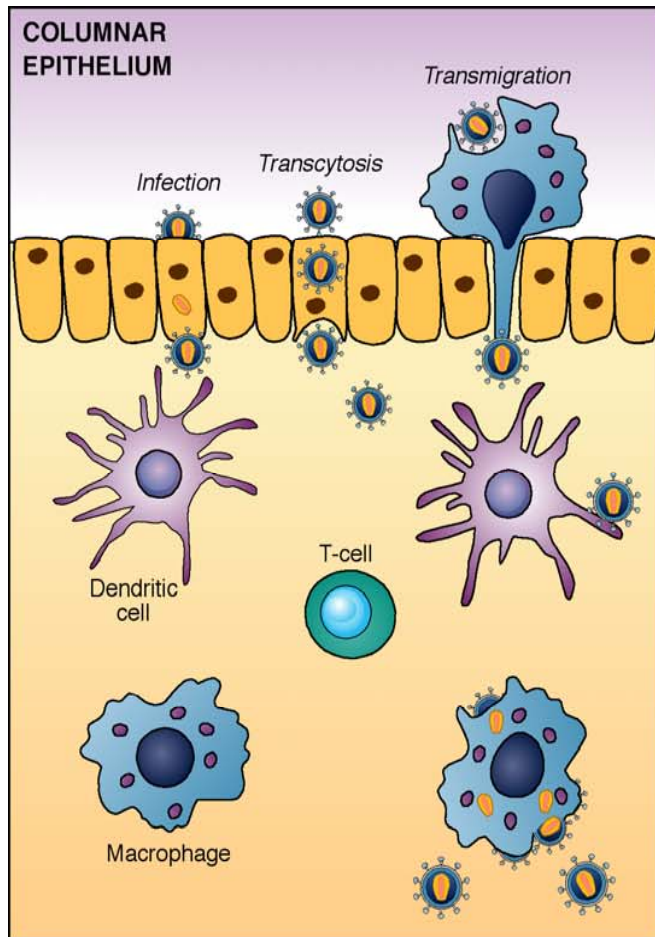


Microbicides are products that can be applied to the vaginal or rectal mucosa with the intent of preventing or significantly reducing the risk of acquiring STIs including HIV

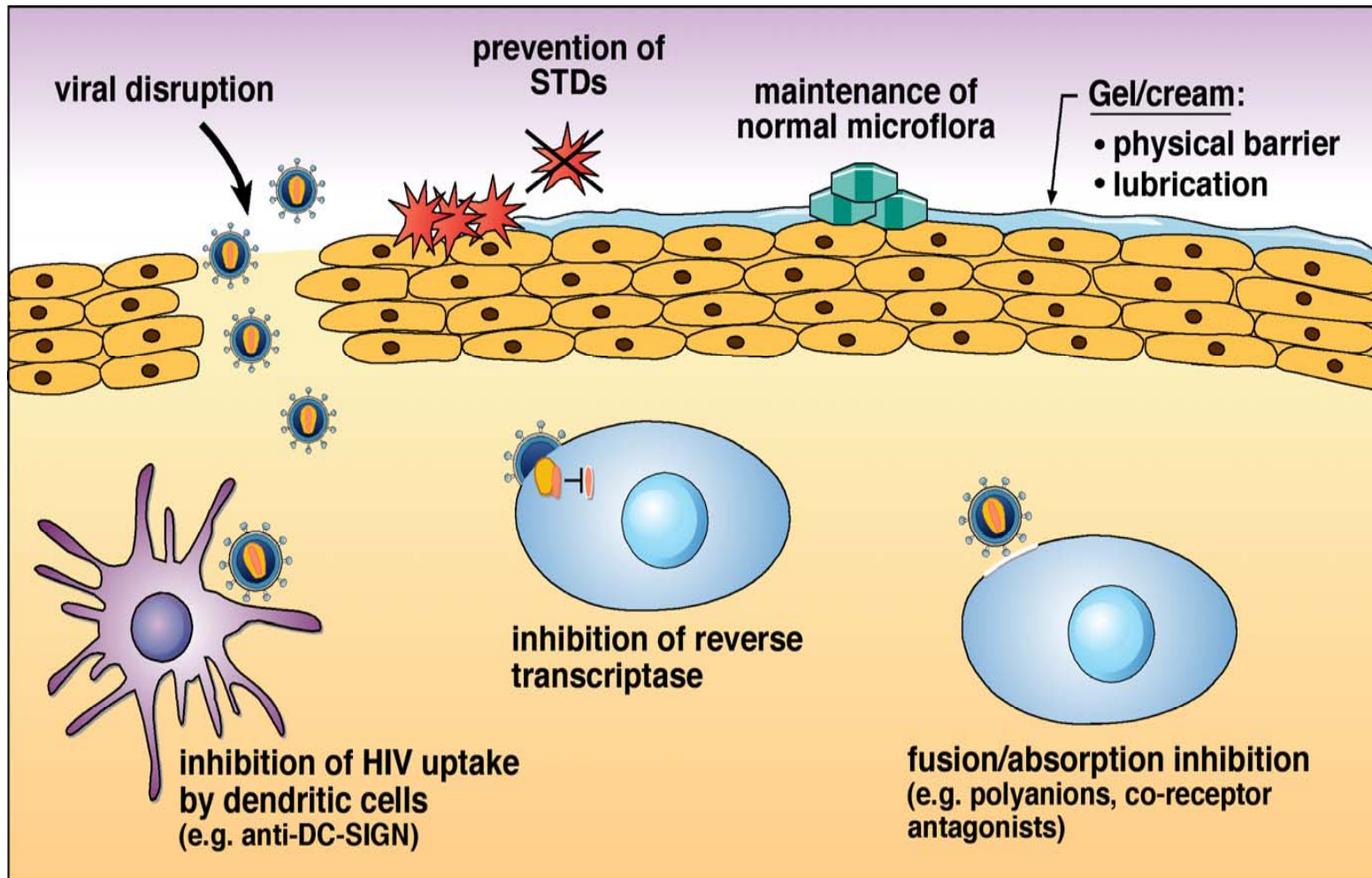


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Mucosal Targets



Mechanism of Action



Preclinical Safety & Efficacy



Safety

Absence of evidence of harm

+

Absence of increased risk of HIV acquisition

but

Efficacy may be > safety



Preclinical Safety

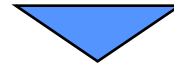
- Cell lines
- Microbiology
- Animal studies
 - Murine
 - Rabbit
 - Non-human primates
- Explants
 - Cervicovaginal
 - Rectal

Non Human Primate

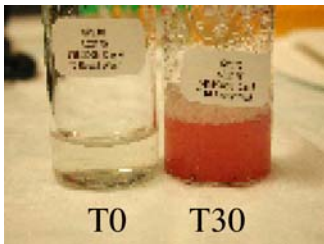


Rectal Lavage Assay

Lavage
fluid

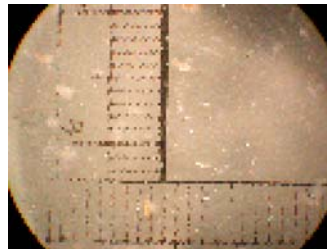


Day 4
Combo
Animal



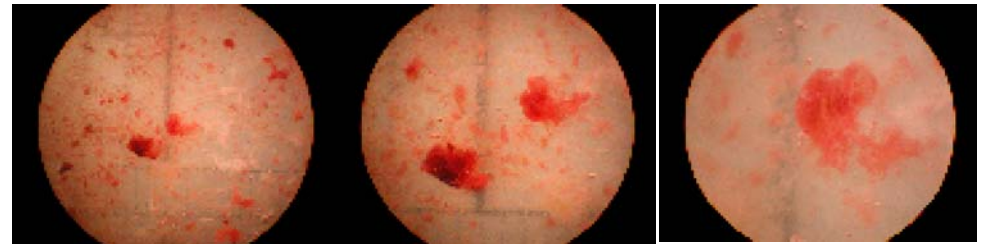
T0 T30

Day 4, T0
24 hrs post
3rd application



7X

Day 4, T30 post 4th application



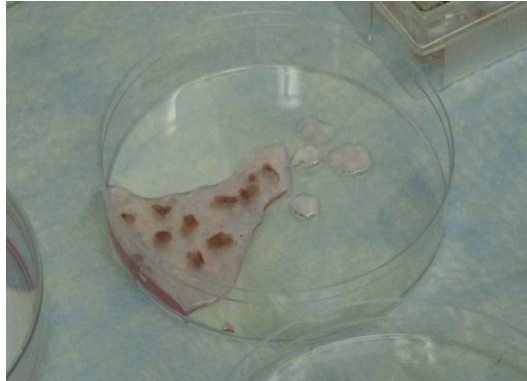
7X

15X

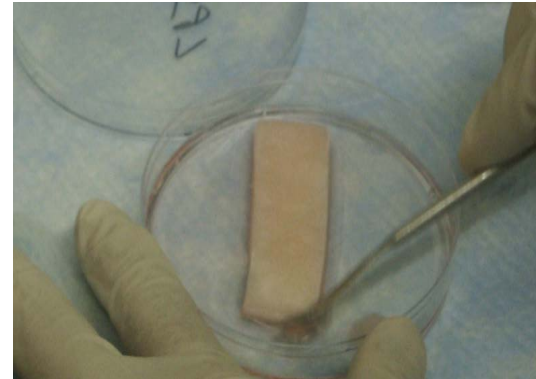
30X

Explant Model

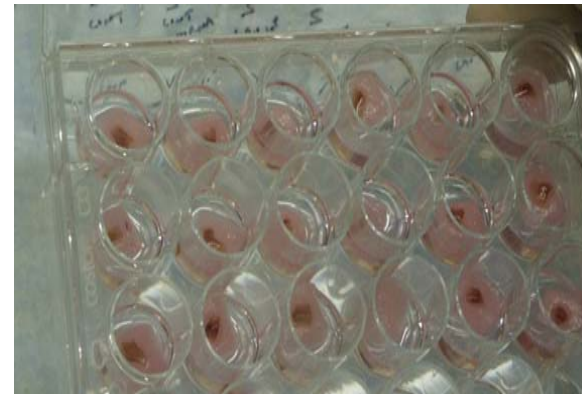
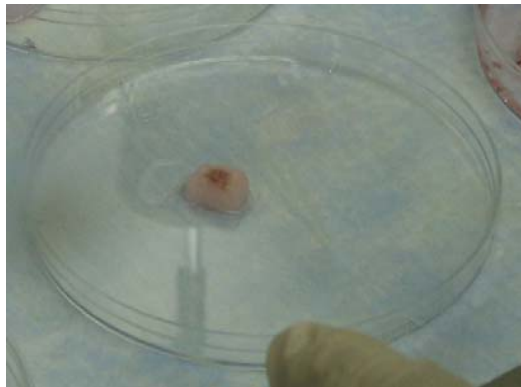
Colorectal Intestinal Explants



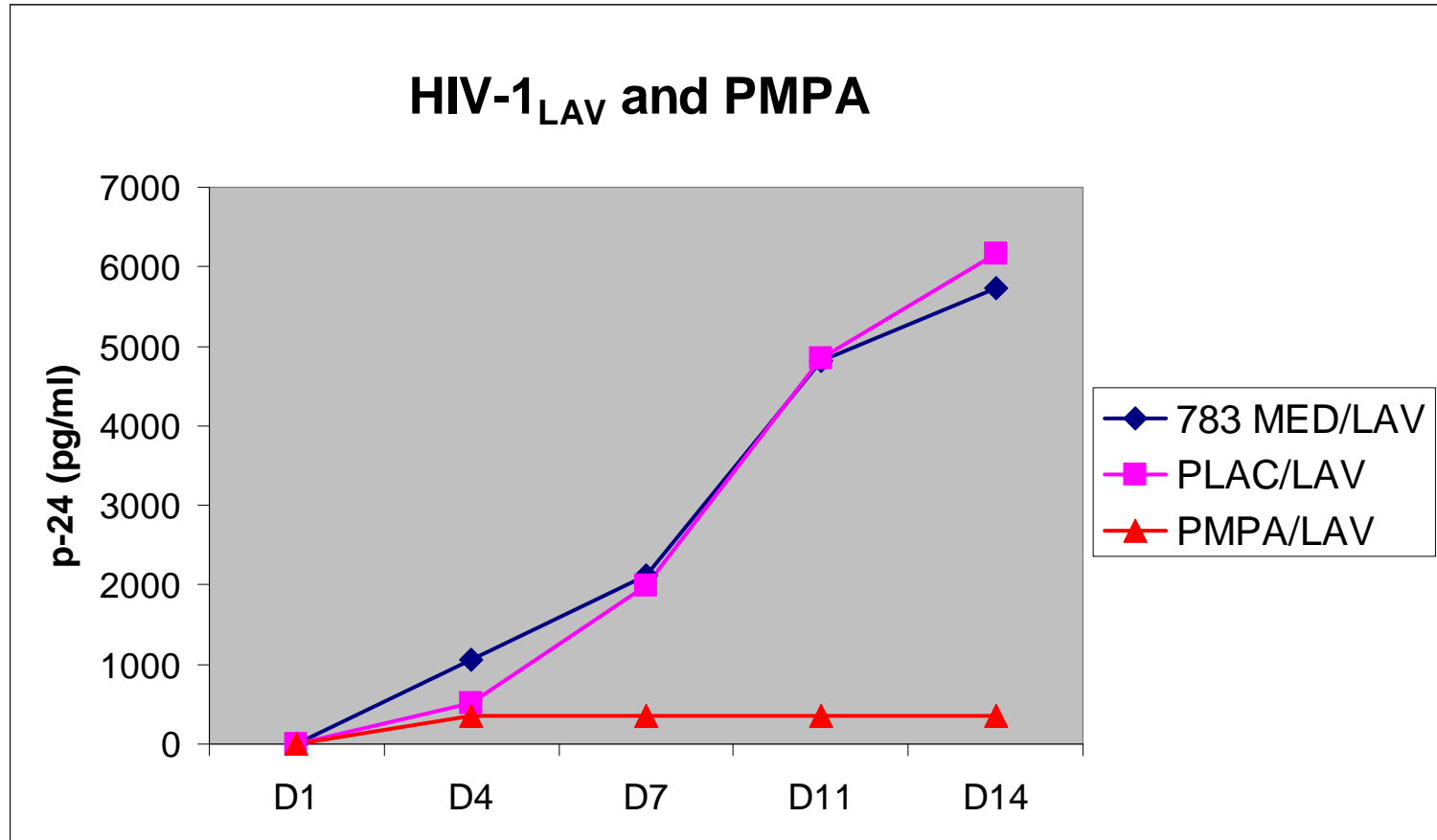
Endoscopic biopsies



Absorbable gelatin sponge



Colorectal Explant Model



Clinical Development of Microbicides



Clinical Evaluation

- Phase 1
 - Sexually abstinent (1-2 weeks; N = 40-60)
 - Sexually active (1-2 weeks; N = 40-60)
 - Male tolerance study
- Phase 2
 - Expanded safety (6 months; N = 200)
- Phase 2B
 - HIV endpoint study (12-18 months; N = 4,000)
- Phase 3
 - HIV endpoint study (12-18 months; N = 9,000)

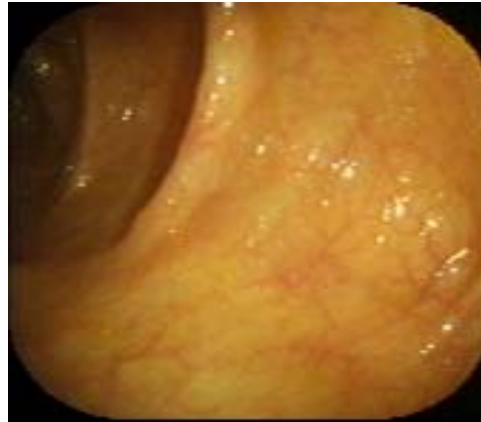
Phase 1 Vaginal Safety Studies



Key Endpoints

- Signs and symptoms
- Colposcopy
- Microflora
- Immune biomarkers
 - Cytokines
 - Antimicrobial peptides
- (Histology)

Phase 1 Rectal Safety Studies

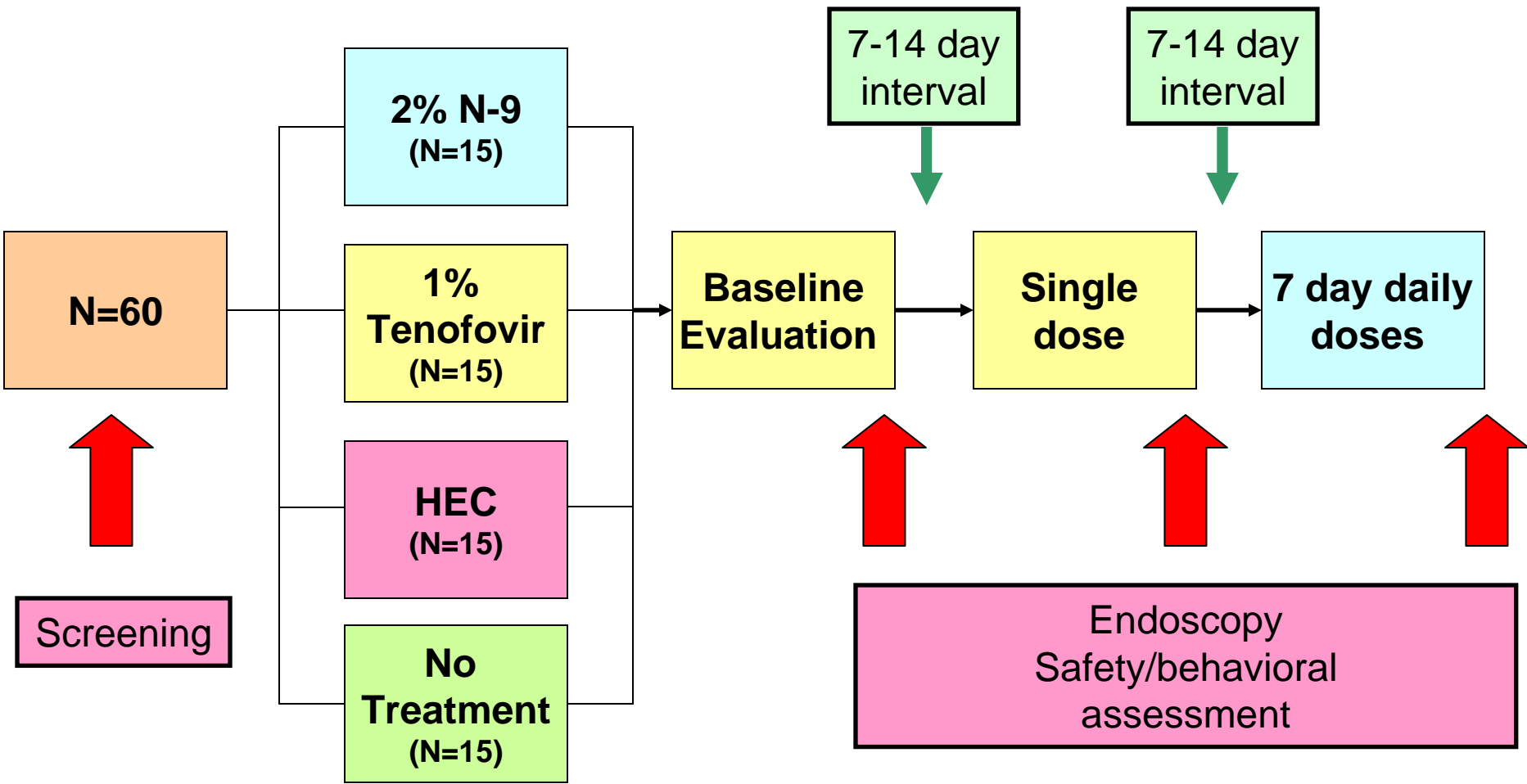




Key Endpoints

- Signs and symptoms
- Sigmoidoscopy / anoscopy
- Mucosal injury
 - Histology
 - Epithelial sloughing
 - Cytokines
 - T cell phenotype
- Microflora
- Explant infection

MTN-007



The Microbicide Pipeline

Microbicide Candidates

Uncertain	Defense Enhancers	Entry / Fusion Inhibitors	
<ul style="list-style-type: none"> □Ciclopiroxolamine □Praneem polyherbal 	<ul style="list-style-type: none"> □MucoCept HIV □Acidform™ gel □BufferGel™ 	<ul style="list-style-type: none"> □Cellulose sulfate □Cellulose acetate □Carraguard □VivaGel □Dextrin-2 sulfate □Cyanovirin-N □C85FL □K5-N, OS(H) □SAMMA 	<ul style="list-style-type: none"> □C52L □Tobacco-derived antibodies / fusion proteins □Anti-ICAM-1 Ab mAb B12, 2G12 □mAb 2F5, 4E10 □CD4 IgG2 □T20 □T-1249
Membrane Disruption	Replication Inhibitors	<ul style="list-style-type: none"> □Invisible condom □Novaflux 	<ul style="list-style-type: none"> □SCH-C, D □UK-427,857 □TAK 779
<ul style="list-style-type: none"> □Alkyl sulfates □Savvy (C31G) □Beta cyclodextrin 	<ul style="list-style-type: none"> □Tenofovir □TMC-120 □UC-781 □MIV-150 □MC1220 □C-731, 988 	<ul style="list-style-type: none"> □Porphyrins □PSC Rantes □BMS-806 □BMS-378806 □CMPD167 	<ul style="list-style-type: none"> □AMD3100 □SFD-1 □Bicyclams □Aptamers

Microbicides in Clinical Trials

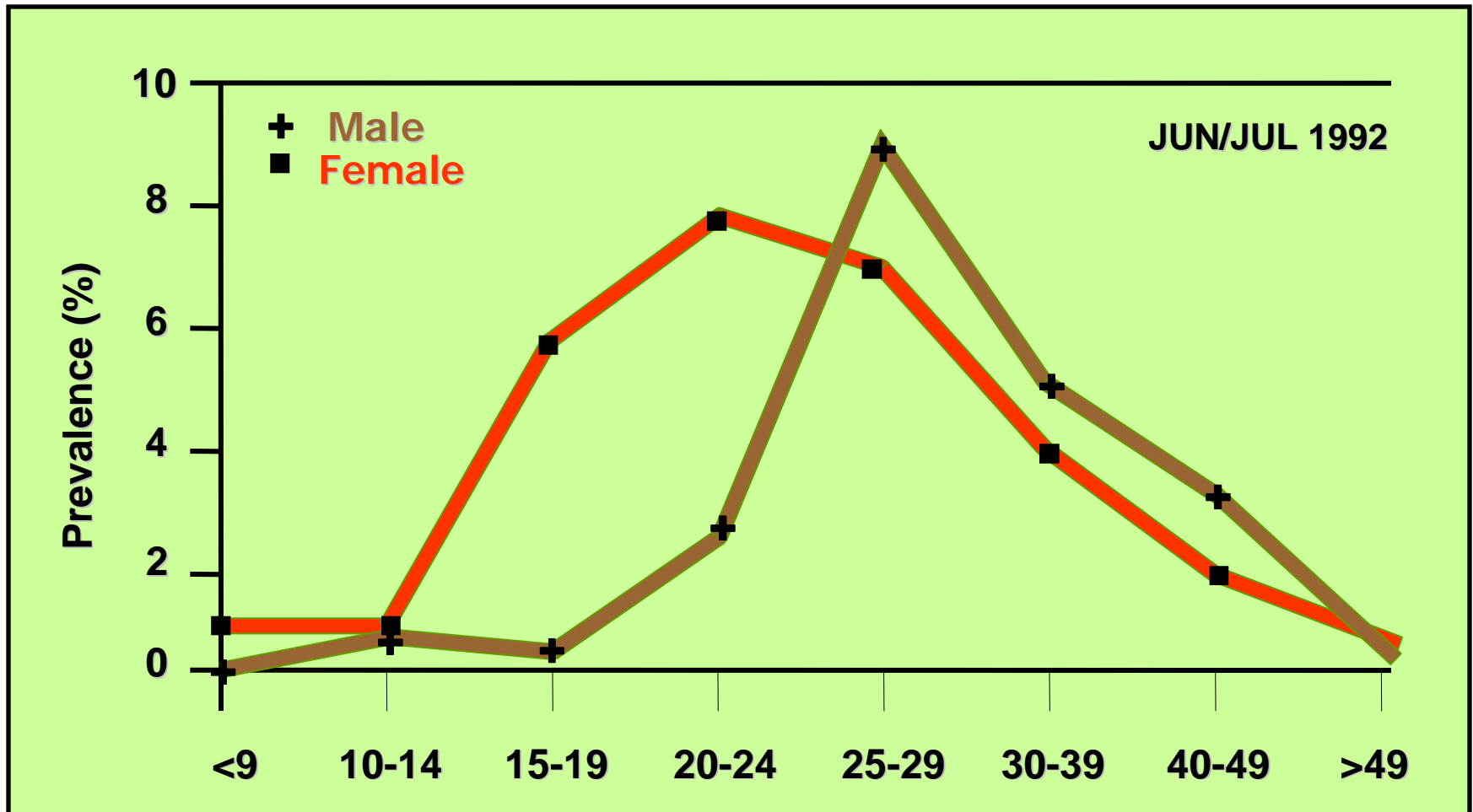
Phase	Membrane Disruption	Defense Enhancers	Entry Fusion Inhibitors	Replication Inhibitors
1	Ethanol in emollient	Lactobacillus	Duet® CAP soft tablet VivaGel™	PC-815 UC-781 TMC-120
2			VivaGel™	
2/2B	Invisible Condom™	BufferGel™	PRO-2000	Tenofovir
3		Acidform™	PRO-2000	

Planned

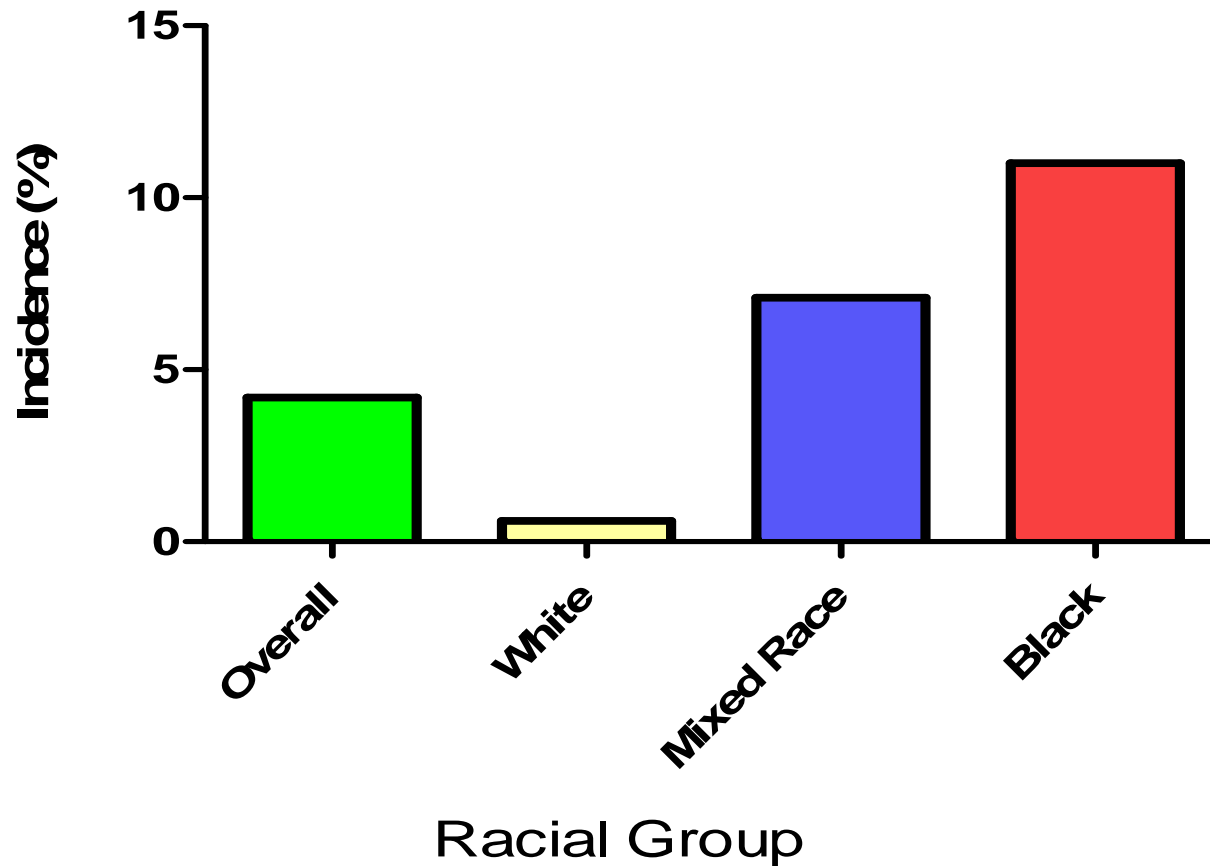
Adolescents



HIV Infection in Adolescents



HIV Incidence in Young US MSM



Baltimore Young Men's Survey: Sifakis F et al. JAIDS 2007



Microbicide Studies Recruiting Younger Participants

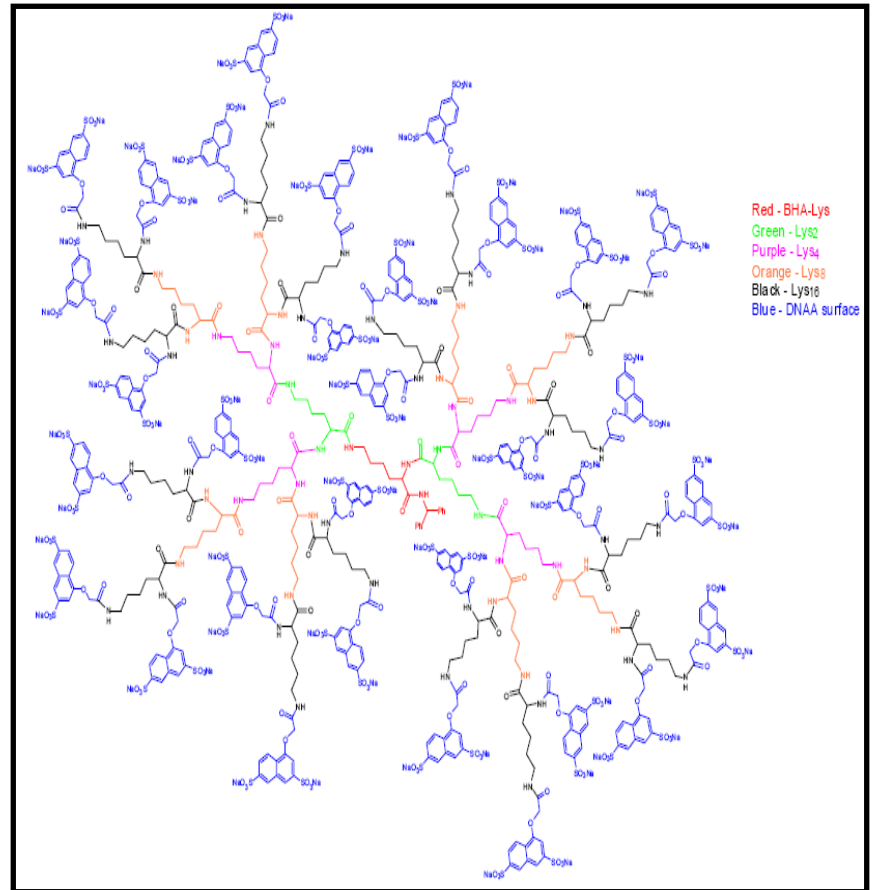
HPTN-035 Demographic Data

	BufferGel	PRO 2000	Placebo	No Gel
Average age (years)	26.2	26.3	26.5	26.3
Attended secondary school	63%	64%	62%	63%
Married	62%	62%	63%	63%
Earns own income	43%	39%	42%	40%

MTN-004 / ATN-062

MTN-004

- Phase 1, SPL7103 (VivaGel®) or placebo gel
- HIV-uninfected sexually active young women
- 18-24 years of age
- NICHD/ATN collaboration
- Includes innovative telephone diary sub study (ATN-062)



MTN-004

- Phase 1, double blind, randomized, controlled comparison with 14 days of twice daily exposure to 3% w/w SPL7103 Gel or placebo gel in HIV-uninfected sexually active women

Arm	Description	N	Frequency
1	SPL7013 Gel	20	BID (14 days)
2	SPL Placebo Gel	20	BID (14 days)
3	HEC Placebo Gel	20	BID (14 days)



MTN-004 Endpoints

- Primary
 - Safety
 - Genital, general, laboratory
- Secondary
 - Adherence
 - Acceptability
 - Vaginal microflora
- Exploratory
 - Biomarkers
 - PK
 - Colposcopy

Microbicide Safety and Acceptability in Young Men



i love my boo.

We're about trust, respect and commitment.

Safer sex is one way we show our love.

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hotline@gmhc.org
www.gmhc.org

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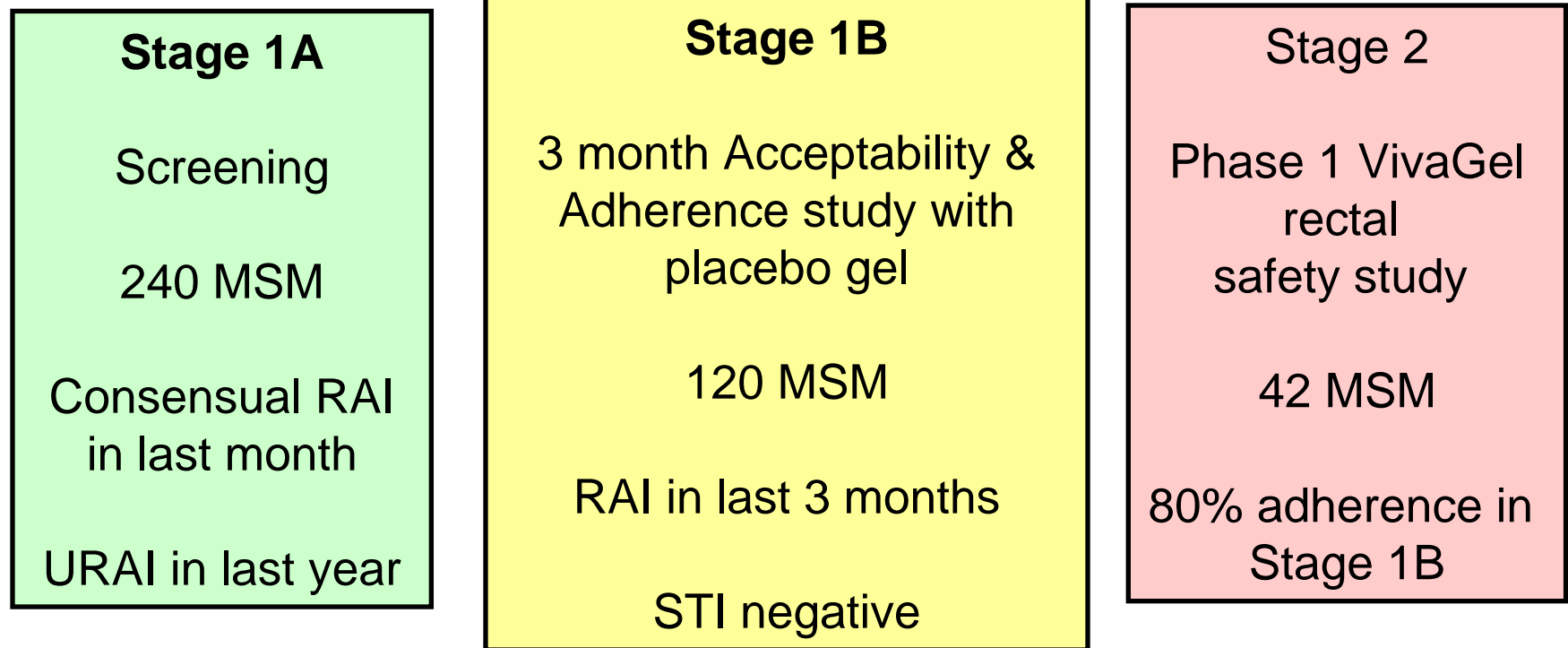
the institute **GMHC**
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Microbicide Safety and Acceptability in Young Men

- NICHD R01 submission
 - McGowan / Carballo-Diequez
 - Pittsburgh, Boston, Puerto Rico
- Phase 1 safety and acceptability of VivaGel
 - Ethnically diverse MSM (18-30)
 - Consensual RAI in last month
 - Unprotected RAI in last year

Microbicide Safety and Acceptability in Young Men





Challenges in Adolescent Recruitment

- Consent
- Perceived coercion
- Community acceptance
- Legal environment
- Regulatory authorities
- Use of contraception / pregnancy



Summary

- Microbicides have the potential to significantly impact HIV transmission
- To date most studies have enrolled women >> 21 years of age
- More recent studies have, or will, enroll from 18 years
- Additional studies are needed to target younger age groups



Acknowledgements

- MTN is funded by NIAID (5U01AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health