



# Welcome to the Microbicide Trials Network

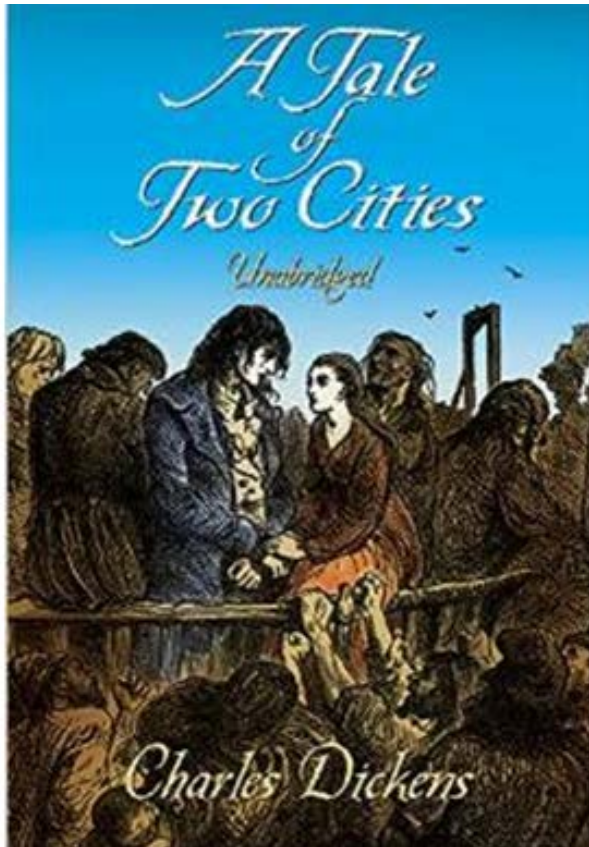
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Annual Meeting  
March 16, 2015

# What We Hope to Accomplish This Week

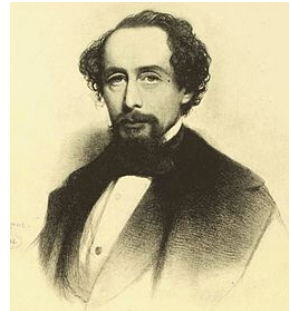
- Updates on our completed and ongoing work
- Learning about new initiatives moving forward
- Opportunity for face to face protocol team meetings
- Review our challenges and opportunities

# For the microbicide field.....



Tale of Two Cities, 1859

“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair.....



Charles Dickens

# The Best of Times

## *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 5, 2015

VOL. 372 NO. 6

### Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

Jeanne M. Marrazzo, M.D., Gita Ramjee, Ph.D., Barbra A. Richardson, Ph.D., Kailazarid Gomez, M.P.A., Nyaradzo Mgodzi, M.Med., Gonasagrie Nair, M.B., Ch.B., M.P.H., Thesla Palanee, Ph.D., Clemensia Nakabiito, M.Med., Ariane van der Straten, Ph.D., Lisa Noguchi, M.S.N., Craig W. Hendrix, M.D., James Y. Dai, Ph.D., Shayhana Ganesh, M.Med., Banning Mkhize, M.B., Ch.B., Marthinette Taljaard, B.S., Urvi M. Parikh, Ph.D., Jeanna Piper, M.D., Benoît Mâsse, Ph.D., Cynthia Grossman, Ph.D., James Rooney, M.D., Jill L. Schwartz, M.D., Heather Watts, M.D., Mark A. Marzinke, Ph.D., Sharon L. Hillier, Ph.D., Ian M. McGowan, M.D., and Z. Mike Chirenje, M.D., for the VOICE Study Team\*

# Continued Misunderstandings About VOICE



The New York Times

SUBSCRIBE

LOG IN



## *A Failed Trial in Africa Raises Questions About How to Test H.I.V. Drugs*

By DONALD G. McNEIL Jr. FEB. 4, 2015

### Blame research design for failed HIV study

*Focus on social and behavioral factors just as important as the medication itself*

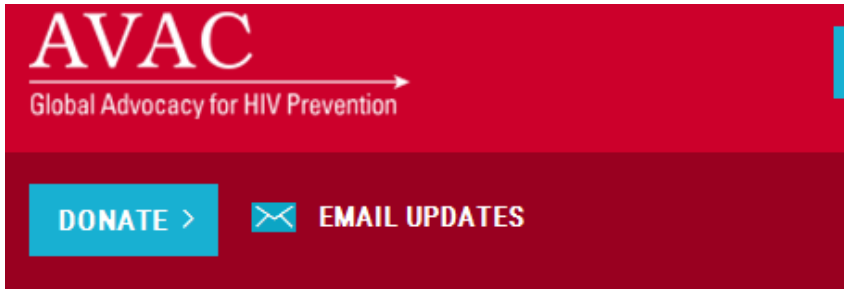
March 5, 2015 2:00AM ET

by [Ida Susser](#)

“Bottom-up research design  
The VOICE study appeared to lack sufficient community involvement”.



# FACTS-001 Results



Why are studies not designed to fit into the lives of people; rather we expect the lives of people to fit into our research?

## FACTS 001 and Me

**MORENIKE FOLAYAN**

THURSDAY, FEBRUARY 26, 2015 | *Microbicides*

I felt extremely disappointed with the results. I ask myself, where do we go from here? How come the FACTS study has no similitude of efficacy? Why does the result of this study not show any complimentary to the CAPRISA 004 study?

How can the IRR be 1.0? How can that be if the women used it even some of the time?

# The MTN Year in Review: 2014 to 2015

- VOICE: Publication of primary study results Feb 2015 in NEJM
- ASPIRE: Completing final visits and study closeout at outstanding quality
- Completing first phase 2 rectal microbicide study, MTN-017
- Contraceptive Action Team successfully diversified contraceptive choice at our sites with major increases in IUDs and implants with major decreases in DMPA and oral contraceptives

# The MTN Year in Review: 2014 to 2015

- New work with tenofovir gel:
  - MTN-011 completed and reported at R4P
  - MTN-014 completed and to be reported at IAS
- New research with the dapivirine ring
  - Launch of MTN-023 (adolescents)
  - Launch and full enrollment of MTN-024 (post-menopausal women)
  - Planning for MTN-025 (HOPE) including stakeholder consultations in S Africa, Zimbabwe, Uganda and Malawi



# The MTN Year in Review

## New partnerships, new drug products

- Merck integrase inhibitor MK-2048 and entry inhibitor vicriviroc MK-4176
  - Combination ring containing both drugs in a combination called MK-2048A
  - MTN-027 and MTN-028 on the launchpad
- IPM dapivirine gel as a rectal microbicide
  - MTN-026 nearing the launch pad
- IPM dapivirine/LNG ring for contraception and HIV prevention beginning protocol development

# What Have We Learned?

- Tenofovir gel *can* prevent HIV if women use it

Study	Measure of Adherence	Publication	Overall Efficacy	Effect Size in Users
CAPRISA-004	>80% applicators used	Science 2010; 329:1168-1174	39% P=0.01	54% P=0.025
VOICE	Tenofovir in blood	NEJM 2015; 372:508-18	15% NS	66% P=0.02
FACTS	Tenofovir in vagina	CROI 2015	0% NS	52% P=0.04

- Tenofovir gel *can't* prevent HIV if women *don't use it.*

# What Have We Learned?

- Tenofovir gel *can* prevent HSV-2 if women use it

Study	Measure of Adherence	Citation	Overall Efficacy	Effect Size in Users
CAPRISA-004	>80% applicators used	Science 2010; 329:1168-1174	51% P=0.025	
VOICE	Tenofovir in blood	HIVR4P 2014	NS	46% P = 0.038

- But not enough women used it overall to demonstrate an impact on HIV or HSV-2 overall except in CAPRISA-004

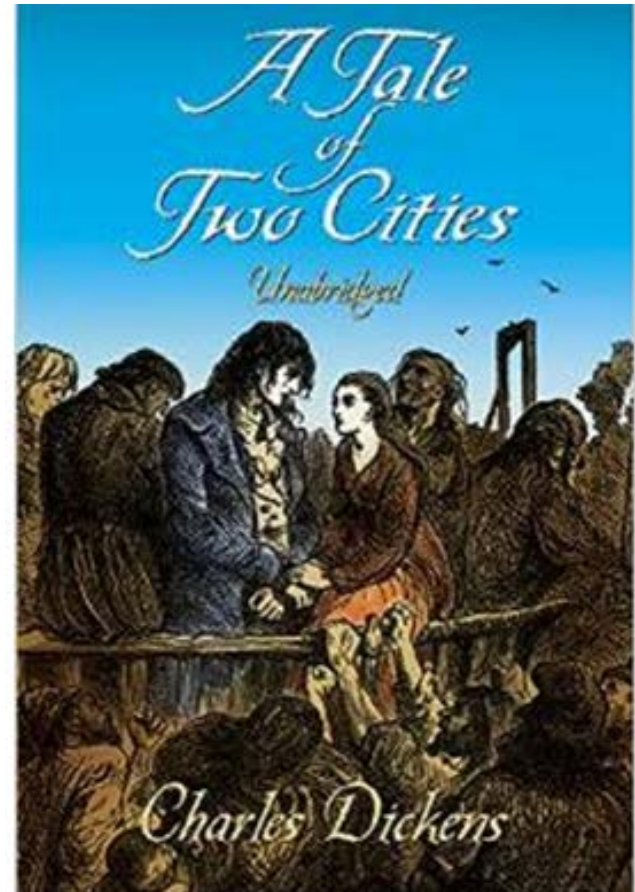
# So We Changed the Way We Did Business

- Integrated real time evaluation of adherence to drug products in our studies
  - ASPIRE
  - MTN-017
- Increased *real* integration of behavioral and social science into the way we do business every day
- Recognized that we have to pay careful attention to developing products that make sense in people's lives

# Looking Ahead....

.....we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way”

Charles Dickens, *A Tale of Two Cities*, 1859





- We probably won't be doing more with tenofovir gel vaginally
- ASPIRE might show that dapivirine rings can substantially reduce HIV, *or not*
  - We do know that adherence is vastly superior to the levels observed in VOICE
  - We do know that we are going to be able to answer the question of whether the product reduces HIV when used by women

# What Happens if ASPIRE Shows Women Using the Dapivirine Ring have Reduced HIV?

- The open label extension study for former ASPIRE participants, HOPE, will be launched
- The data from ASPIRE will have to be integrated with the data from the sister RING study so that IPM can submit to the regulatory authorities
- We need to “fill in the gaps”
  - Pregnant and breastfeeding women
  - Sex workers
  - Adolescents
- These studies would continue while the regulatory dossier is being reviewed

# What is Ahead for the MTN?

- For rectal microbicides
  - We might need a better applicator
  - We might need a solid dosing form instead of gel
  - We may decide to move forward with tenofovir gel in a phase 2 or 3, *or not*
- Success in the Ipergay and PROUD studies have taught us that oral PrEP is extremely effective when it is used



# New Studies of PrEP in MSM

- Ipergay: placebo-controlled study of Truvada in MSM reporting receptive anal sex in France (CROI 2015)
  - 414 men instructed to use product (oral Truvada or placebo) at the time of sex, with another dose 24 and 48 hours after sex
  - **86% reduction (95% CI 40-99%, P=0.002)** in HIV infection
- PROUD: Immediate vs deferred use of daily oral Truvada in MSM in the UK (CROI 2015)
  - **86% reduction (95% CI 58-96%, P=0.0002)** in HIV among men using daily oral PrEP

# In the meantime...

- Dapivirine gel will be evaluated as an alternative drug as a rectal microbicide
- Discussions regarding clinical trial designs for rectal microbicides are ongoing
  - Statistical considerations
  - Ethical considerations
  - Community views
- Discussions are being initiated regarding a different applicator for rectal use

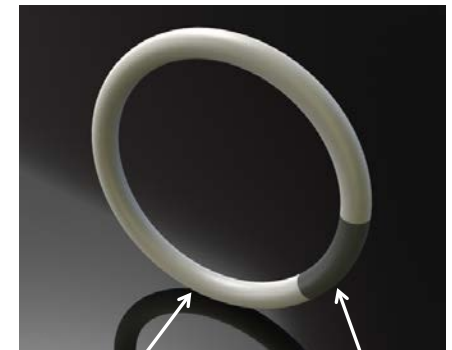
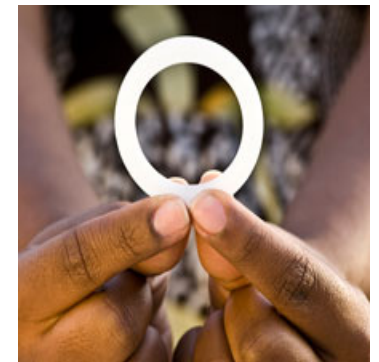
# Hormonal Microbicide Rings

## Discussion Tomorrow

- HIV, Contraception
  - Dapivirine + LNG Vaginal Ring (IPM)
    - 90 day use
    - MTN-030 in protocol development
- HIV, STI, Contraception
  - TNF/LNG 90 day IVR (CONRAD)
    - HIV, HSV, pregnancy protection
    - Segmented design; co-extruded reservoir LNG segment
    - Phase 1 study ongoing



**USAID**  
FROM THE AMERICAN PEOPLE



**TNF**

**LNG**

# Why is MTN-030 so important?

- First contraceptive microbicide ring evaluated in the MTN
- Only the second ring to move forward into phase 1 study to date
- “Next generation” dapivirine ring
- Builds on MTN work in contraception provision through the Contraception Action Team

# Contraceptive ARV Rings

## Many Scientific Questions

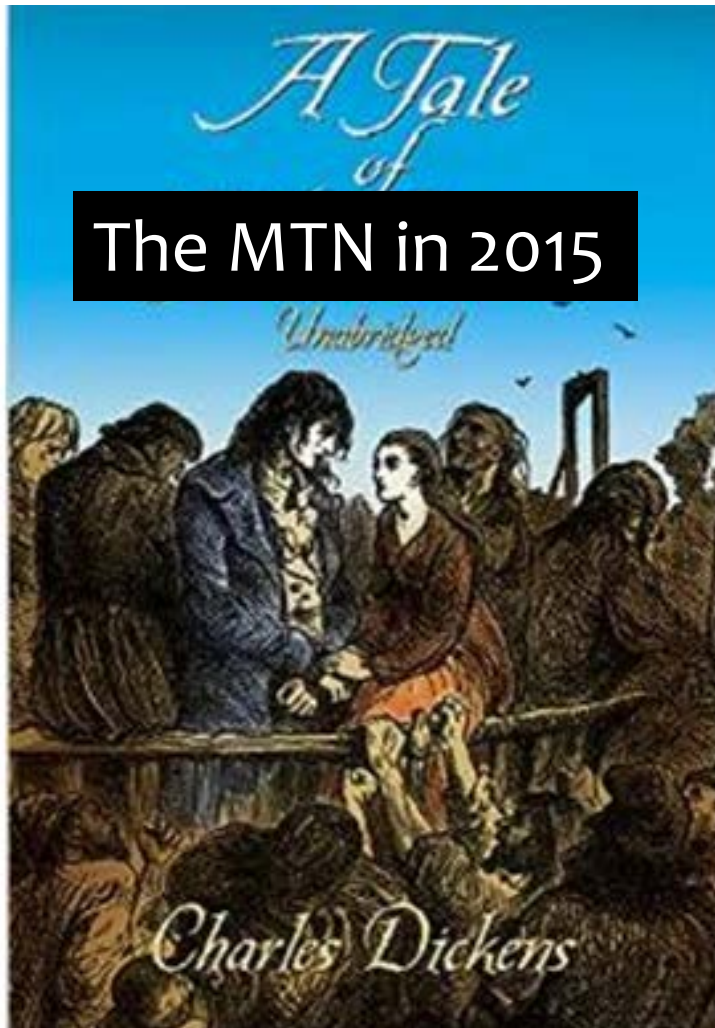
- Local pharmacokinetics , how much LNG?
- Mechanism of action for contraception: mucus thickening, anovulation
- Acceptability of a continuous use ring
  - Effect on bleeding patterns/breakthrough bleeding
  - Safety of continuous progestins, concerns about DMPA and HIV risk
- New collaborations/new opportunities

# New Kinds of Rings/New Molecules

- MTN-027 and MTN-028 will be the first to evaluate
  - More flexible EVA ring as a microbicide
  - Safety and pharmacokinetics of the integrase inhibitor MK-2048 and vicriviroc delivered vaginally
- This could be provide a platform for a combination ARV/hormonal contraceptive ring building on success with the NuvaRing

# At this point, the MTN is

- Anticipating ASPIRE, but optimistic
- Looking forward to seeing the results of MTN-017 and planning next steps
- Planning for follow on studies of dapivirine ring
- Moving forward with evaluation of next generation products while paying careful attention to the developments with oral and injectable PrEP



- It is the best of times,  
it is the age of wisdom,  
it is the season of Light  
it is the spring of hope



# It is the Best of Times

- Welcome to the MTN Annual Meeting
- Enjoy the great work we are doing
- Try to meet someone new
- Have fun
- Come to our reception tonight
- Help us think hard about how to make develop products that make sense in people's lives