

# Welcome and MTN State of the Network

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# Directions

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Where we  
were



Where we  
are headed

Where we are

# 2005



# Microbicide Trials Network

## Reverse Site Visit

Washington D.C.

October 19, 2005



# Microbicide Trials Network Mission Statement

The mission of the Microbicide Trials Network is to reduce the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally.

The goal is to conduct scientifically rigorous and ethically sound clinical trials of safety and effectiveness that will support licensure of topical microbicide products



# What MTN Will Do

- Develop and/or execute 14 separate clinical trials of microbicides over a 7 year period
- Maintain an extremely focused timeline driven research agenda
- Make tough decisions regarding both science and sites
- Not try to be all things to all people

# Product Pipeline in 2005\*

	Membrane Disruption	Defense Enhancers	Entry Inhibitors	Replication Inhibitors	Other
Pre-Clinical			PSC-Rantes Cyanovirin	MIV-150 TMC-125	Aptamers
Phase 1		Acidform™ Lime Juice Lactobacillus crispatus	Cellulose acetate VivaGel™ Invisible condom™	UC781 TMC 120 ring	
Phase 2/2B		Lactobacillus		PMPA TMC120 gel	Praneem Polyherbal
Phase 3	C31G	BufferGel™	Carraguard Cellulose Sulfate PRO 2000 (0.5%, 2%)		

\*Active planning, ongoing, or recently completed studies

Source: Alliance for Microbicide Development, October 2005



# The MTN Portfolio

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# Completed Studies

	Phase	Product (s)	Route
HPTN-059	2	Tenofovir	V
HPTN-035	2/2B	PRO2000, BufferGel®	V
MTN-001	2	Tenofovir	O, V
MTN-002	1	Tenofovir	V
MTN-004	1	VivaGel®	V
RMP-02 / MTN-006	1	Tenofovir	R
MTN-007	1	Tenofovir	R
MTN-009	N/A	Resistance	N/A
MTN-012	1	Dapivirine Gel	P

# Ongoing Studies

	Phase	Product (s)	Route
MTN-003 MTN-003B MTN-003C MTN-003D MTN-003-P01	2B	TVD/TDF/Tenofovir	O, V
MTN-005	1	Placebo ring	V
MTN-008	1	Tenofovir	V
MTN-013	1	Dapivirine, Maraviroc	V
MTN-015	Seroconverter	N/A	N/A
MTN-016	Pregnancy registry	N/A	N/A

# Gone but not Forgotten Studies

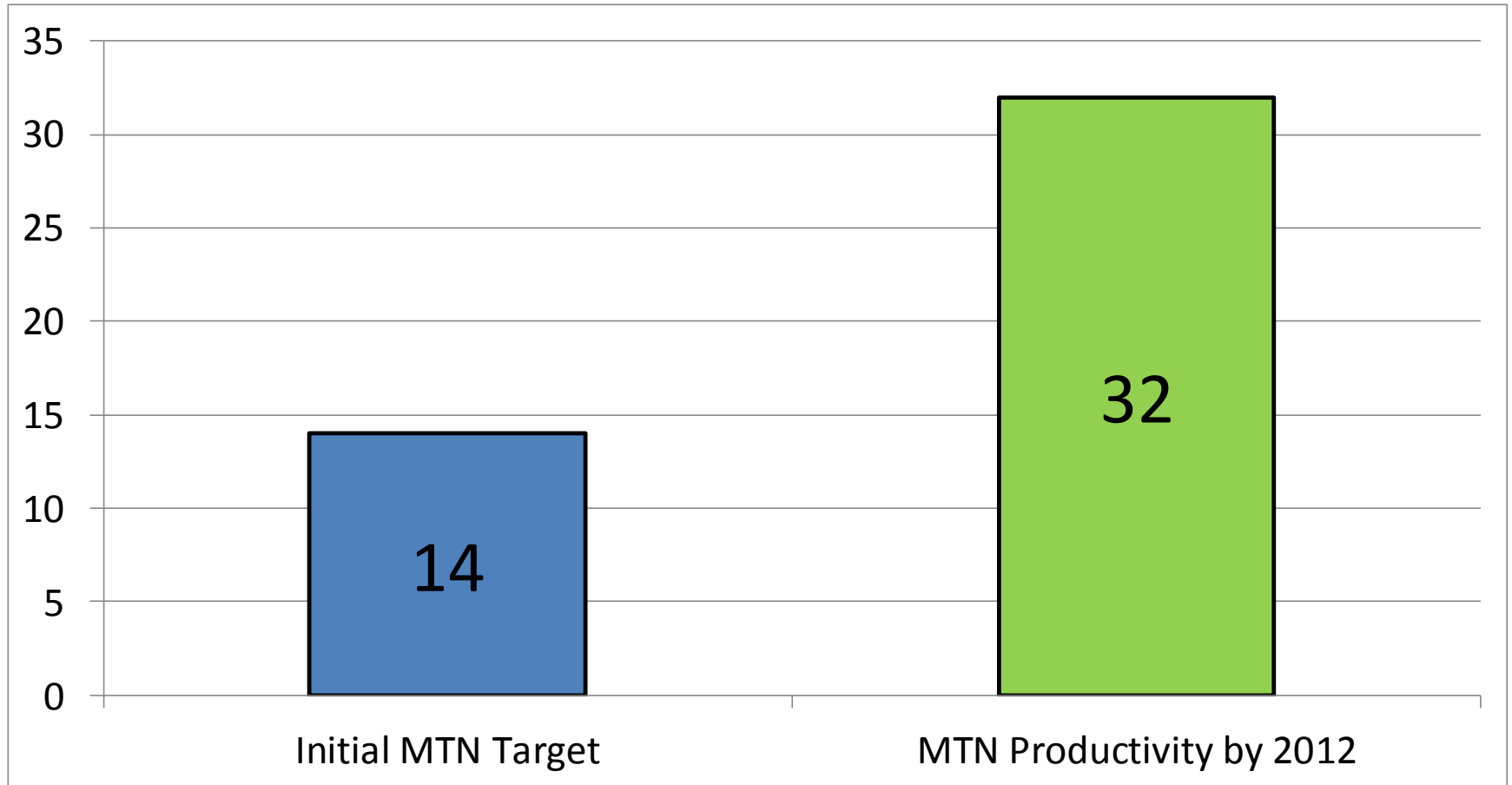
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	Phase	Product (s)	Route
<b>MTN-010</b>	<b>1</b>	UC781	V
<b>MTN-019</b>	<b>1</b>	Tenofovir	V
<b>MTN-021</b>	<b>1</b>	Tenofovir	V

# Studies in Preparation

	Phase	Product (s)	Route
MTN-011	1	Tenofovir	V
MTN-014	1	Tenofovir	V, R
MTN-017	1	Truvada, Tenofovir	O, R
MTN-018 MTN-018B MTN-018C	3B	CHOICE	O
MTN-020	3	Dapivirine ring	V
MTN-022	2	Tenofovir, Truvada HIV vaccine	V
MTN-023	1	Dapivirine ring	V
MTN-024	1	Dapivirine ring	V

# Protocol Summary in 2012



# MTN's Contributions to HIV Prevention

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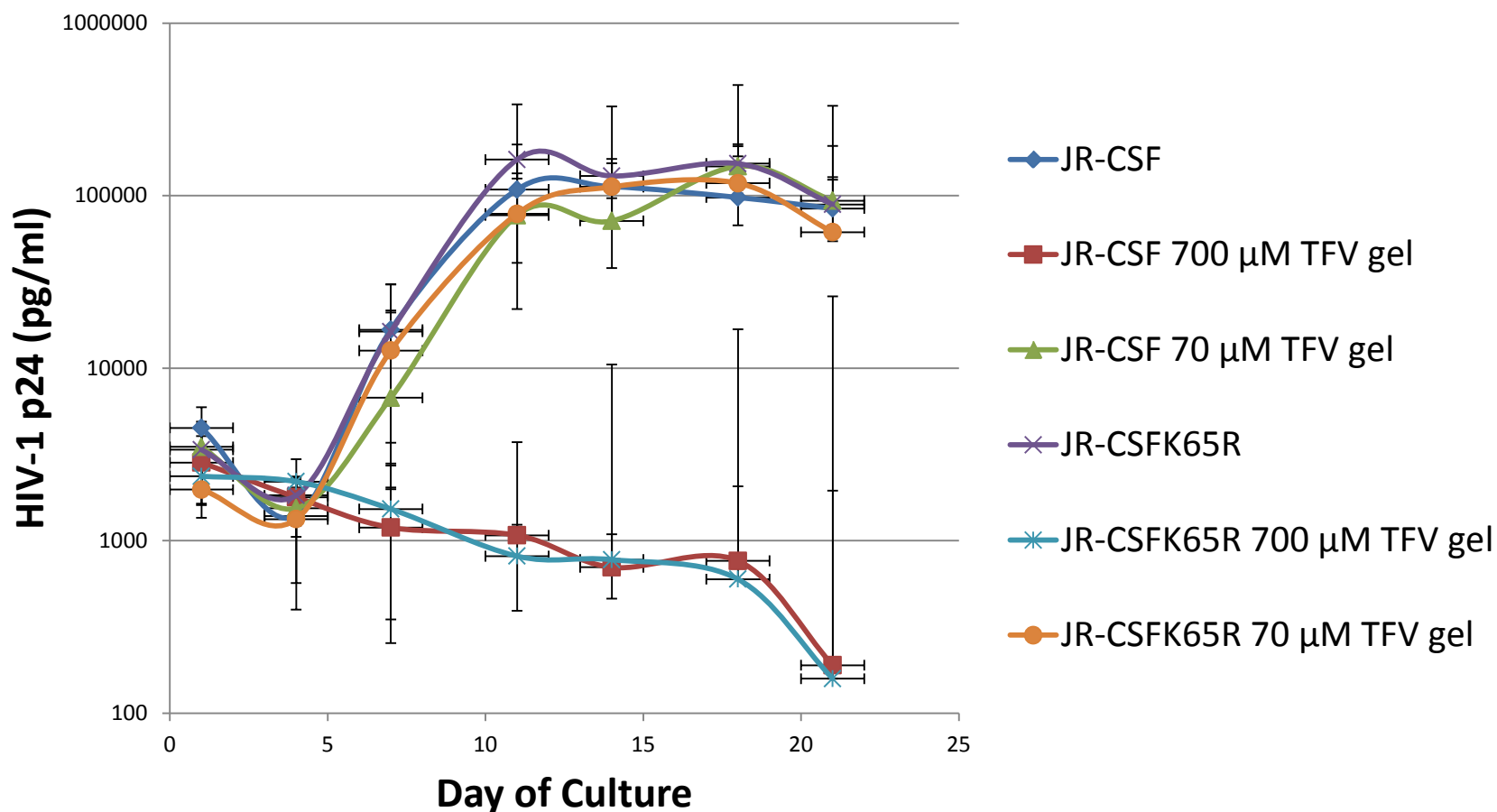
# MTN Contributions

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- Preclinical evaluation of candidate microbicides
  - Comparative evaluation core
- Phase 1 pharmacokinetic / pharmacodynamic studies
- Clinical evaluation of candidate microbicides
  - Vaginal
  - Rectal
- Behavioral research agenda
- Pregnancy
- Antiviral resistance

# Preclinical Evaluation

## Colorectal explant infection product evaluation



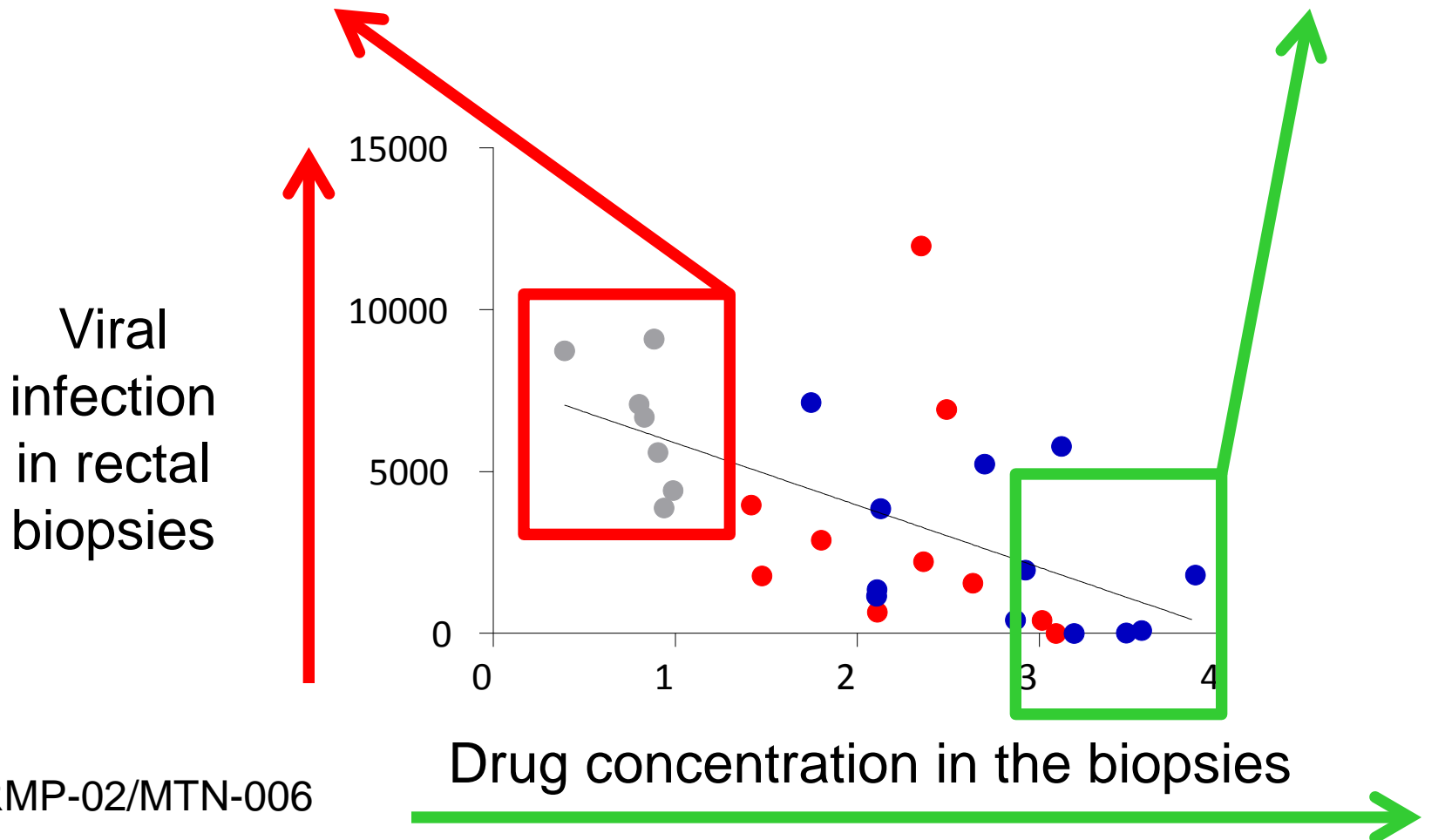


# PK / PD Studies

● Oral Dose

● Single Rectal Dose

● Multiple Rectal Dose



# Clinical Evaluation of Microbicide Candidates

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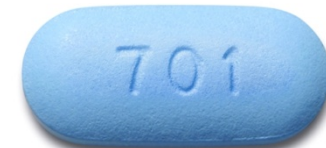
VAGINAL + ORAL INTERVENTIONS  
TO CONTROL THE EPIDEMIC



**Tenofovir  
Tablets**



**Tenofovir Gel**



**Truvada  
Tablets**

Which is effective?  
Is each safe?  
Which will women use?

# VOICE Related Studies

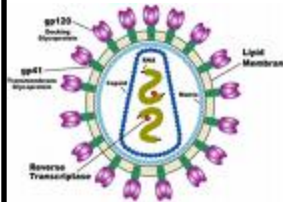
## VOICE Study

Pregnancy



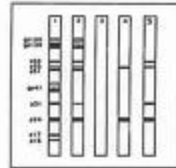
MTN-016

Resistance



MTN-009

HIV  
Seroconverters



Figures:  
Examples of reactions by an RT-1 Western Blot:  
1. Positive control (strong)  
2. Positive control (weak)  
3. Test sample  
4. Indeterminate result (striped appearance)

MTN-015

Bone health



VOICE-B

Community  
Perceptions



VOICE-C

# Rectal Microbicides

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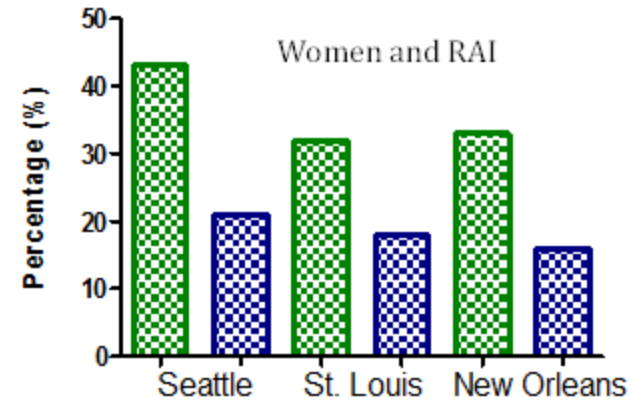


# Anorectal Anatomy

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# Populations Needing RM



**PROJECT** **ARM**  
AFRICA FOR RECTAL MICROBICIDES



# MTN Rectal Microbicide Portfolio

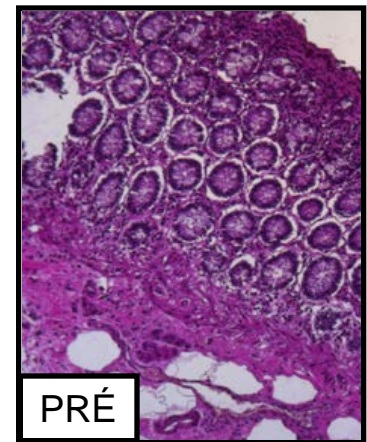
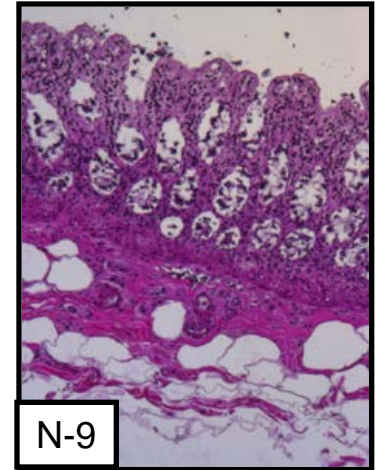
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- RMP-02/MTN-006
  - Phase 1 rectal safety study of vaginal 1% tenofovir gel
- MTN-007
  - Phase 1 rectal safety study of reduced glycerin 1% tenofovir gel



# Mucosal Safety

- Epithelial sloughing
- Histopathology
- Mucosal mononuclear cell phenotype by flow cytometry
- Cytokines
  - RT-PCR
  - Microarray
  - Luminex
- Fecal calprotectin
- Rectal microflora



Data from Charlene Dezzutti MTN Core Laboratory



# Behavioral Research Agenda

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- Integration of behavioral scientists into all MTN studies
- Ancillary behavioral studies
  - MTN-003C, MTN-003D
- Development and use of new approaches and technology
  - ACASI, Wisebags, VASP counseling
- Increased integration of biomedical and behavioral approaches to adherence monitoring

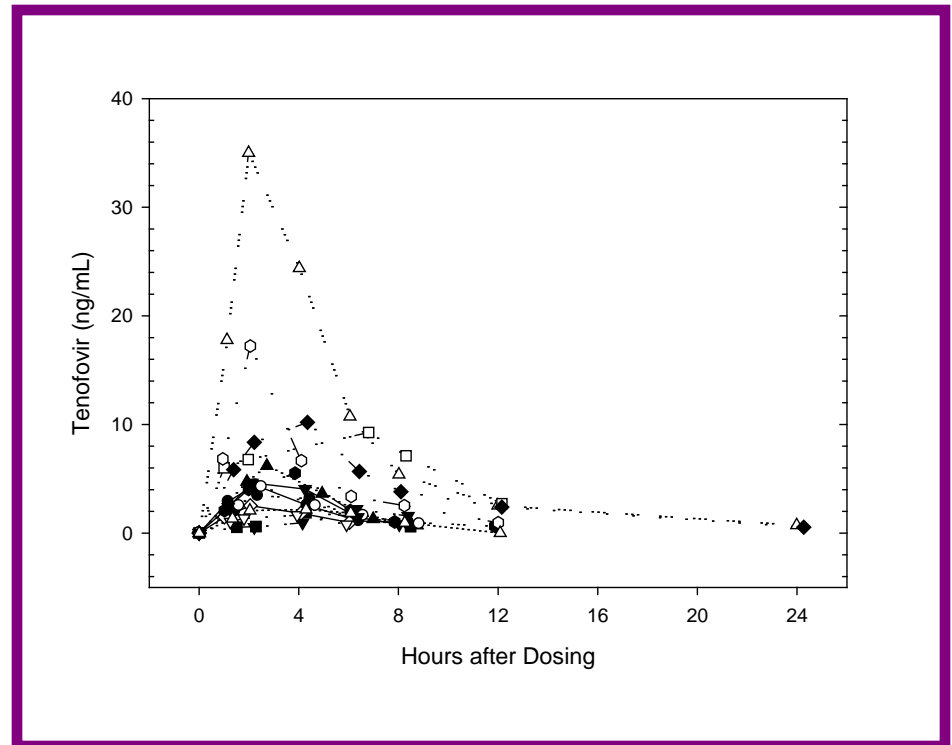
# Pregnancy

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# MTN-002

- Single dose study of tenofovir gel prior to elective CS
- Maternal pharmacokinetics and placental transfer of tenofovir 1% vaginal gel
- Study completed
  - Pittsburgh, PA



Maternal tenofovir PK

# MTN-008

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- Expanded safety of tenofovir 1% gel in pregnancy and lactation
- Study sites
  - Pittsburgh, PA
  - Birmingham, AL
- Study ongoing





# MTN-016

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- MTN pregnancy registry for women who become pregnant during MTN studies
- Primary objectives
  - Pregnancy loss: mothers exposed/not exposed to an active study agent
  - Major malformations: infants exposed/not exposed to active study agent *in utero*

# Sustained Release Products

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# MTN-005

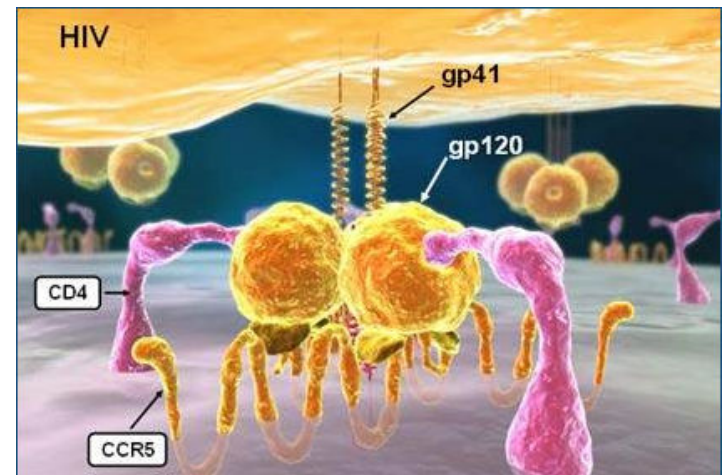
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- Safety and acceptability of a non-medicated intravaginal ring
  - Bronx-Lebanon, NY
  - Birmingham, AL
  - Pune, India
- Study ongoing in the US and India

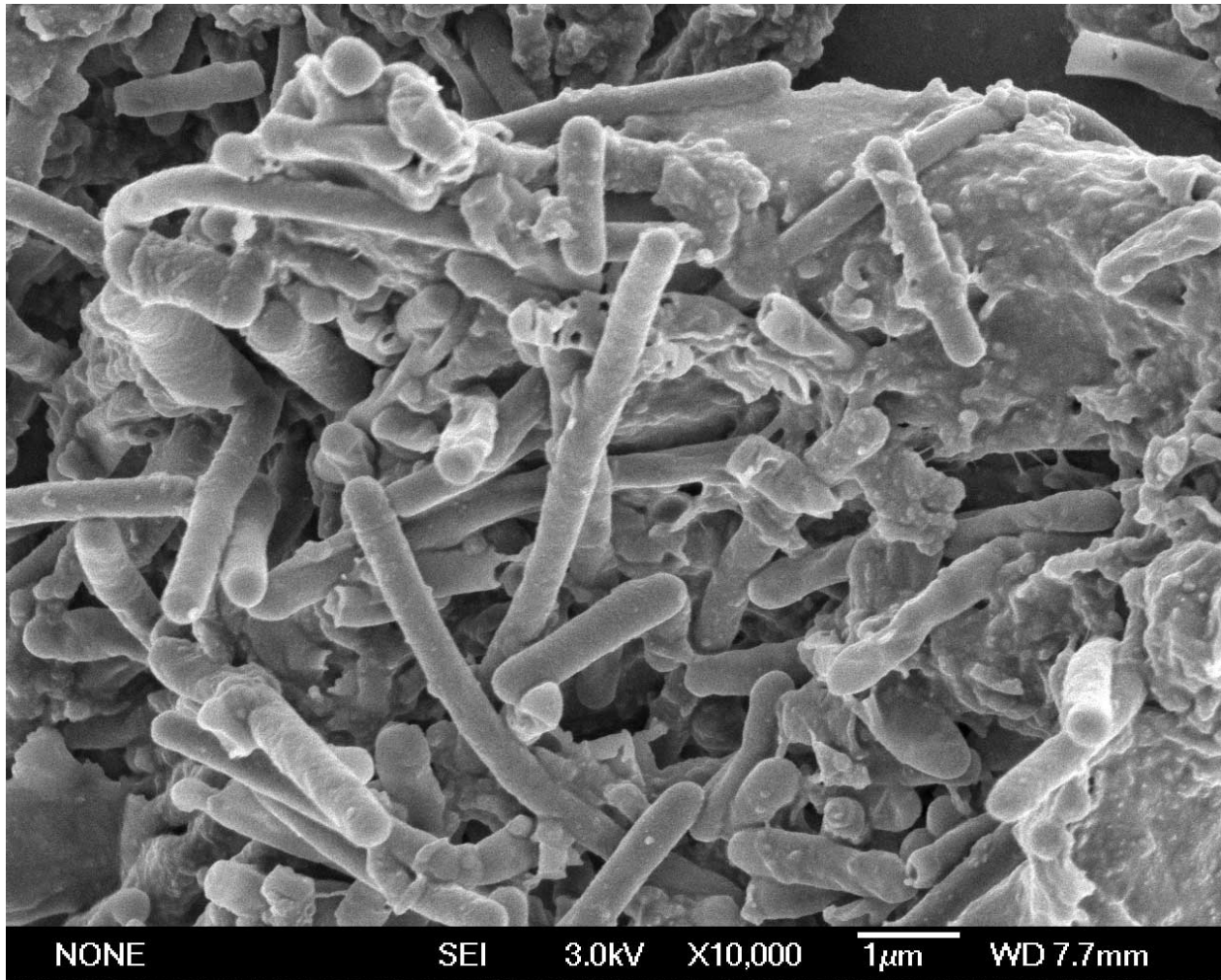


# MTN-013

- Phase 1 safety and PK/PD of vaginal rings :
  - Dapivirine
  - Maraviroc
  - Dapivirine & Maraviroc
  - Placebo
- Sites
  - Pittsburgh, PA
  - Boston, MA
  - Birmingham. AL



# Objective Measures of Ring Use



MTN-005

# Challenges

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# Discordant PrEP/Microbicide Results

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- Evidence of efficacy
  - CAPRISA 004, Partners in Prevention, CDC TDF2, and iPrEx
- Futility
  - FEM-PrEP, VOICE
- Reasons for PrEP failure in FEM-PrEP and VOICE
  - Not known yet
  - Possibilities include population characteristics, adherence, PK, or biology

# Hormonal Contraception and HIV

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- Hormonal contraception may be associated with modest increase in risk of HIV acquisition
  - Heffron R et al. Lancet Infectious Diseases, 2012
- Recent WHO guidance\* is for women to continue using hormonal contraception + condoms to avoid unwanted pregnancy and HIV infection
- MTN needs to consider dual protection strategies as part of the MTN portfolio

\*[http://www.who.int/mediacentre/news/notes/2012/contraceptives\\_20120216/en/index.html](http://www.who.int/mediacentre/news/notes/2012/contraceptives_20120216/en/index.html)

# Combination Prevention

## Conventional HIV Prevention Package + PrEP



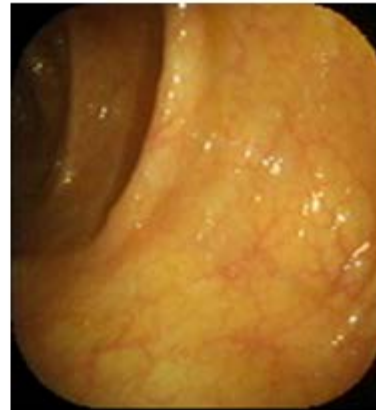
SC

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Oral

±



Rectal

±



Vaginal

± HIV Vaccine



# Additional Research Challenges

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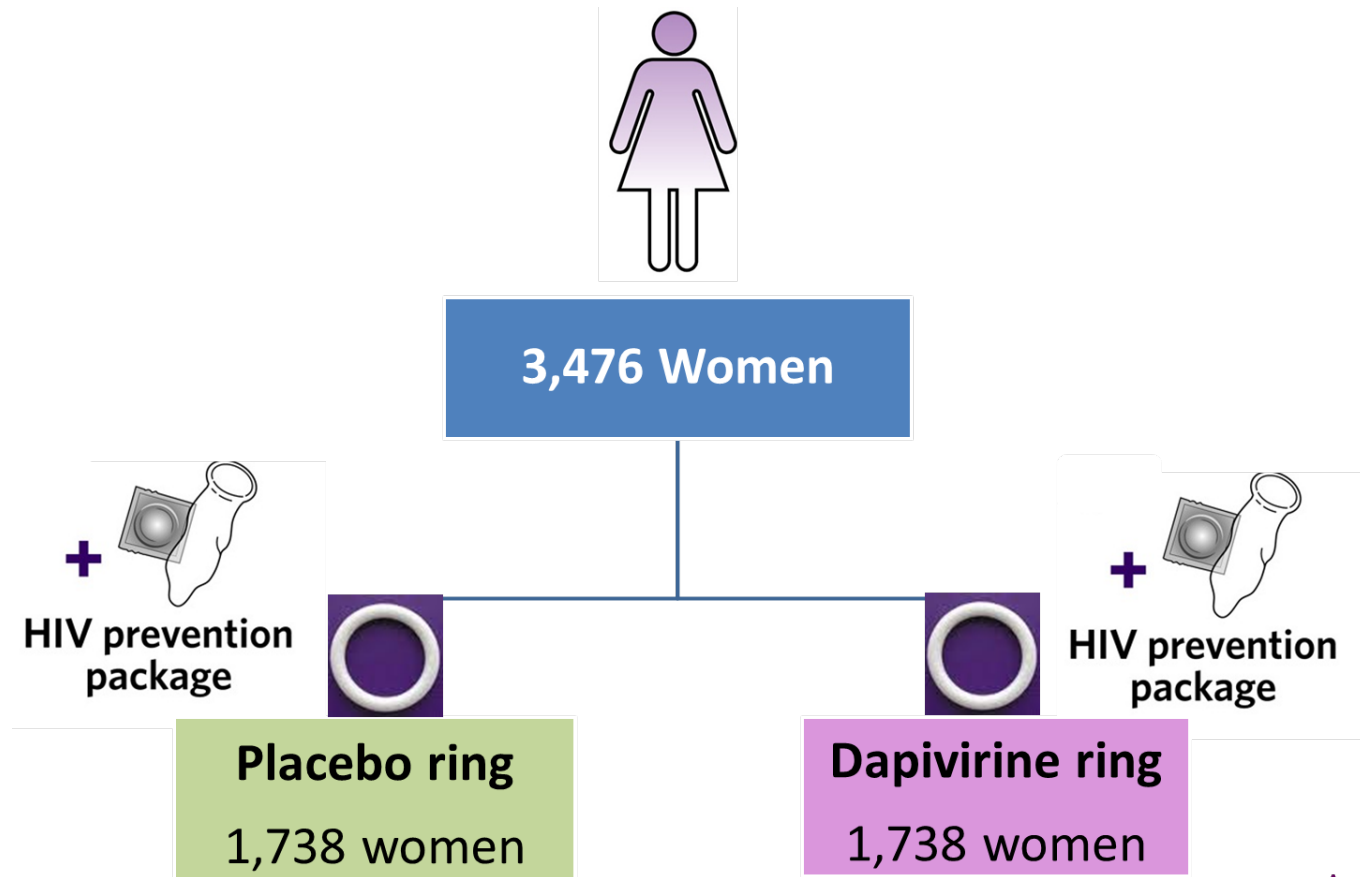
- Development / optimization of biomarkers for use in clinical trials
  - Sexual exposure, adherence, safety, and efficacy
- Designing trials without placebo arms
- Bridging between the end of PrEP effectiveness trials and community availability of PrEP agents
- Managing concerns around antiviral resistance
- Developing and managing the PrEP pipeline

# Looking Towards the Future

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# Sustained Delivery Products



# Rectal Microbicide Development

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- MTN-017
- Phase 2 rectal safety study of tenofovir gel
- International sites
  - United States
  - Thailand
  - South Africa
  - Peru
- Endpoints
  - Safety
  - Adherence
    - Self report
    - Objective measures
  - Acceptability
  - PK/PD
- Initiation Q1 2013

# MTN-017

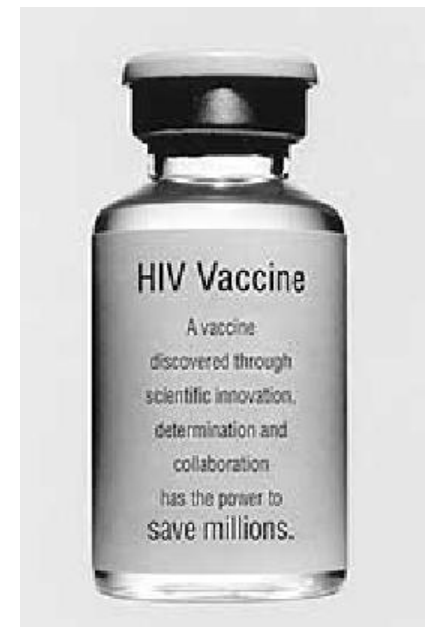
	8 weeks		8 weeks		8 weeks	
BL	TNF Gel Daily		TNF Gel With sex		Oral Truvada	
BL	TNF Gel With sex		TNF Gel Daily		Oral Truvada	
BL	Oral Truvada		TNF Gel With sex		TNF Gel Daily	



# Vaccine PrEP Interactions

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- MTN-022 / HVTN-095
- Exploration of potential interactions between oral/topical PrEP and HIV vaccine
  - DNA NYVAC prime boost
  - Truvada
  - Vaginal tenofovir gel
- Primary objectives
  - Safety
  - Acceptability
  - Systemic immunogenicity



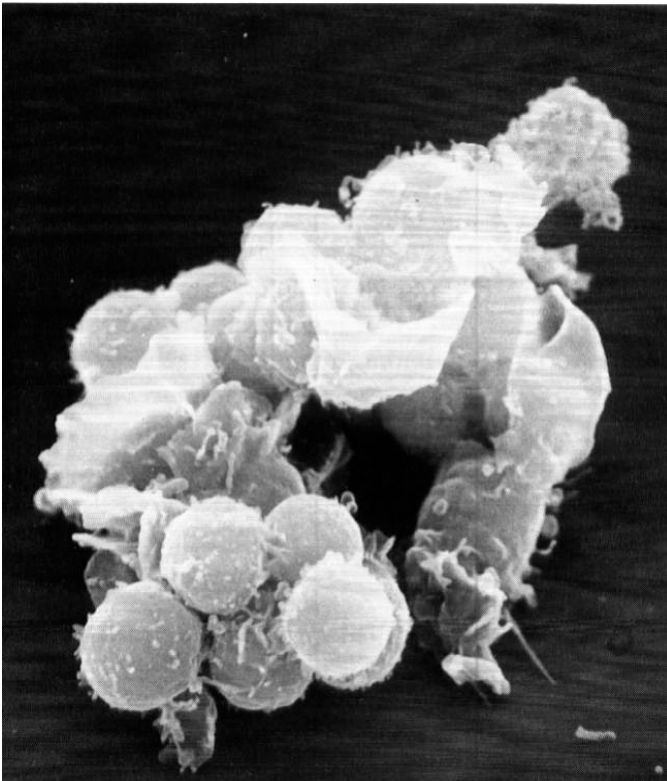
# Sustained Delivery Injection

- Rilpivirine NNRTI
- IM nanosuspension
- Potential for 1-3 month delivery
- Phase 1 PK/PD studies ongoing
  - Colorectal explants
  - Cervicovaginal explants
- MWRI-01\*
  - University of Pittsburgh
  - Liverpool University

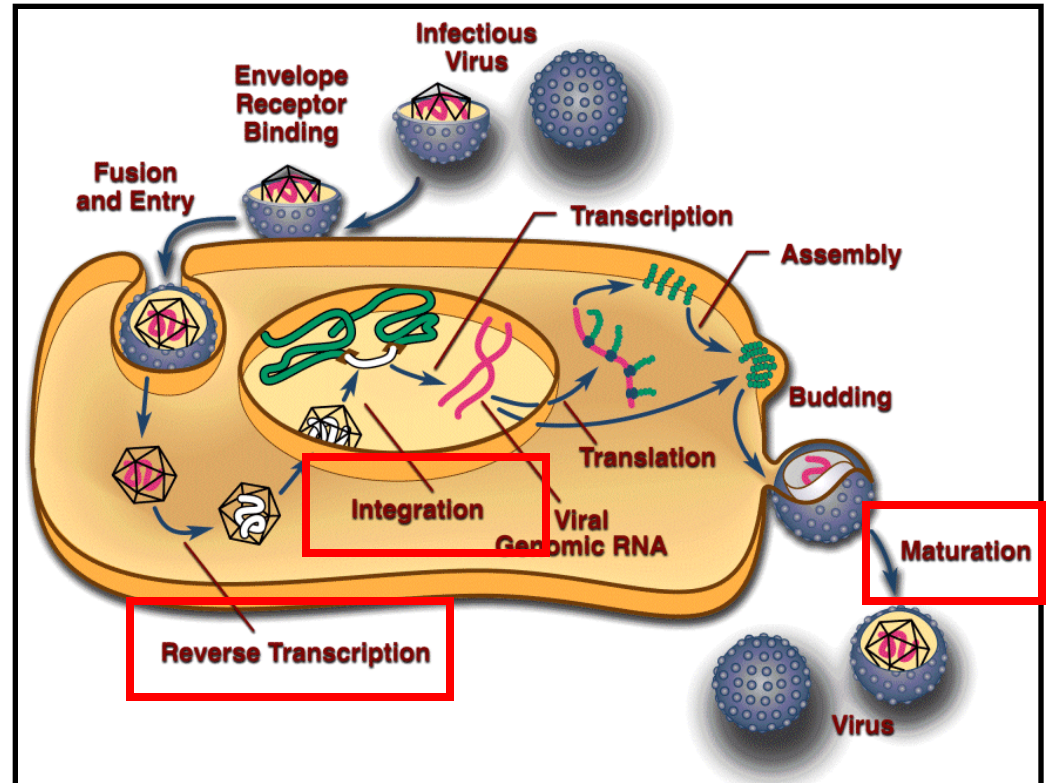


\*Funded by the Bill and Melinda Gates Foundation

# New Drug Targets



Host



Virus



# MTN Network Recompetition

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- RFA released
  - 27<sup>th</sup> January, 2012
- Submission due date
  - 29<sup>th</sup> September, 2012
- Next steps
  - Defining the research agenda for the MTN
  - Preparing the submission



# MTN Strategic Priorities

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- Continued development of sustained delivery products for HIV prevention
  - Phase 1 – Phase 3
  - Access / implementation studies during licensure review period
- Vulnerable populations
  - Pregnancy, adolescence, MSM, mature women
- Partner with other agencies to facilitate product development
  - DAIDS Networks, CONRAD, Bill and Melinda Gates Foundation, Corporate Sponsors





# Summary

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- Development of safe and effective PrEP agents including microbicides remains a critical focus for HIV prevention research
- Increased interest in sustained delivery products
- Rectal microbicide development important for both domestic and international MSM and others at risk of infection through RAI
- Innovative trial design will be needed to sustain prevention research agenda

# MTN Partners

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BILL & MELINDA  
GATES *foundation*

# The National Institutes of Health



NIAID



National Institutes of Health  
*Eunice Kennedy Shriver*  
National Institute of Child Health & Human Development

# MTN Presence at M2012

Type of Presentation	# Accepted
Oral presentations	12
Oral poster discussions	7
Posters	16
<b>Total # of presentations</b>	<b>35</b>
<b>M2012 scholarships</b>	<b>18</b>

