

# Where We Have Been and Where We are Going

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# Directions

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Where we  
were



Where we  
are headed

Where we are

# 2005



“The size of your dreams must always exceed your current capacity to achieve them. If your dreams do not scare you, they are not big enough.”

# 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



So How Did We Do?

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# The MTN Portfolio in 2012

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## □ Completed Studies

- HPTN 035
- HPTN 059
- MTN-001
- MTN-002
- MTN-003
- MTN-P01
- MTN-003C
- MTN-004
- MTN-005

- RMP-02/MTN-006
- MTN-007
- MTN-009
- MTN-012
- MTN-013

## □ Ongoing studies

- MTN-003B
- MTN-003D
- MTN-008
- MTN-015/MTN-016
- MTN-020



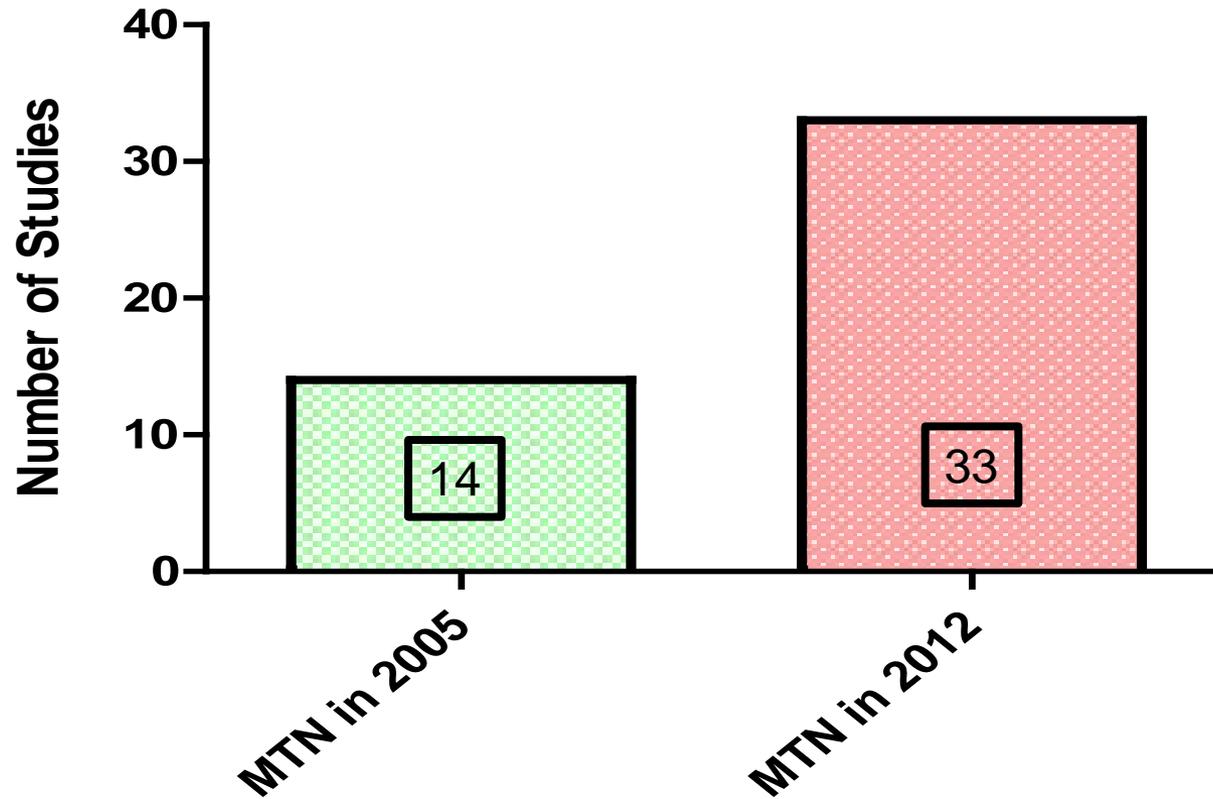
# MTN Portfolio in 2012

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- Studies in development or awaiting activation
  - MTN-011
  - MTN-014
  - MTN-017
  - MTN-018/B/C
  - MTN-021
  - MTN-022
  - MTN-023
  - MTN-024
  - MTN-025

# The MTN Scorecard

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# MTN's Contributions to HIV Prevention

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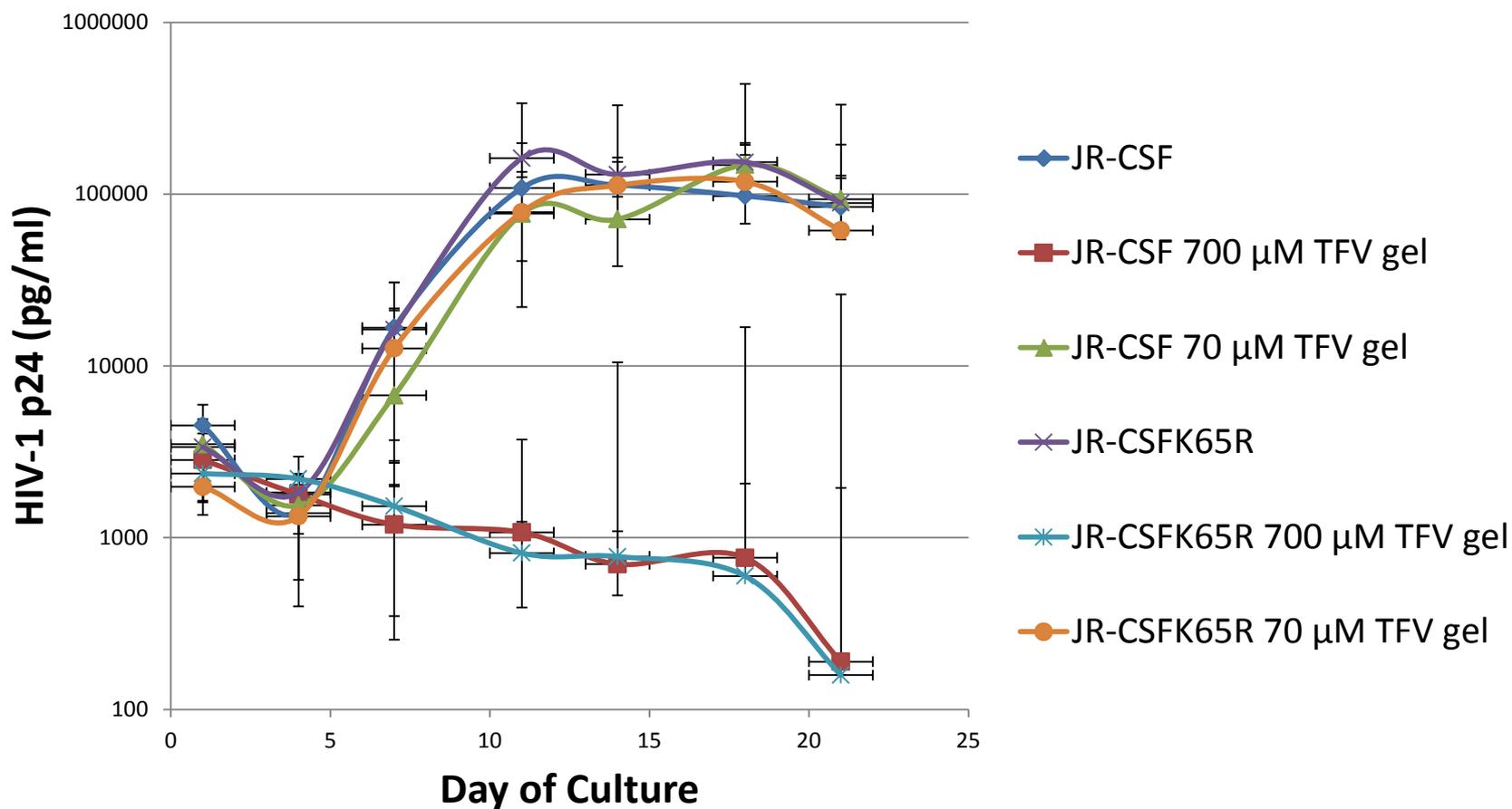
# MTN Contributions

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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

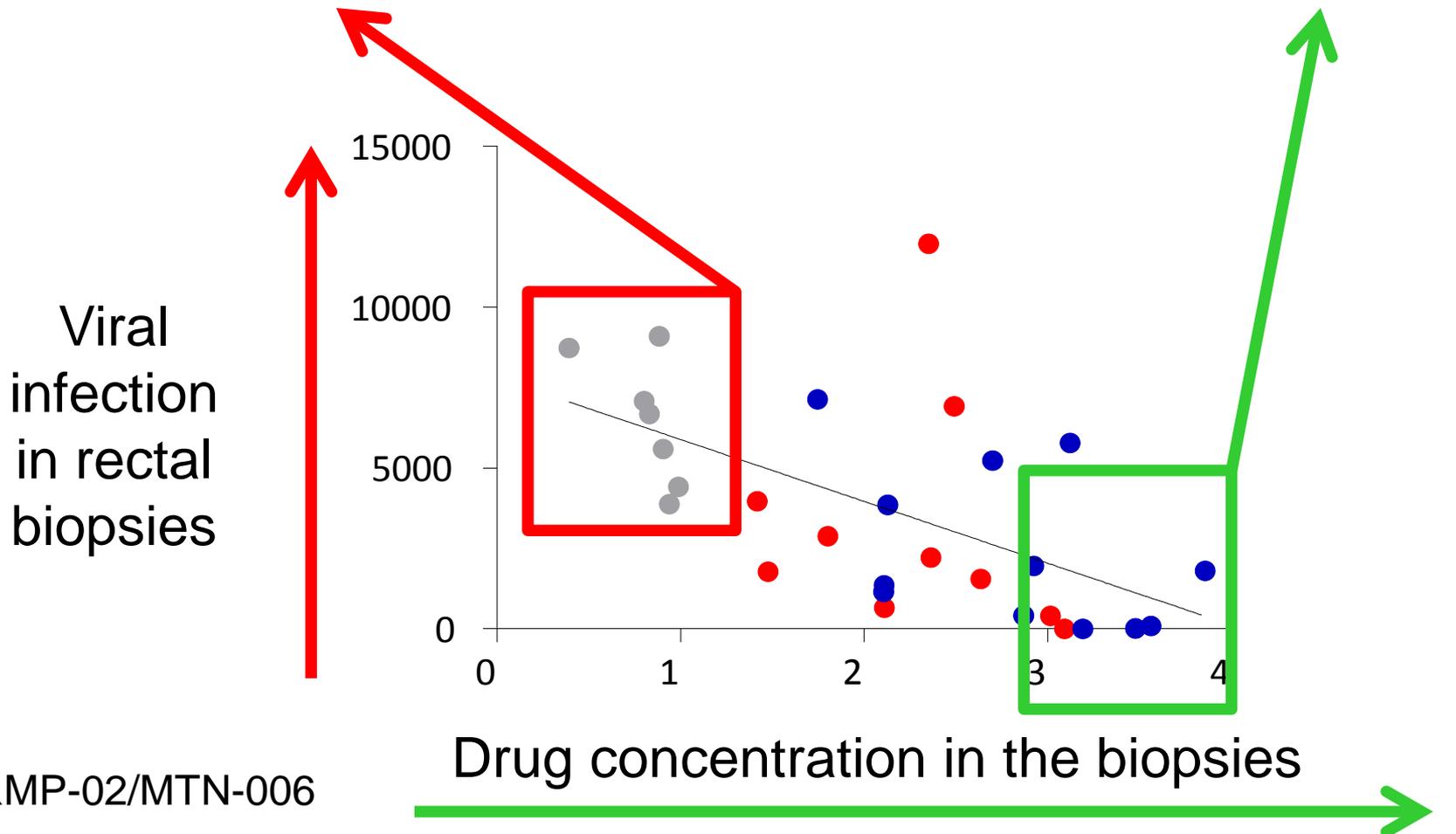


# PK / PD Studies

● 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

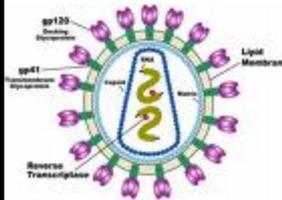
## VOICE Study

Pregnancy



MTN-016

Resistance



MTN-009

HIV  
Seroconverters

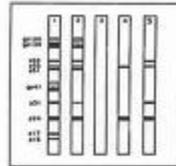


Figure 1  
Examples of reactions by an RT-1 Western blot:  
1. Positive control (strong)  
2. Positive control (weak)  
3. Negative control  
4. Indeterminate result (striped appearance)

MTN-015

Bone health



VOICE-B

Community  
Perceptions



VOICE-C

# Rectal Microbicides

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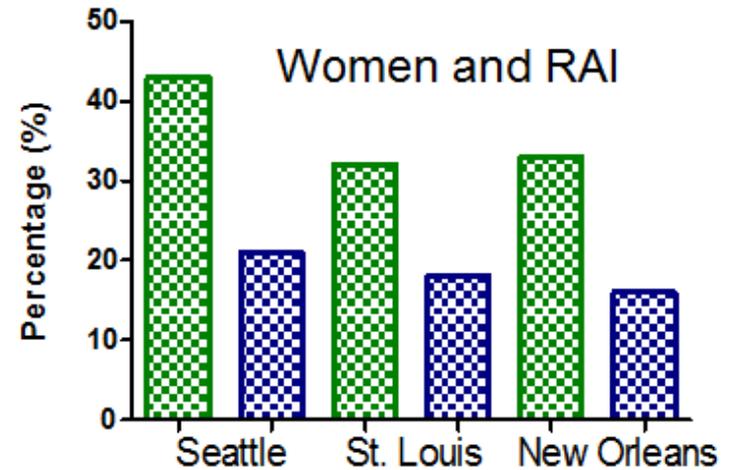


# Anorectal Anatomy

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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

- MTN-017

- Phase 2 expanded safety study of reduced glycerin 1% tenofovir gel

# Rectal Microbicide Development

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- 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
    - Objective measures
  - Acceptability
  - PK/PD
- Initiation Q1 2013

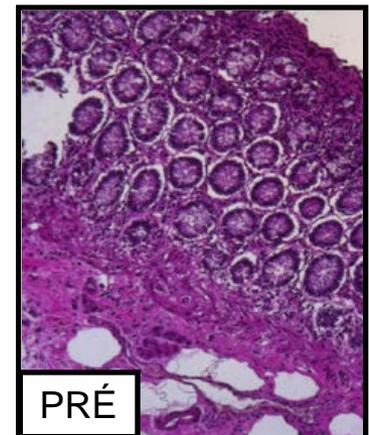
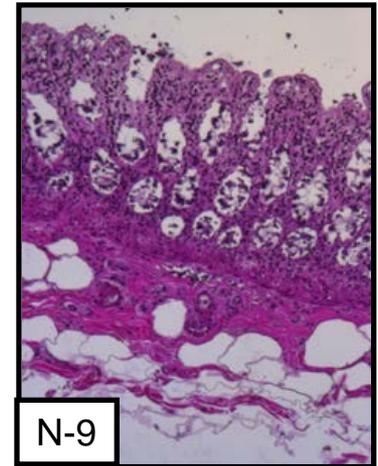
# MTN-017

	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	



# Mucosal Safety

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







# Behavioral Research Agenda

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- Integration of behavioral scientists into almosts 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

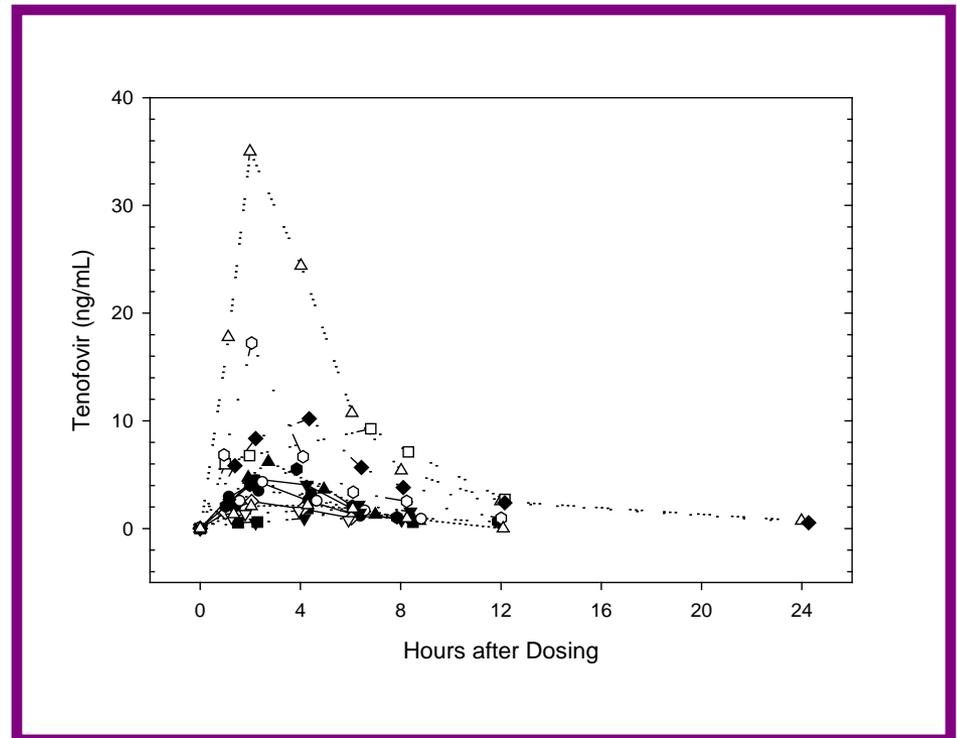
# Pregnancy

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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
- Group 1 (Weeks 37-39) completed
- Group 2 (Weeks 34-36) initiated





# 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*
- Enrollment to date
  - Mothers: 275
  - Infants: 234

# Sustained Release Products

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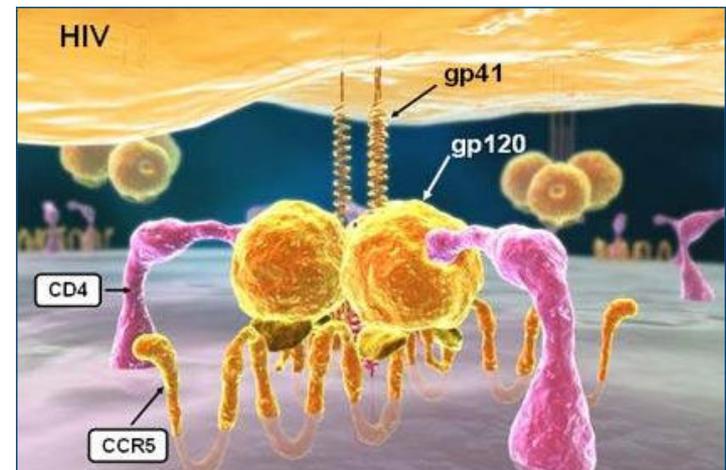
# MTN-005

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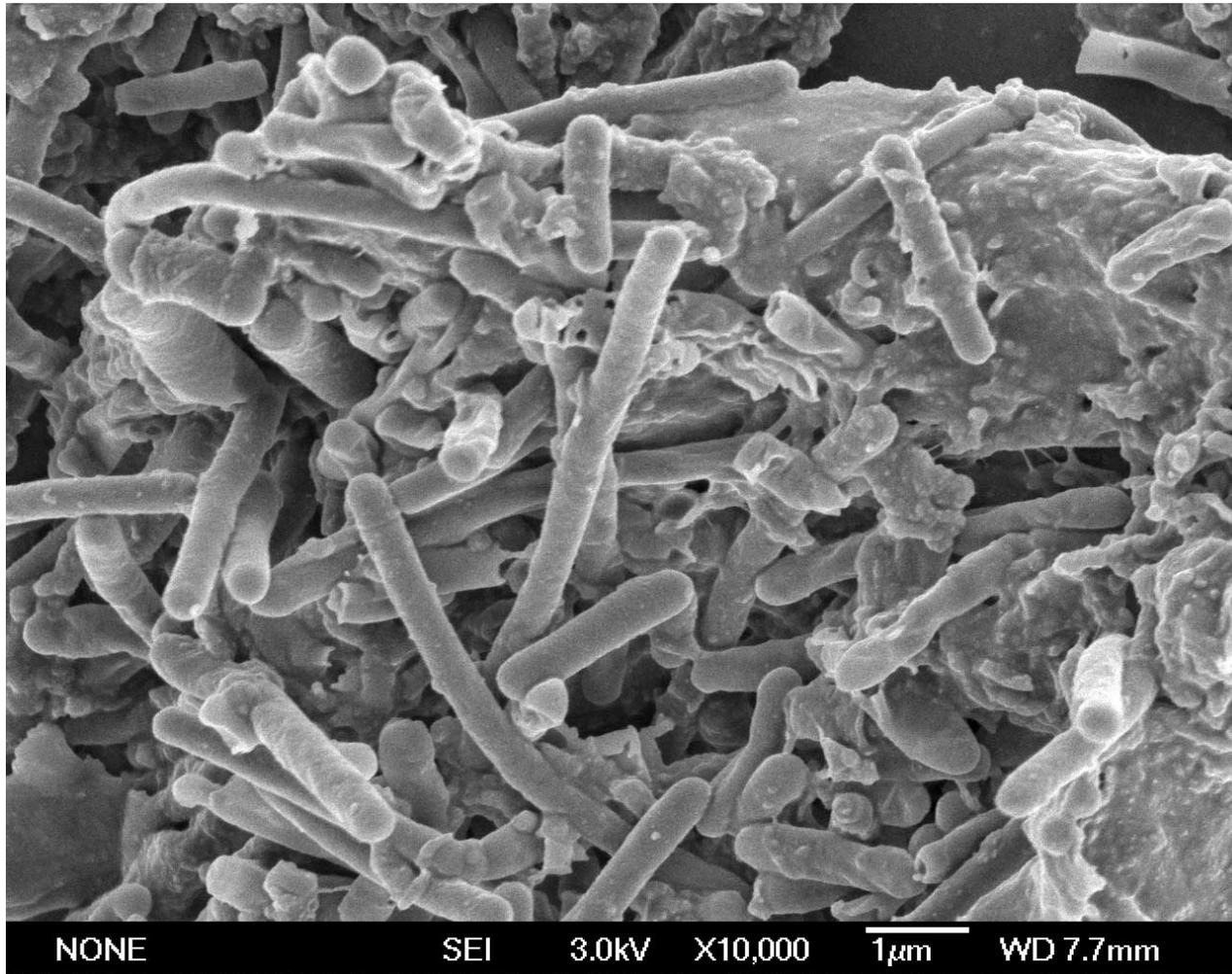
- Safety and acceptability of a non-medicated intravaginal ring
  - Bronx-Lebanon, NY
  - Birmingham, AL
  - Pune, India
- Study completed in the US and India
- Analysis ongoing

# MTN-013

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



# 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



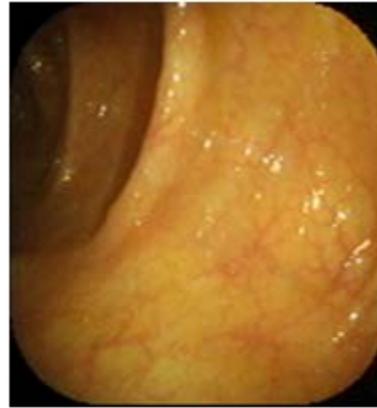
SC

±



Oral

±



Rectal

±



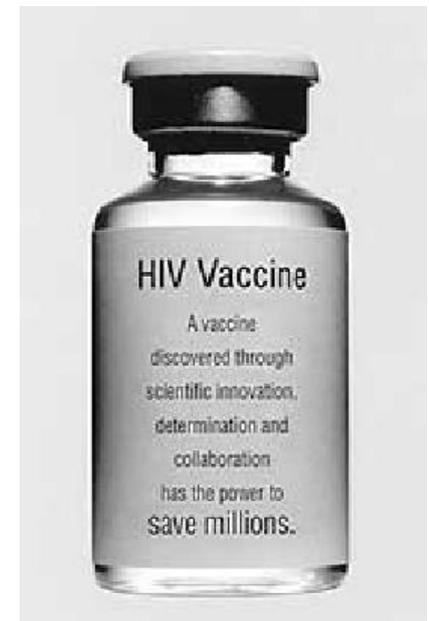
Vaginal

± HIV Vaccine

# 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





# 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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# The MTN Recompetition

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- Safe and effective vaginal microbicides
- Safe and effective rectal microbicides
- Combination hormonal contraceptive and antiretroviral vaginal ring
- Special populations
  - Pregnancy
  - Adolescence
  - Post menopausal women
  - MSM and transgender women



# New Products & Formulations

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## □ Candidates

- Griffithsin
- 5P12-RANTES
- MIV-150
- IQP-0528
- Tenofovir  
disoproxil  
fumarate ring

## □ Formulations

- Intravaginal rings
  - Combination
- Films
- Suppositories

# The MTN Portfolio

Study	Product	Formulation	Population	Phase	N	2013	2014	2015	2016	2017	2018	2019	2020
MTN-015	N/A	N/A	Seroconverters	N/A	N/A								
MTN-016	N/A	N/A	Pregnancy and infants	N/A	N/A								
MTN-020 (ASPIRE)	Dapivirine	Ring	Women	3	3476								
MTN-018 (CHOICE)	Truvada	Oral	Women	3B	TBD								
MTN-017	Truvada and TFV	Oral / Rectal Gel	MSM TG	2	186								
MTN-026	Maraviroc	Rectal Gel	Men/Women	1	45								
MTN-027	TFV	Rectal Gel	Men/Women	1	45								
MTN-028	MIV-150	Vaginal Gel / Ring	Women	1	45								
MTN-029	MIV-150	Rectal Gel	Men/Women	1	45								
MTN-030	TFV	Rectal Gel	MSM/TG	3	5000								
MTN-031	HC/ART	Ring	Women	1	45								
MTN-032	IQP-0528	Vaginal Gel	Women	1	45								
MTN-033	5P12-RANTES	Rectal Gel	Men/Women	1	45								
MTN-034	Dapivirine	Film	Women	1	45								
MTN-035/HVTN 117	HIV Vaccine/TFV	Oral/Rectal Gel	Men/Women	1	120								
MTN-036	TBD	Rectal Gel	Men/Women	1	45								
MTN-037	HC/ART	Ring	Women	2	200								
MTN-038	Griffithsin	Vaginal Gel	HIV+ Women	1	45								
MTN-039	Dapivirine	Film	Women	2	200								
MTN-040	Dapivirine	Film	Pregnancy	1	45								
MTN-041	HC/ART	Ring	Women	3	5000								
MTN-042	TDF	Ring	Women	2	200								
MTN-043	IQP-0528	Ring	Women	1	45								
MTN-044	Griffithsin	Rectal Gel	Men/Women	1	45								
MTN-045	Dapivirine	Film	Adolescent girls	1	45								
MTN-046	HC/ART	Ring	Lactating women	1	45								

# Vaginal Microbicides

Study	Phase	Population	Product(s)	N
<b>MTN-028</b>	1	Women	MIV-150 gel/ring	45
<b>MTN-032</b>	1	Women	IQP-0528 gel	45
<b>MTN-034</b>	1	Women	DPV film	45
<b>MTN-038</b>	1	HIV + Women	Griffithsin gel	45
<b>MTN-039</b>	2	Women	DPV film	200
<b>MTN-040</b>	1	Pregnancy	DPV film	45
<b>MTN-042</b>	2	Women	TDF ring	200
<b>MTN-043</b>	1	Women	IQP-0528 ring	45
<b>MTN-045</b>	1	Adolescents	DPV film	45
<b>MTN-046</b>	1	Lactation	HC/ARV	45

# Rectal Microbicides

Study	Phase	Population	Product(s)	N
<b>CHARM-03 / MTN-026</b>	1	Men/Women	MVC gel	45
<b>MTN-027</b>	1	Men/Women	TFV gel	45
<b>MTN-029</b>	1	Men/Women	MIV-150	45
<b>MTN-030</b>	2B/3	MSM and Transgender women	TFV gel	5,000
<b>MTN-033</b>	1	Men/Women	5P12-RANTES	45
<b>MTN-035 HVTN 117</b>	1	MSM and Transgender women	Oral TDF/FTC TFV gel HIV vaccine	120
<b>MTN-036</b>	1	Men/Women	TBD	45
<b>MTN-044</b>	1	Men/Women	Griffithsin	45

# Combination Rings

Dual Protection VR	Indications	Status	Developer
<b>TFV + LNG</b>	HIV + pregnancy (+ HSV)	Preclinical	CONRAD
<b>MIV-150+ZN acetate + LNG</b>	HI + pregnancy + HSV (+HPV)		Population Council
<b>DPV + HC (TBD)</b>	HIV + pregnancy		IPM
<b>TDF + progestin type HC</b>	HIV + pregnancy		AECOM, U Utah
<b>AZT + ferrous gluconate</b>	HIV + pregnancy		Weill COM, Cornell
<b>AZT + l-ascorbic acid</b>	HIV + pregnancy		Weill COM, Cornell
<b>Nuvaring + ARV (TBD)</b>	HIV + pregnancy		Merck

# Proposed Ring Studies

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<b>Study</b>	<b>Phase</b>	<b>Population</b>	<b>Product(s)</b>	<b>N</b>
<b>MTN-031</b>	1	Women	HC/ARV ring	45
<b>MTN-037</b>	2	Women	HC/ARV ring	200
<b>MTN-041</b>	3	Women	HC/ARV ring	5,000

# MTN Affiliated Sites



Country	Sites
USA	9
Malawi	2
Zambia	1
Uganda	1
Zimbabwe	3
South Africa	12
India	1
Thailand	2
Peru	1
<b>Total</b>	<b>32</b>



# 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 the HIV 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