Rectal Microbicides in 2014

Ian McGowan MD PhD FRCP

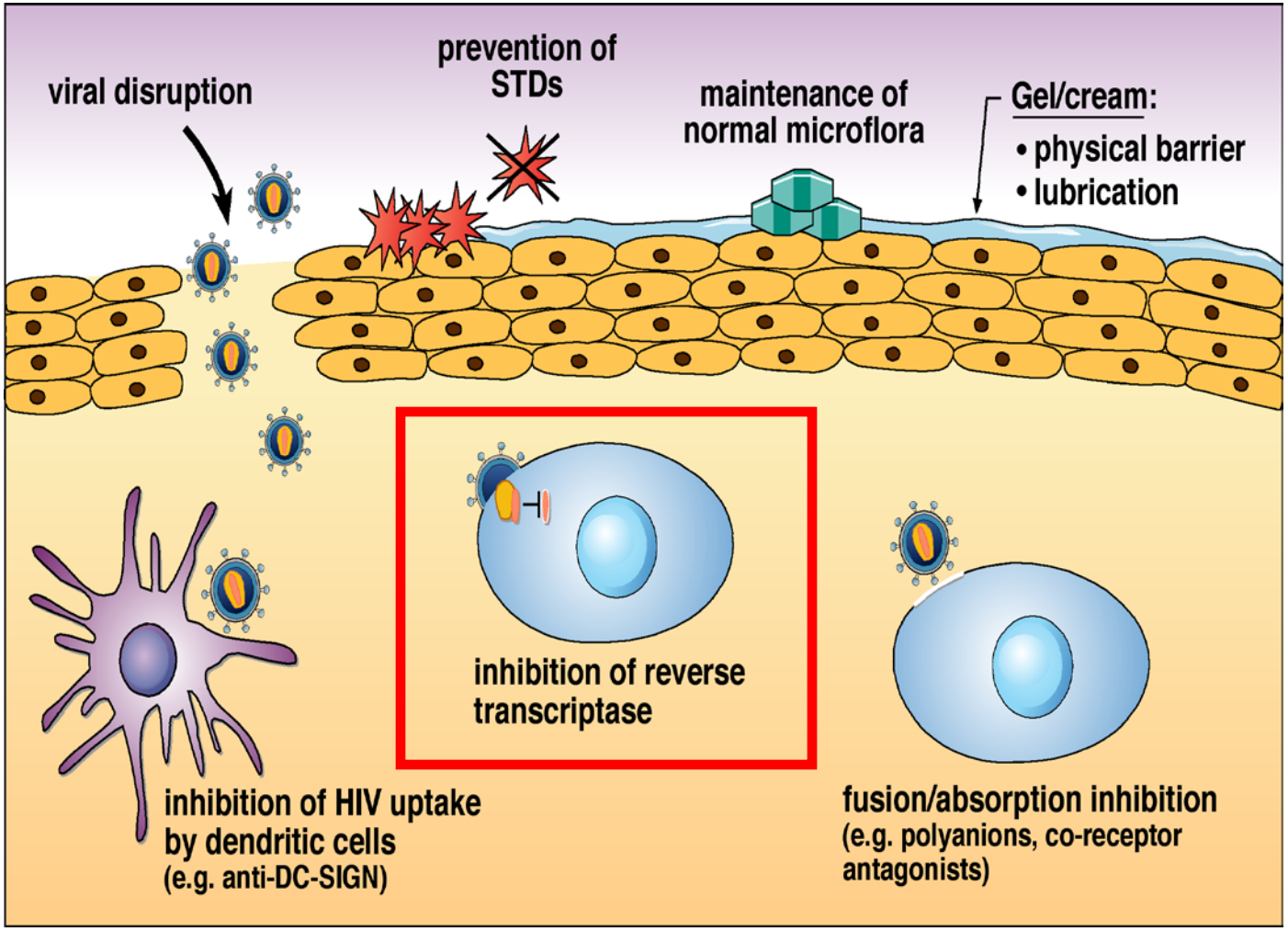
Creating Desire Meeting

Arlington, VA

13th May, 2014

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

Microbicide Mechanism of Action



McGowan I, *Biologicals*, 2006

Microbicides

A Brief History of Rectal Microbicides

Early Events

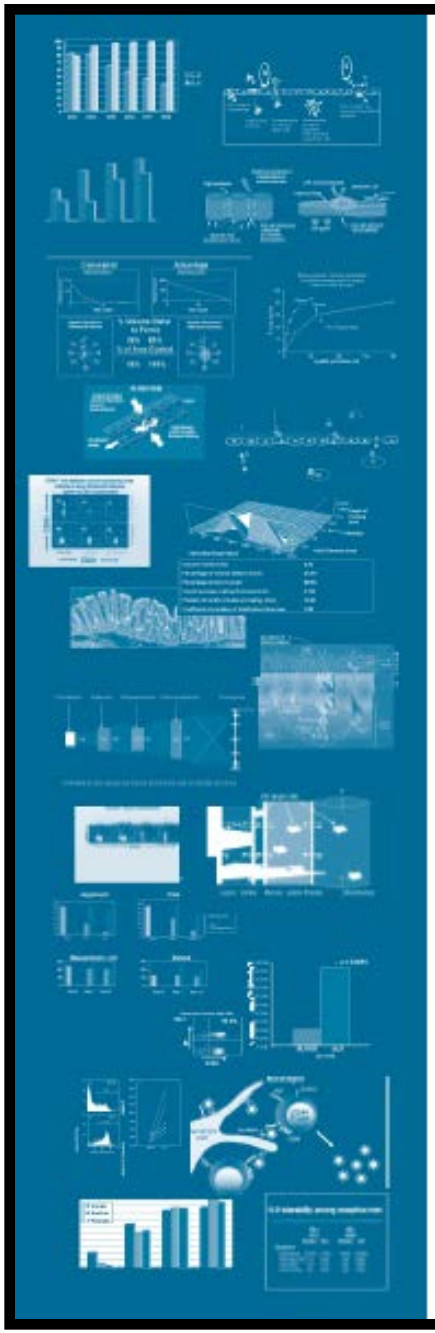
1999: Beyond condoms - life after latex Michael Scarce

THE BODY
The Complete HIV/AIDS Resource
With 550+ Topic Areas!

1999: Microbicides: Anna Forbes & Polly Harrison

Second LGBTI Health Summit. Colorado

2000: Rectal Microbicides: Anna Forbes



Creating a Research and Development Agenda for

Rectal Microbicides that Protect Against HIV Infection

Report from the Workshop:
Baltimore, Maryland, June 7–8, 2001

This report was published by the
American Foundation for AIDS Research.

amfAR
AIDS RESEARCH

Goals of the 2001 Symposium

- Establish the current state of knowledge across those disciplines that bear on rectal microbicide research and development
- Identify biomedical and behavioral research priorities for advancing an understanding of rectal physiology, particularly in the context of sexual acts, mechanisms of HIV transmission, and the potential role of topical agents in conferring protection against rectal HIV infection

- Outline key considerations associated with studies of product acceptability, including applicator design
- Propose an appropriate clinical strategy for rectal microbicides

What Happened Next?

Key Events in RM Development

2005
IRMA

2006
MTN
MTN-006
MTN-007
MTN-017

2009
Project Gel

2014
MTN

2014
DREAM Program
U19 IPCP
Grant

2004
MDP Program
U19 IPCP
Grant

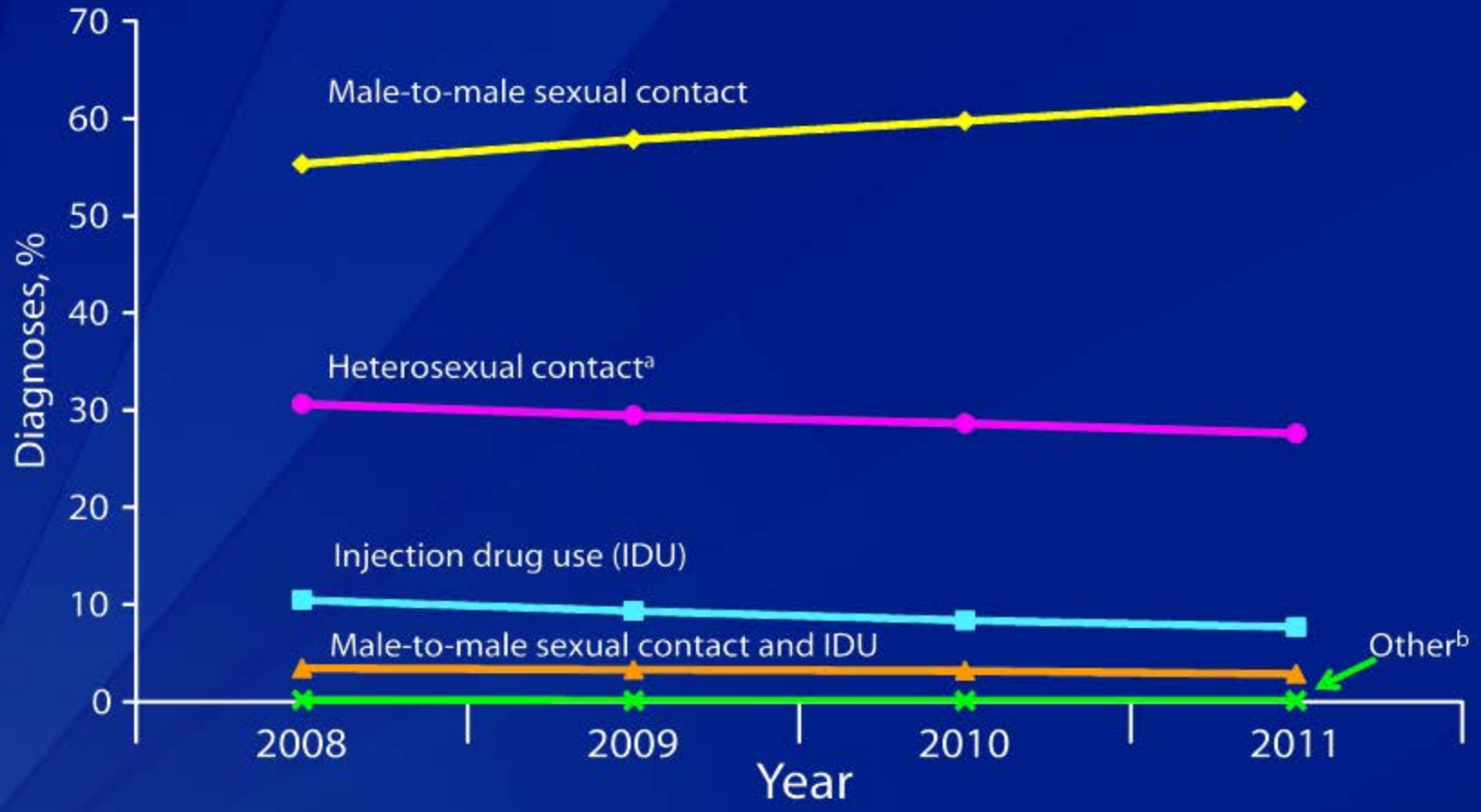
2005
Aptamer
U01
Grant

2009
CHARM Program
U19 IPCP
Grant

2014
PREVENT Program
U19 IPCP
Grant

Are Rectal Microbicides Needed in 2014?

Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2008–2011—United States and 6 Dependent Areas



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

[a] Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

[b] Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

CDC

Would Anyone Use a Rectal Microbicide?

Lubricant Use is Common Among MSM

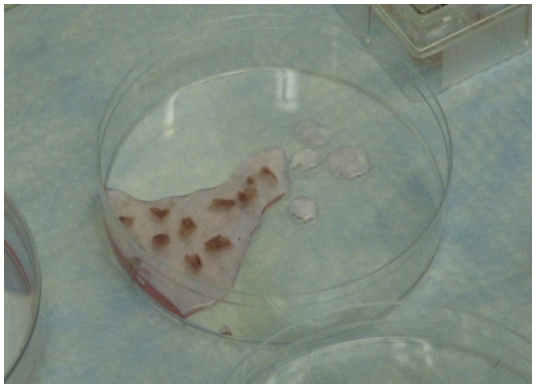
Carballo-Dieguez A et al., *Am J Pub Health,* 2000

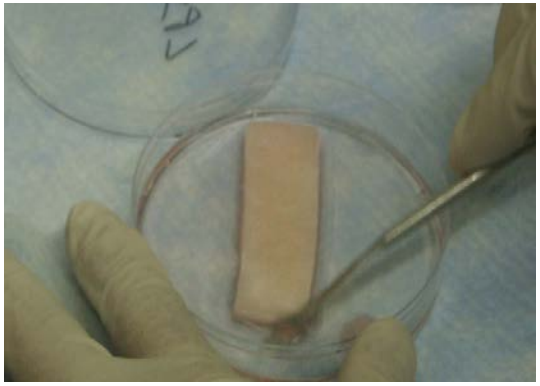
Where is the Science?

Non Human Primate Studies

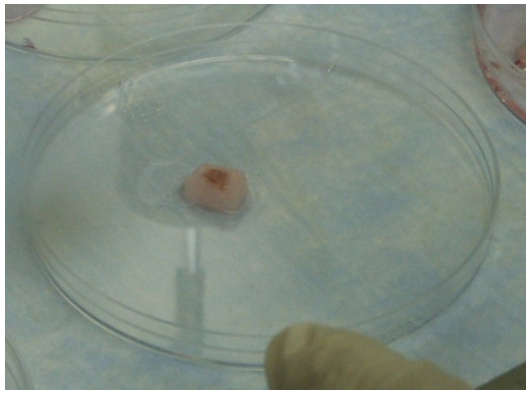
- Cyanovirin-N / SHIV89.6P
  - Tsai CC et al., *AIDS Res Hum Retroviruses,* 2003
- Tenofovir / SIVmac251/32H
  - Cranage M et al., *PLOS Med,* 2008
- MIV-150 / SIVmac239
  - Singer R et al., *J Virol,* 2011
- Maraviroc
  - Dobard C et al., Abstract, 2013

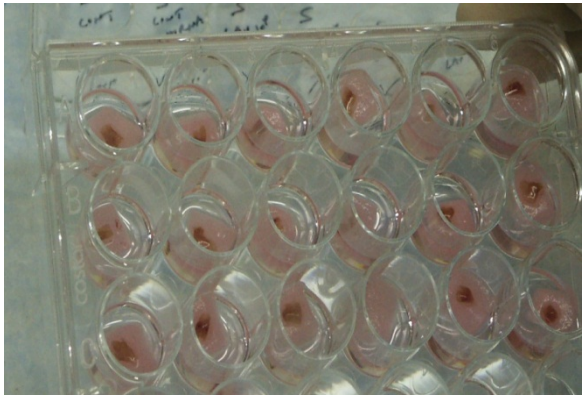
Colorectal Intestinal Explants





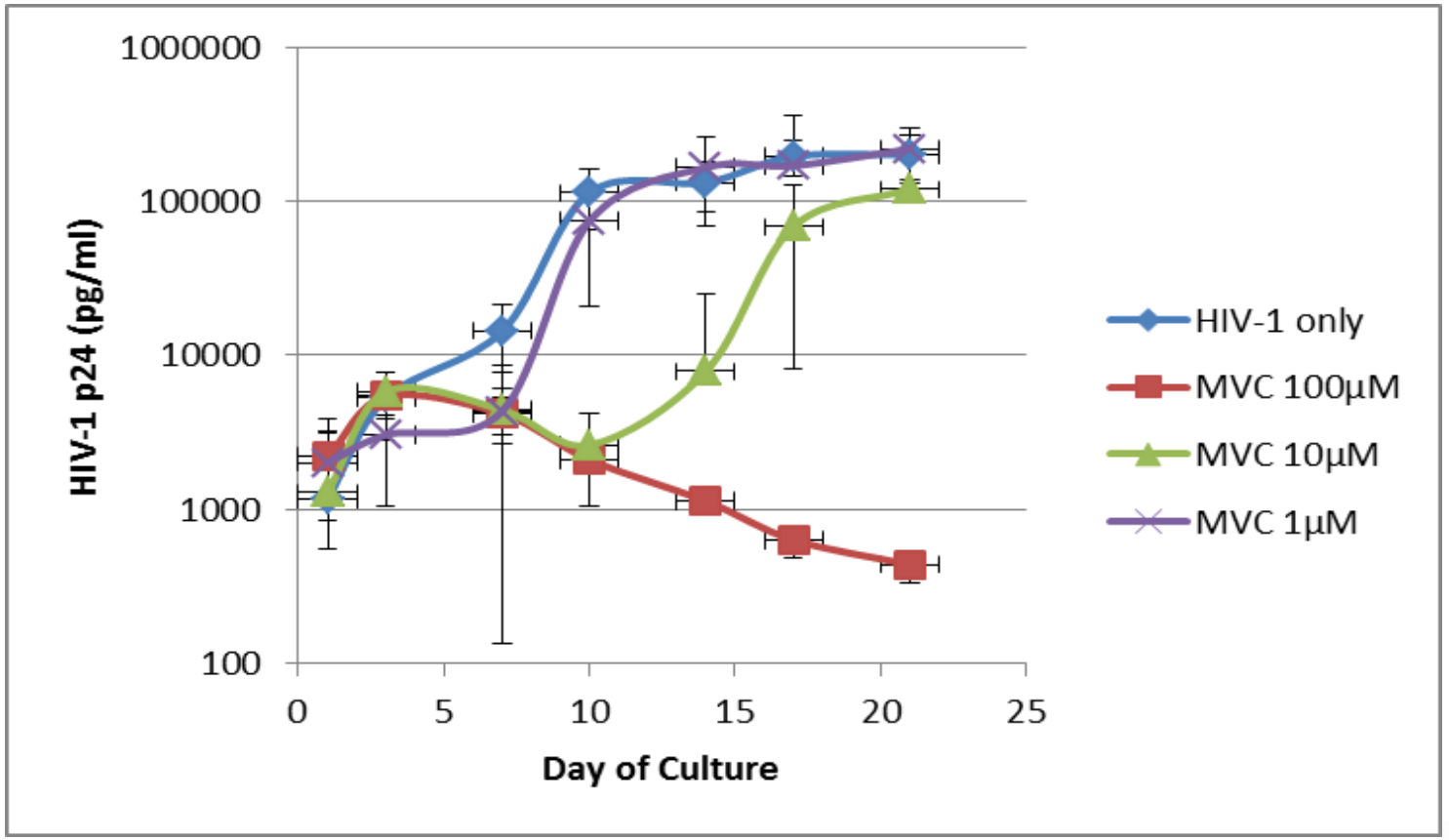
Endoscopic biopsies **+** **Absorbable gelatin sponge**





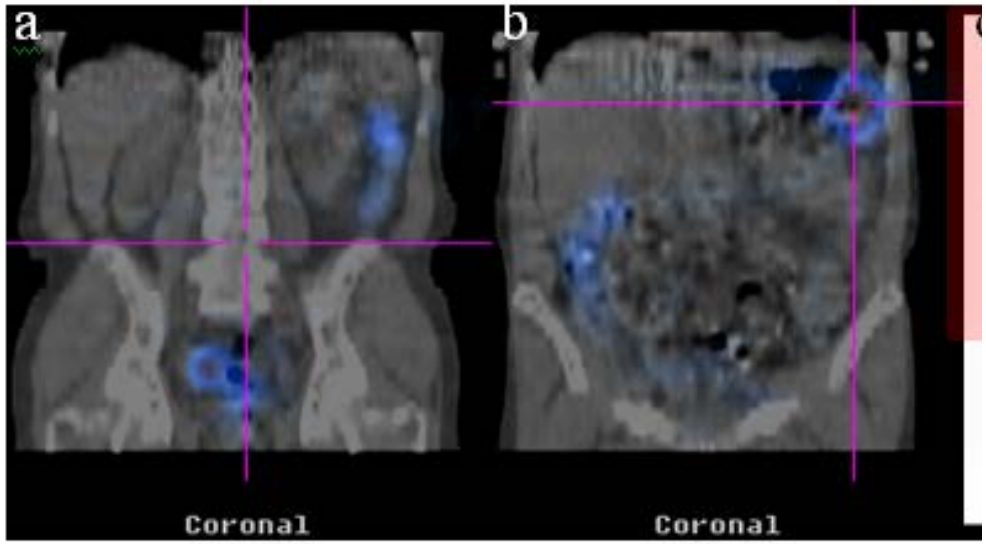
Abner SR et al., *JID*, 2005
Watts P et al., *AIDS*, 2006

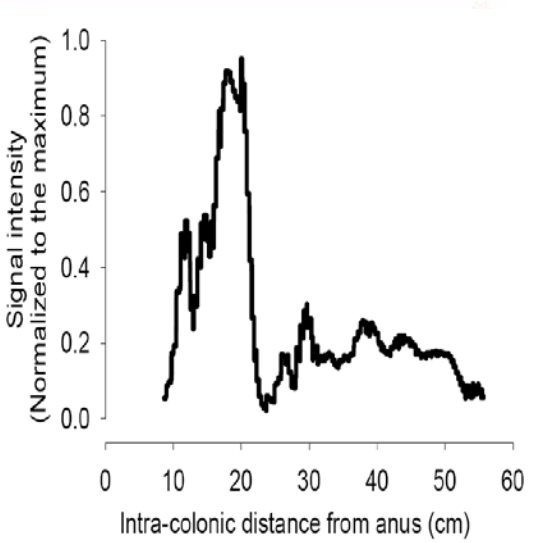
Maraviroc *In Vitro* Colorectal Explant Efficacy Data



Dezzutti C et al., CHARM Project 1, unpublished data

Product Distribution





Goldsmith J et al., *Ann Stat App,* 2011

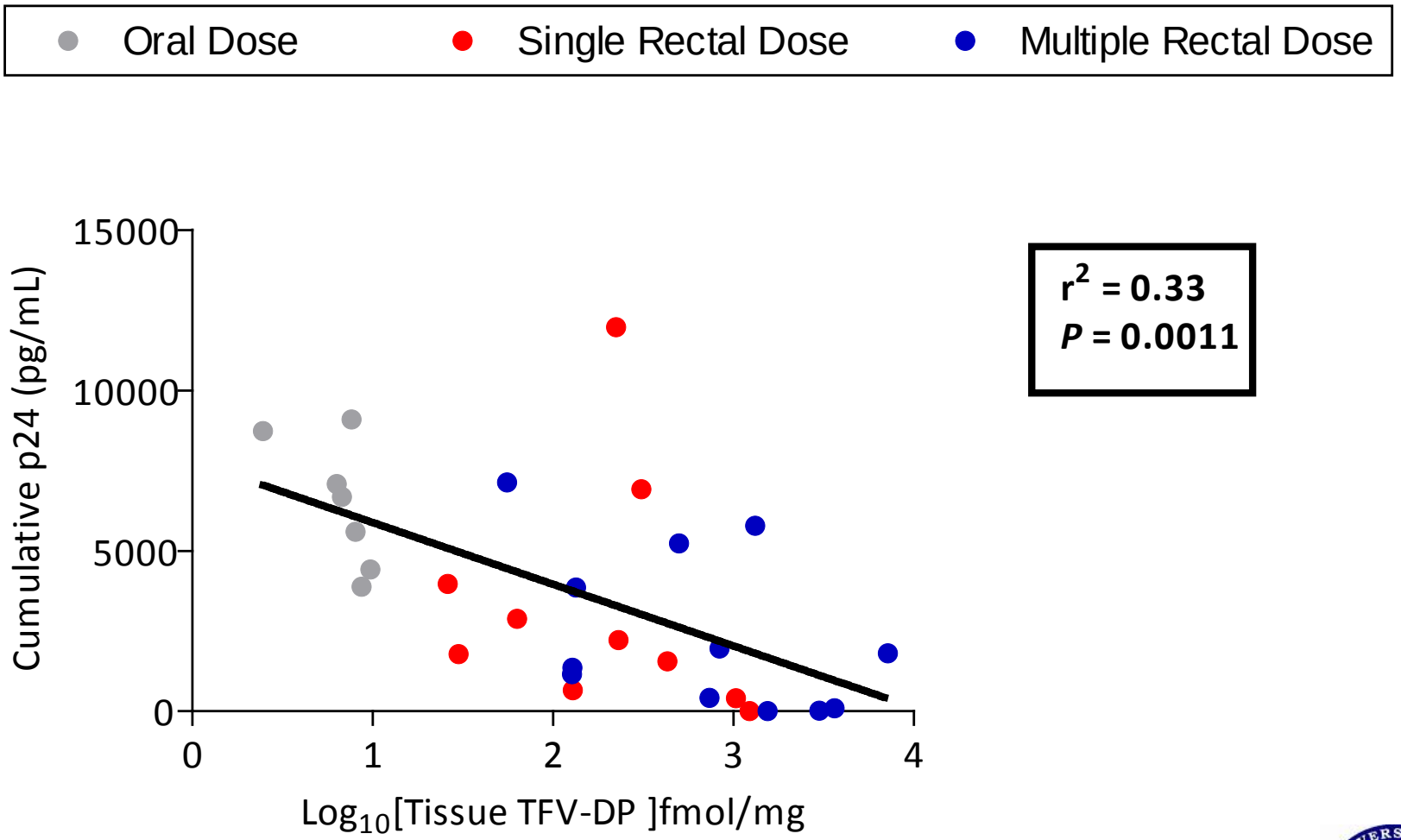
Phase 1 Development

- Nonoxynol-9 (HIVNET-008 study)
  - Tabet S et al., *Sex Transm Infect,* 1999
- UC781 (RMP-01 study)
  - Anton PA et al., *PLOS ONE,* 2011
- Tenofovir (original formulation) (RMP-02/MTN-006 study)
  - Anton PA et al., *AIDS Res Hum Res,* 2012
- Tenofovir (reduced glycerin formulation) MTN-007
  - McGowan I et al. *PLOS ONE,* 2013

Adverse Events in Trials

GI Adverse Events in the Tenofovir Arm	MTN-007 (N = 16)		RMP-02/MTN-006 (N = 12)	
			N	%
Abdominal pain	3	16%	6	50%
Rectal urgency	0	0%	5	42%
Bloating	0	0%	5	42%
Nausea	0	0%	4	33%
Diarrhea	1	6%	7	58%
Flatulence	6	38%	3	25%
Proctalgia	1	6%	0	0%
Other	4	25%	5	42%
Total	**9**	**56%**	**12**	**100%**

PK/PD Relationship



Anton et al. *AIDS Res Hum Res*, 2012

CHARM U19 Program Grant

- Combination HIV Antiretroviral Rectal Microbicide Program
  - Preclinical evaluation
  - Humanized mouse model
  - Phase 1 studies
    - CHARM-01 (TFV)
    - CHARM-02 (TFV)
    - CHARM-03 (MVC)

PI: Ian McGowan

Project Gel

PIs: Alex Carballo-Diéguez & Ian McGowan

MTN-017

- Phase 2 rectal safety study of tenofovir gel
- N = 186
- International sites
  - United States (4)
  - Thailand (2)
  - South Africa (1)
  - Peru (1)

- Endpoints
  - Safety
  - Adherence
    - Self report
    - Real time PK
  - Acceptability
  - PK/PD

PI: Ross Cranston, University of Pittsburgh

MTN-017

	8 weeks		8 weeks		8 weeks	
BL	TFV Gel Daily		TFV Gel With sex		Oral Truvada	
BL	TFV Gel With sex		TFV Gel Daily		Oral Truvada	
BL	Oral Truvada		TFV Gel With sex		TFV Gel Daily	

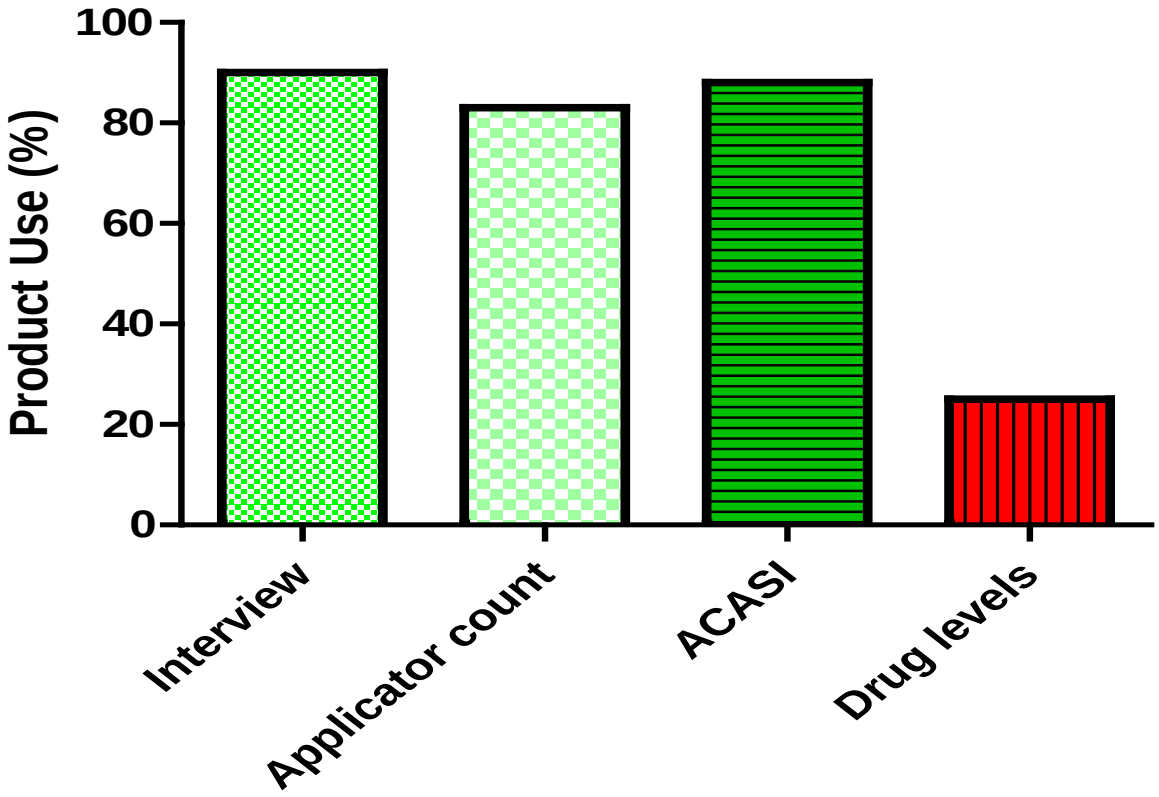
Mucosal PK/PD subset (N = 36)

Phase 3 Development

- Contingent upon supportive data from MTN-017
- Placebo controlled trial of RG-TFV gel on expanded prevention package including access to oral PrEP
- N = 5,000 MSM & transgender women
- One year follow-up period
- US, Latin America, Asia, ± Europe

Why Are We Here Today?

Vaginal Gel Adherence Data



Marrazzo J et al. CROI 2013

Meeting Priorities

- How can we increase desire for rectal microbicide use within clinical trials
  - At an individual level
  - At a community level
- What can we learn from previous studies
- What can be done over the next 2-3 years to maximize the success of product roll-out
- Where are the research gaps?

Funding

- NIH/NIAID/ DAIDS
  - U19 AI060614
  - U19 AI082637
  - U01AI068633-01
  - UM1AI068633
- NIH/NIAID/DMID
  - U01 AI066734
- NIH/NICHD & NIH/NIMH
  - R01 HD059533-01A1

Thank You