

Development of Rectal Microbicides

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Overview

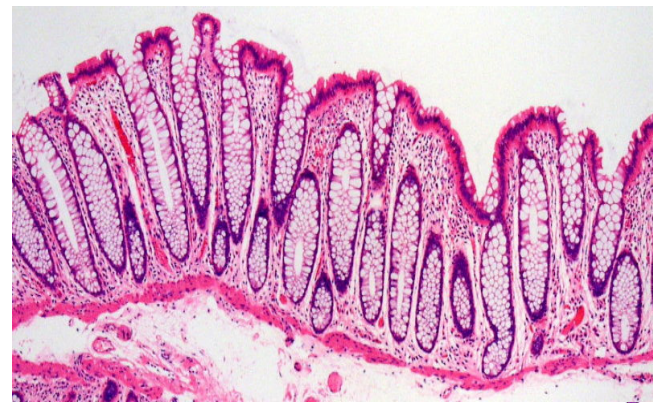
- Rationale for rectal microbicide development
- Preclinical development of candidate rectal microbicides
- Formulation considerations
- Design of Phase 1 rectal safety studies
- Moving towards effectiveness studies

Rationale for Rectal Microbicide Development

Why Do We Need Rectal Microbicides?

- Unprotected receptive anal intercourse (RAI) is the highest risk sexual activity for HIV transmission
- Men and women in the developed and developing world practice RAI
- Murine and non human primate studies have shown proof of concept that rectal application of ARV microbicides can prevent SIV/HIV infection

Rectosigmoid Anatomy



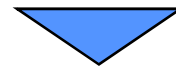
Preclinical Development of Candidate Rectal Microbicides



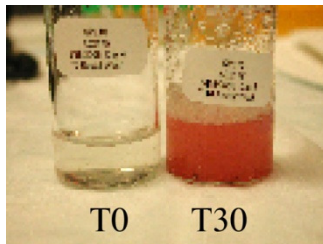
Rectal Model
Development
*Macaca
nemestrina*

Rectal Lavage Assay

Lavage
fluid

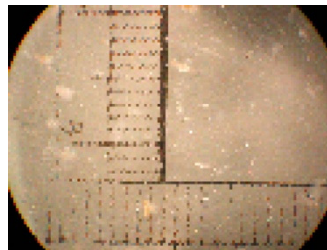


Day 4
Combo
Animal



T0 T30

Day 4, T0
24 hrs post
3rd application



7X

Day 4, T30 post 4th application



7X

15X

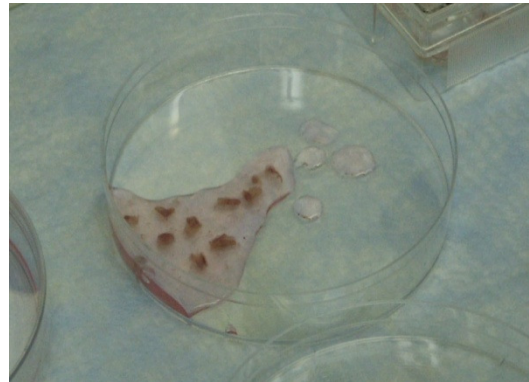
30X

**Microbicides 2008 Poster #TA-057*

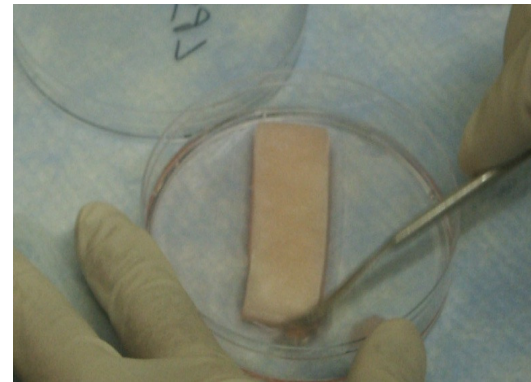
Microbicide Toxicity in NHP Model

Product	Toxicity
BufferGel	Acceptable
Nonoxynol-9	Acceptable
C31G	Acceptable
Octylglycerol	Acceptable
Polystyrene sulfates	Acceptable
Cellulose sulfates	Acceptable
VivaGel	Acceptable
Carraguard	Acceptable
UC781	Acceptable
VivaGel + BufferGel	Unacceptable

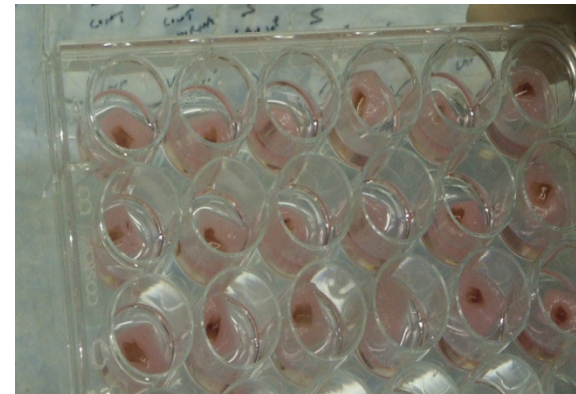
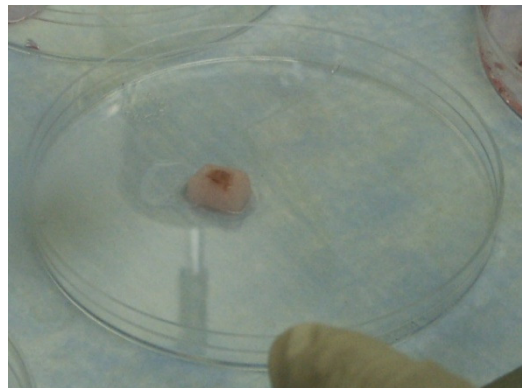
Colorectal Intestinal Explants



Endoscopic biopsies

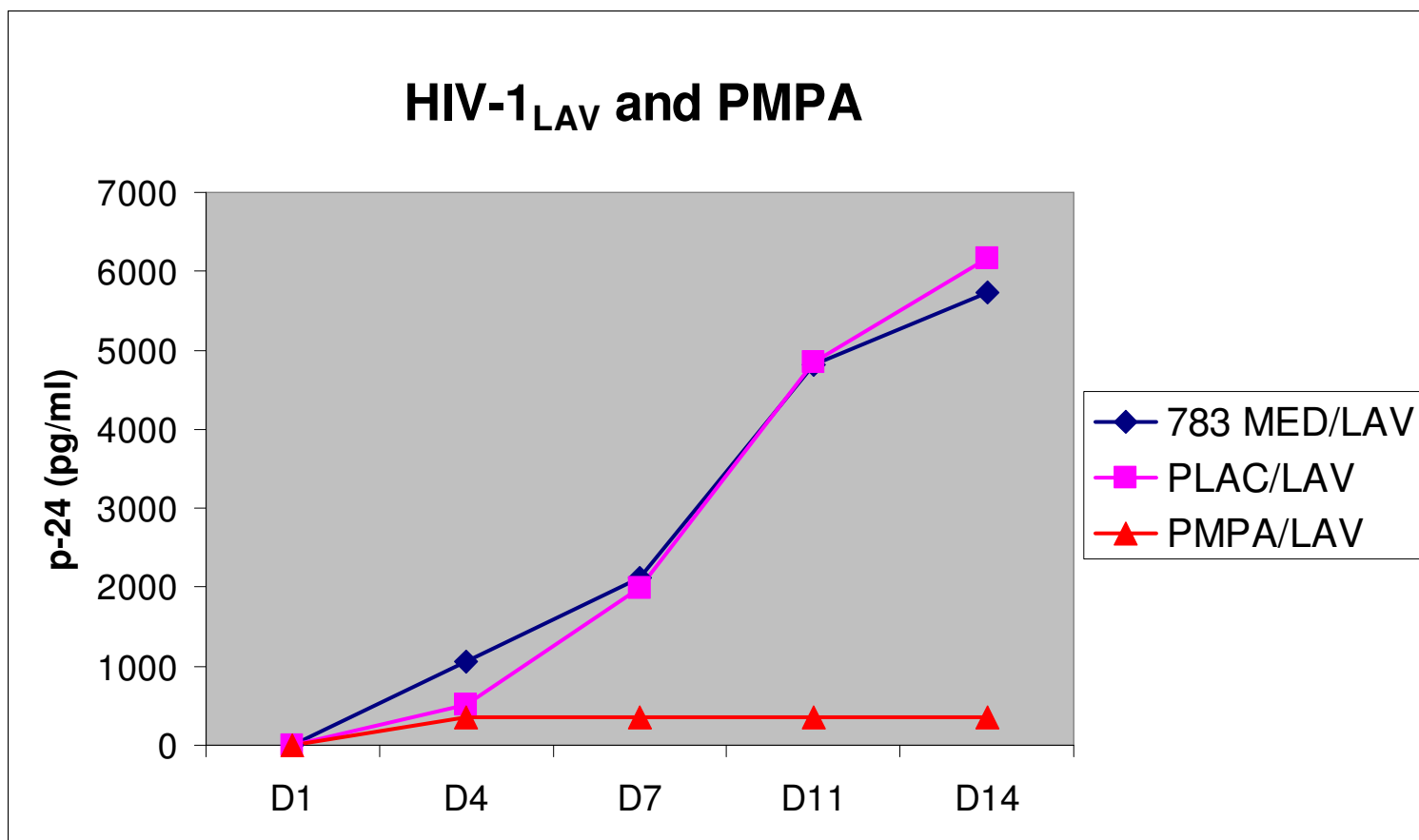


+ Absorbable gelatin sponge

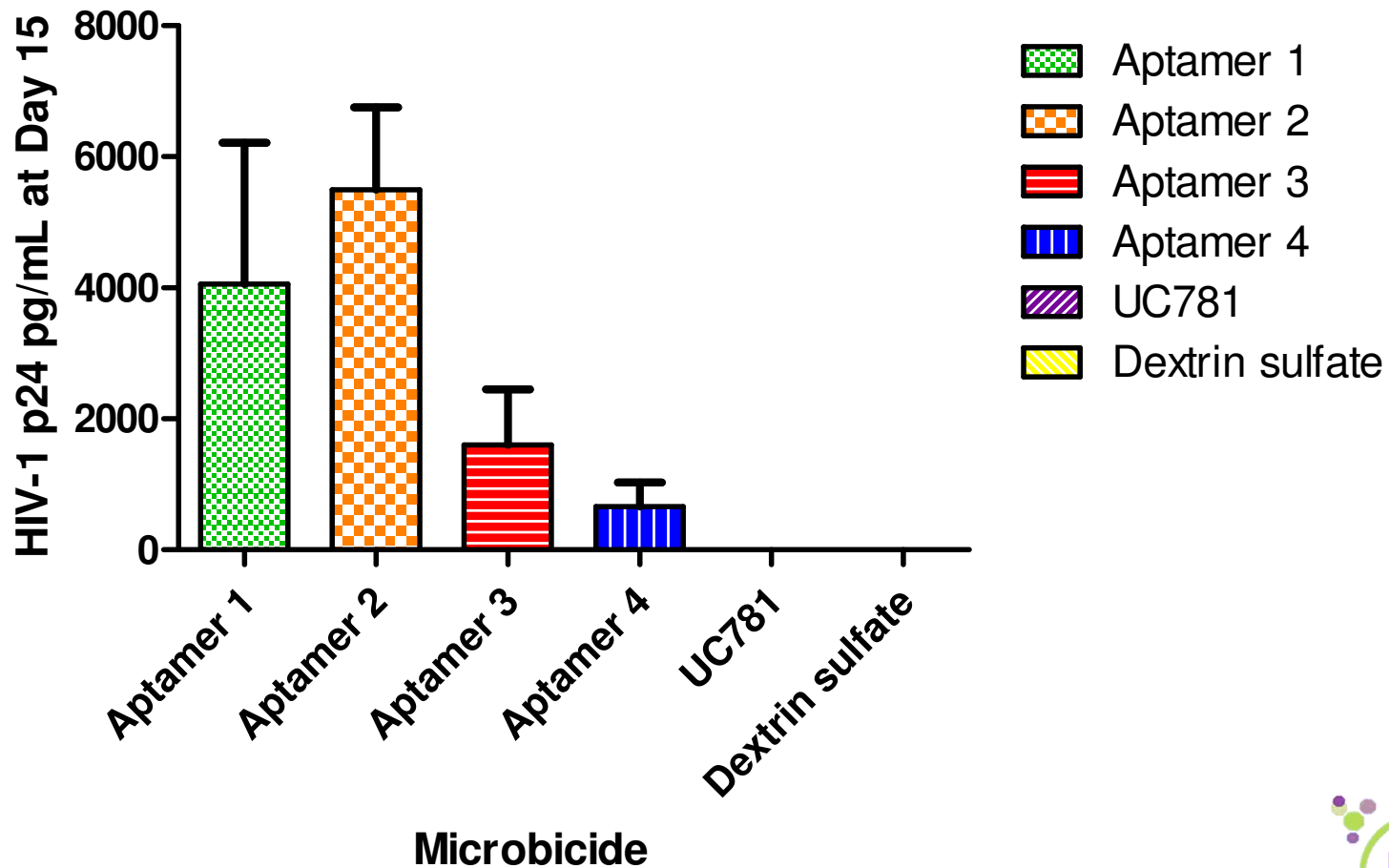


Abner SR et al. JID 2005, Fletcher P et al. AIDS 2006

Tenofovir Explant Data



Aptamer Explant Data



Formulation Considerations

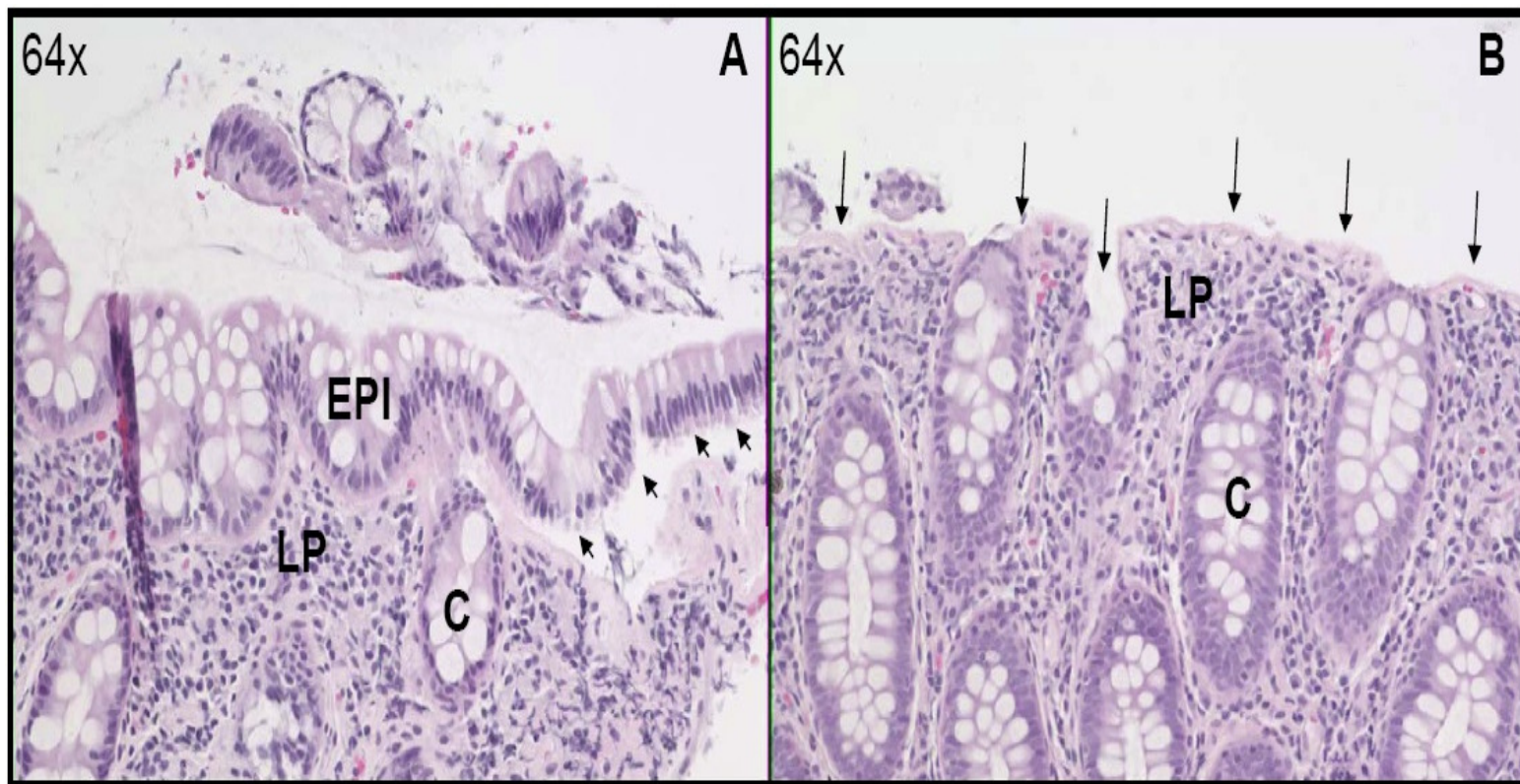
Lubricants Vary in Osmolality

Product	Osmolality (Median mOsm/Kg)
Tap water	3
Femglide	42
Semen	340
Gynol II	1182
Fleet enema	2127
KY Jelly	2424
Astroglide	3126
Prepair	4026

Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar



Fuchs et al J Infect Dis 2007

Rectal Specific Applicators

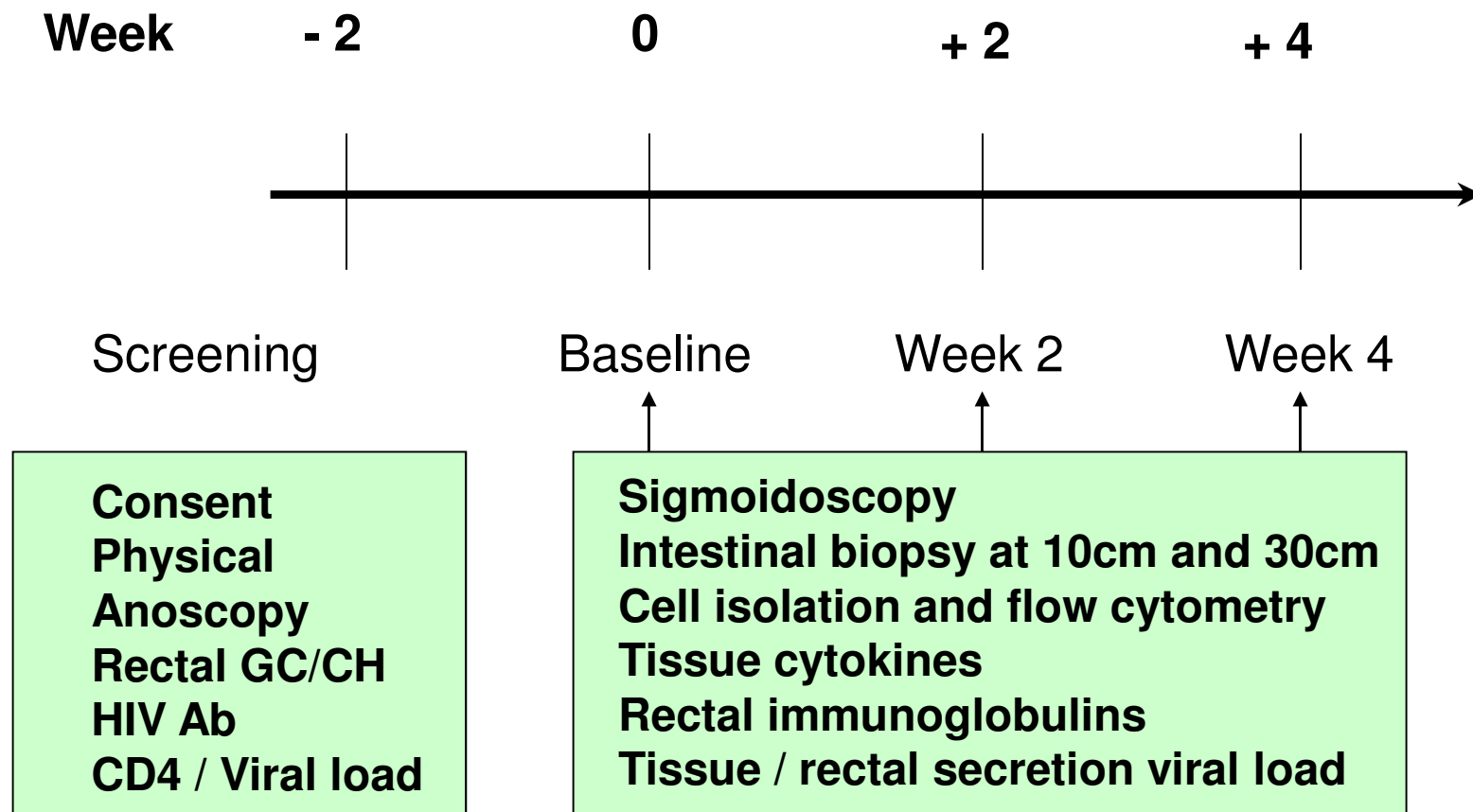
- Incorporates Fleet TM tip
- Can be operated with one hand
- Has grips for the fingers
- Can deliver a precise dose up to 10 ml
- Used across clinical trials, this MDD will reduce sources of acceptability and adherence variability
- Can be manufactured in gray color

Carballo-Dieguez et al.



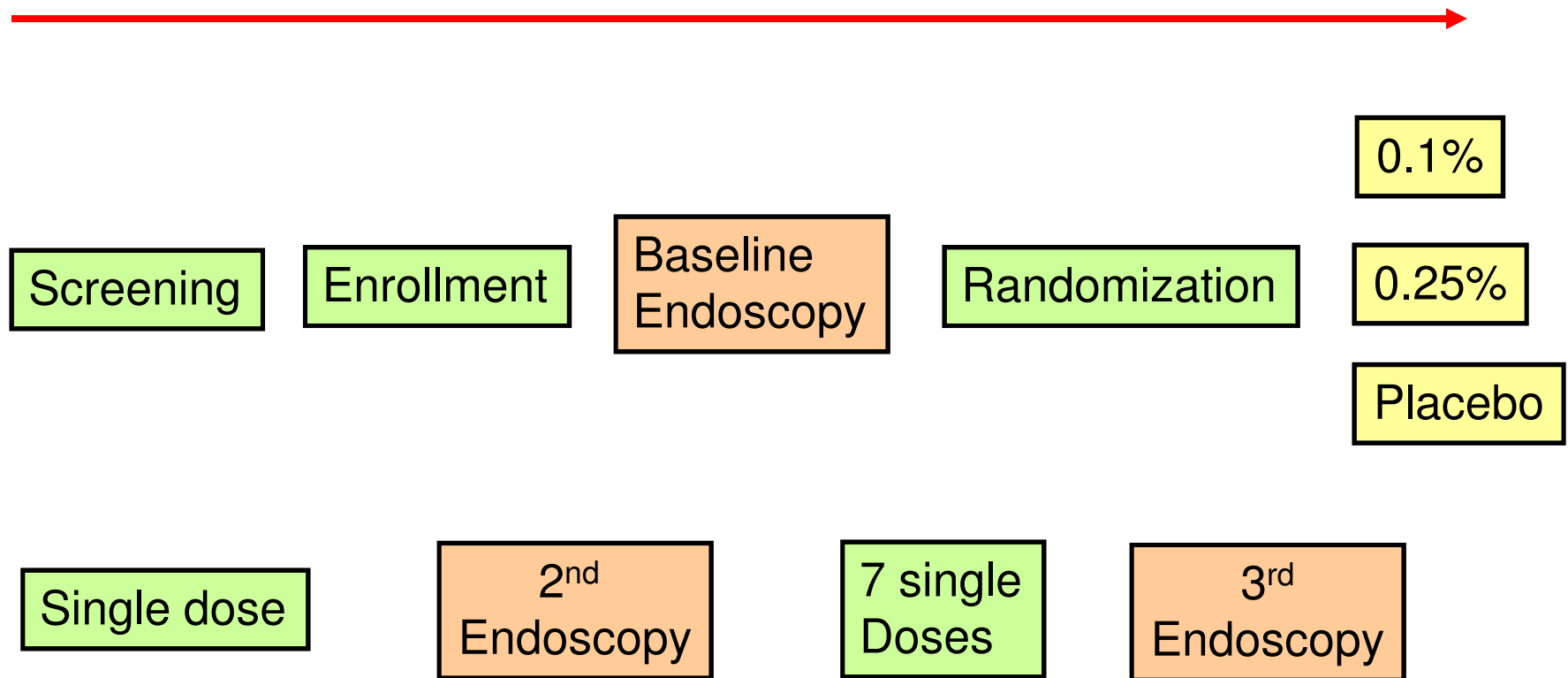
Design of Phase 1 Rectal Safety Studies

HPTN 056 Study Design

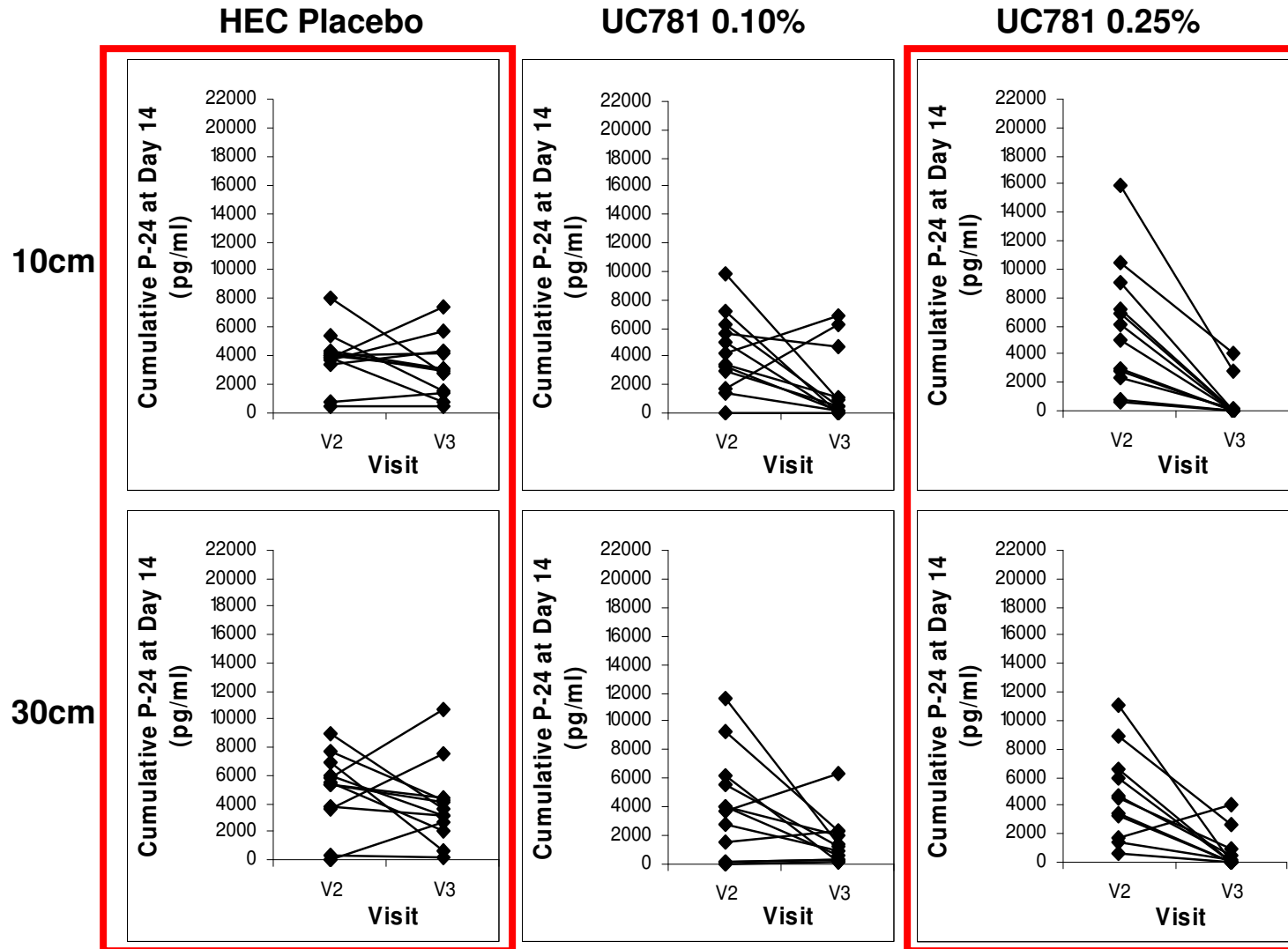


McGowan et al. JAIDS 2007

UC-781 Trial Design



Colorectal Explant Data

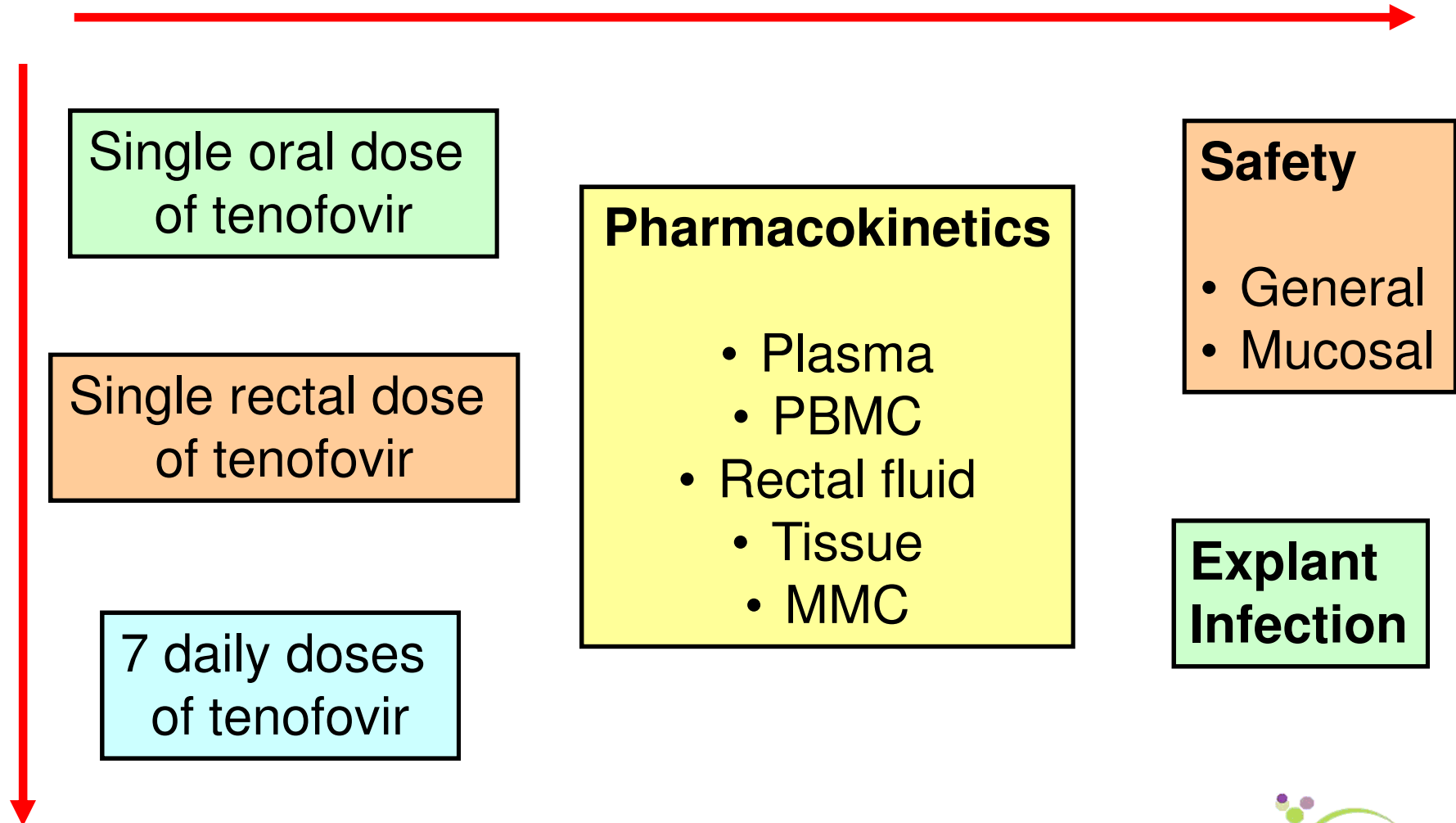


Anton et al. CROI 2009

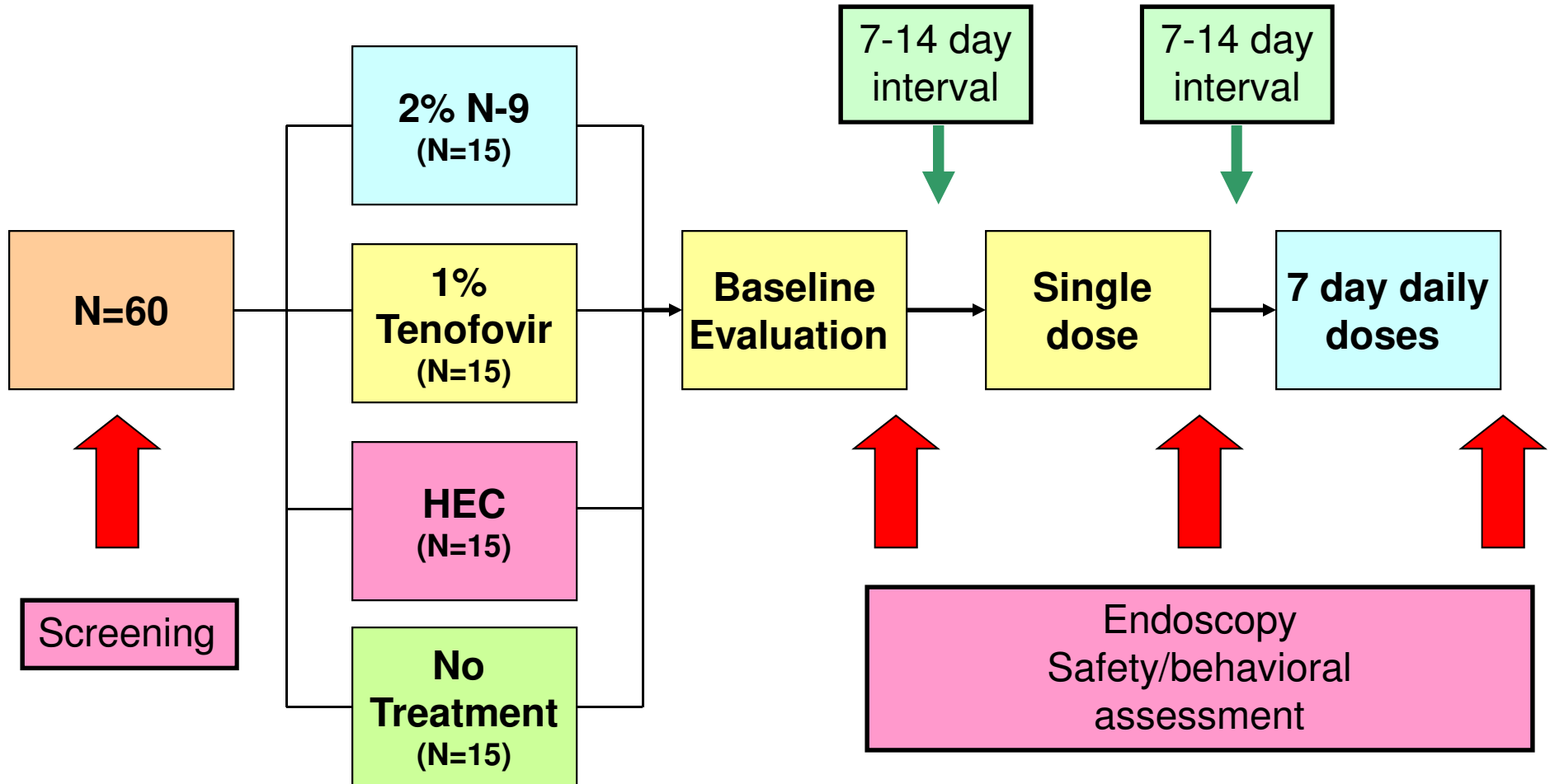
Phase 1 Rectal Microbicide Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Completed		DAIDS
MTN-007	Planned	Q3 2009	DAIDS
RMP-02 /MTN-006	Planned	Q3 2009	DAIDS
VivaGel	Planned	Q3 2010	NICHD
PRO-2000	Planned	Q1 2010	MRC-UK
Tenofovir (RF)	Planned	Q4 2010	DAIDS

RMP-02 / MTN-006



MTN-007



Moving Towards Effectiveness Studies



“For this reason, NIAID places a priority on developing HIV prevention tools that women can implement independently. One such method under study is a microbicide—a gel, cream or foam intended to prevent the sexual transmission of HIV when applied topically inside the vagina or **rectum**.

Statement of Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health on National Women and Girls HIV/AIDS
Awareness Day
March 10, 2009



Next Steps

- Identify relevant populations
- Develop rectal specific products
- Design rectal specific applicator
- Expanded safety study
- Effectiveness study

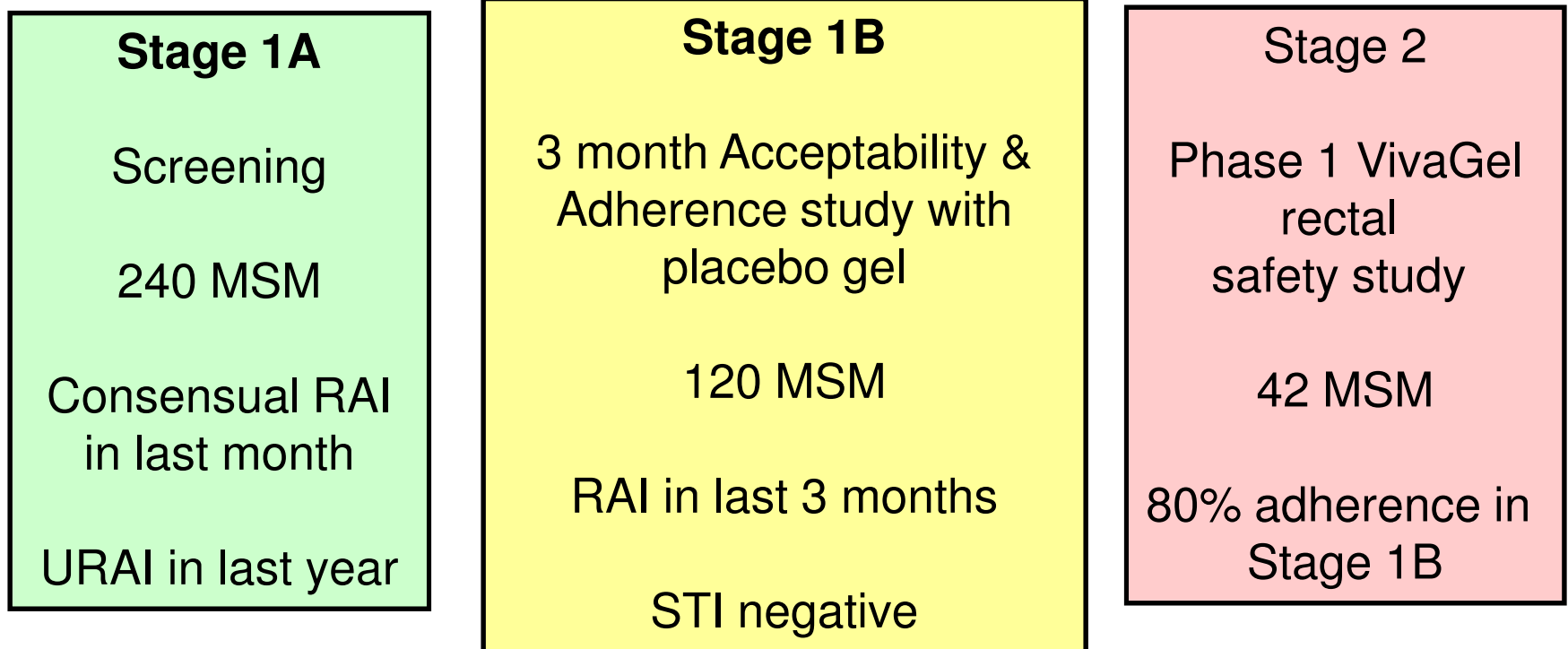
Populations for RM studies

- Phase 2 studies
 - RAI sexually active men and women
 - Higher risk populations
- Phase 2B studies
 - 3% seroincidence MSM populations
 - North America
 - Latin America
 - Asia
 - Africa

Microbicide Safety and Acceptability in Young Men

- NICHD R01
 - 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



McGowan & Carballo-Diequez 2009

Rectal Specific Products

- CHARM Program
 - Combination HIV Antiretroviral Microbicide Program
 - DAIDS IPCP Program
 - PI: Ian McGowan MD PhD
 - Consortium
 - University of Pittsburgh
 - UCLA
 - Johns Hopkins
 - UNC
 - CONRAD

Phase 2 Expanded Rectal Safety Study

- Double blind placebo controlled
- Population:
 - 300 RAI sexually active men and women with 6 month follow-up
- Three study arms:
 - Oral tenofovir + placebo tenofovir gel
 - Placebo oral tenofovir + tenofovir gel
 - Oral tenofovir + tenofovir gel
- Study endpoints
 - Safety
 - PK substudy
 - Explant efficacy substudy

Phase 2B Rectal Safety and Effectiveness Study

	Placebo Study
Study Arms	Oral tenofovir + Placebo gel
	Oral placebo + Tenofovir gel
	Oral tenofovir + Tenofovir gel
	Oral placebo + Placebo gel
Seroincidence	4%
Power	90%
Endpoints per pair wise comparison / total	90-100 2 pair wise comparisons Total: 180-200
Person years per endpoint	40-50
Follow-up	2 years
Sample size	3,500 – 5,000

	Placebo Study	Active Comparator Study
Study Arms	Oral tenofovir + Placebo gel	Oral tenofovir
	Oral placebo + Tenofovir gel	Oral tenofovir + Tenofovir gel
	Oral tenofovir + Tenofovir gel	
	Oral placebo + Placebo gel	
Seroincidence	4%	4%
Power	90%	90%
Endpoints per pair wise comparison / total	90-100 2 pair wise comparisons Total: 180-200	88 1 pair wise comparison Total: 88
Person years per endpoint	40-50	120
Follow-up	2 years	2 years
Sample size	3,500 – 5,000	5,000

Summary

- There is a clear rationale for the development of rectal microbicides
- The design of rectal safety studies now includes immunotoxicity assays
- Rectal specific products and applicators are being developed
- It is time to move to the Phase 2 and beyond

Acknowledgements

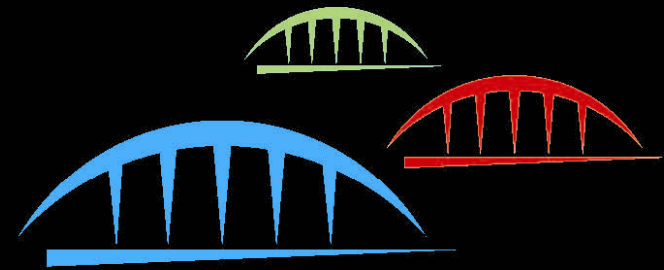
MTN is funded by NIAID (5U01AI068633-03),
NICHD and NIMH, all of the U.S. National
Institutes of Health.



SAVE THE DATE!

May 22-25, 2010
Pittsburgh, Pennsylvania, USA

www.microbicides2010.org



M2010

MICROBICIDES:
Building Bridges
in HIV Prevention