

Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir- emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003)

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The VOICE Study

- Phase 2B, randomized, double-blind, placebo-controlled, five-arm trial of **daily use** of the following for prevention of HIV acquisition in women:
 - Vaginal tenofovir (TFV) 1% gel (40 mg)
 - Oral tenofovir (TDF, 300 mg)
 - Oral tenofovir / emtricitabine (TDF / FTC; 300 mg / 200 mg)



VOICE Design

5,029 HIV- women

Vaginal sex in prior 3 months
Not pregnant or breastfeeding
Willing to use effective contraception

Randomized to once daily use

Oral TDF

Oral FTC/TDF

Oral
Placebo

Vaginal TFV

Vaginal placebo

Monthly visits

Comprehensive HIV prevention counseling, condoms, contraception, pregnancy test, STI evaluation & treatment, provision of study product

1° endpoints: HIV infection, safety

Who were the 5,029 Women in VOICE?



- **UGANDA: 322 participants**
 - Makerere Univ./JHU, Kampala (1 site)

- **ZIMBABWE: 630 participants**
 - UZ-UCSF, Harare (1 site)
 - UZ-UCSF, Chitungwiza (2 sites)

- **SOUTH AFRICA: 4,077 participants**
 - Durban Area
 - Medical Research Council (7 sites)
 - CAPRISA eThekweni (1 site)
 - Johannesburg Area
 - WRHI (1 site)
 - PHRU Soweto (1 site)
 - Klerksdorp Area
 - Aurum Institute (1 site)

Variation Across Countries

Women in the VOICE study were between 18-45 years old, but most were in their 20' s.

	South Africa	Uganda	Zim
Average Age	24.7	28.3	28.1
Percentage younger than age 25	55%	25%	26%
Percentage who are married	8%	50%	94%
Education (\geq secondary school)	54%	3%	60%

Key Findings from VOICE

- No product – tenofovir gel, oral tenofovir or oral Truvada – proven effective in preventing HIV
 - Most participants did not use daily as recommended
- Compared to older, married women, young single women **less** likely to use products and **more** likely to get HIV
 - New infections in young women more frequent than expected
 - Nearly 10 of every 100 women got HIV in 1 year at some South African sites



Daily Use Not Acceptable

- Results are disappointing but clear
 - Daily use (gel or tablet) is **not** the right approach for women like those in VOICE (mostly young and unmarried)
- We still need safe and effective HIV prevention methods that young, unmarried women will actually use

Amount of Drug in Blood

- Researchers tested blood samples from 773 participants
 - Some blood samples had drug in them
 - Most blood samples that should have had drug in them did not (less than 1 out of 3 women had drug found in their blood)
 - This was true for oral tenofovir, Truvada, and tenofovir gel groups
- These results indicate that most women did not use them daily as recommended
- Also, those least likely to use their products, single women under age 25, were also most likely to get HIV

Incidence of HIV Acquisition

	South Africa	Uganda / Zimbabwe
Age <25 y	8.7 (7.6, 10)	2.6 (1.1, 5.1)
≥ 25 y	4.7 (3.8, 5.8)	0.8 (0.4, 1.7)
Married	0.9 (0.2, 2.7)	0.9 (0.4, 1.7)
Unmarried	7.5 (6.6, 8.4)	2.8 (1.1, 5.7)

Incidence per 100-person-years (95% C.I)



Quality of the Study

- Most women came to their study visits and completed study procedures
- Most women stayed in VOICE until they were scheduled to be finished coming to visits (good participant retention)
- Completion of study procedures and good retention are important for the quality of a study



Product Safety

- **No safety concerns** were identified for any of the study products tested in the VOICE Study

- Based on findings from various types of exams
 - Physical exam
 - Pelvic exam
 - Laboratory test results
 - Other health outcomes

Results of Sub-Studies

- VOICE had three sub-studies:
 - VOICE-B – Effects of oral products on bone health
 - VOICE-C – Community factors and beliefs that can influence adherence
 - VOICE-D – Individual behaviors and attitudes about HIV risk and impact on adherence

- Results being analyzed separately
 - Final results of VOICE-C and -D expected mid-2013
 - Results of VOICE-B will be later in 2013 - participants are being followed until August 2013



Conclusions

- Incidence of HIV substantially higher than anticipated
- No study drug significantly reduced risk of HIV acquisition
- Adherence to study products was low, especially among younger, unmarried women
- Results consistent with Fem-PrEP
 - Consider PrEP agents / delivery systems that are long acting and require minimal daily adherence
- Understanding HIV risk perception and biomedical, social and cultural determinants of adherence in this high-risk population urgently needed



VOICE Study Team

- Protocol Co-Chairs: Mike Chirenje, Jeanne Marrazzo
 - Durban, S. Africa: Gita Ramjee, Marwah Jenneker, Yuktेशwar Sookrajh, Shahnaaz Kadwa, Vimla Naicker, Linda Zako, Arendevi Pather, Nicola Coumi, Sarita Naidoo, Sharika Gappoo, Vijayanand Guddera, Shayhana Ganesh, Gonasagrie Nair, Kalendri Naidoo
 - Johannesburg, S. Africa: Thesla Palanee, Godspower Akpomiemie, Banningi Mkhize, Wilma Pelser, Ithabeleng Morojele
 - Klerksdorp, S. Africa: Marthinette Taljaard, Ronel Brown, Kathy Mngadi, Pearl Selepe
 - Kampala, Uganda: Clemensia Nakabiito, Flavia Matovu, Kenneth Kintu
 - Harare, Zimbabwe: Nyaradzo Mgodhi, Tsitsi Magure, Margaret Mlingo, Petina Musara
- SCHARP: Barbra Richardson, Cliff Kelly, Benoit Masse, Karen Patterson, Missy Cianciola, Molly Swenson, James Dai, Holly Gundacker, Janne Abullarade, Jennifer Schille, Craig Silva, Della Wilson, Stacie Kentop, Jenny Tseng, Martha Doyle, Hongli Li, Jami Moksness, Joleen Borgerding, Sharavi Gandham, Kate Bader, Lynda McVarish
- FHI360: Kailazarid Gomez, Kristine Torjesen, Lisa Levy, Katie Schwartz, Ashley Mayo, Vivian Bragg, Ayana Moore, Katherine Richards, Stephanie Horn, Rhonda White
- MTN Network Lab: Ted Livant, Lorna Rabe, Yaw Agwei, Charlene Dezzutti, Urvi Parikh, Craig Hendrix, John Mellors
- NIH: Jeanna Piper, Roberta Black, Scharla Estep, Usha Sharma, Sheryl Zwierski (NIAID); Heather Watts (NICHD); Cynthia Grossman, Andrew Forsyth (NIMH)
- MTN core: Sharon Hillier, Ian McGowan, Lisa Noguchi, Ariane van der Straten, Barbara Mensch, Ross Cranston, Katie Bunge, Devika Singh, Sharon Riddler, Ken Ho, Cindy Jacobson, Lisa Rossi
- Gilead (oral study drug): Jim Rooney, Howard Jaffe, Rebecca Guzman and Farideh Said
- CONRAD (vaginal study drug): Jill Schwartz; Henry Gabelnick, Gustavo Doncel, David Friend

VOICE - What are the Implications for Rectal Microbicide Research?



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Overview

- Key messages from VOICE
 - Lack of product efficacy
 - Problematic adherence and self report
- Where are rectal microbicides in April 2013?
- VOICE - what are the implications for rectal microbicide research?
 - Phase 2 development
 - Phase 3 development



Key Messages from VOICE

- A strategy of asking women to use Truvada, Viread, or tenofovir gel was not successful in reducing rates of HIV acquisition in women
- The majority of women never used the product AND were unable to tell us that
- HIV incidence rates, especially in KZN, are extremely high

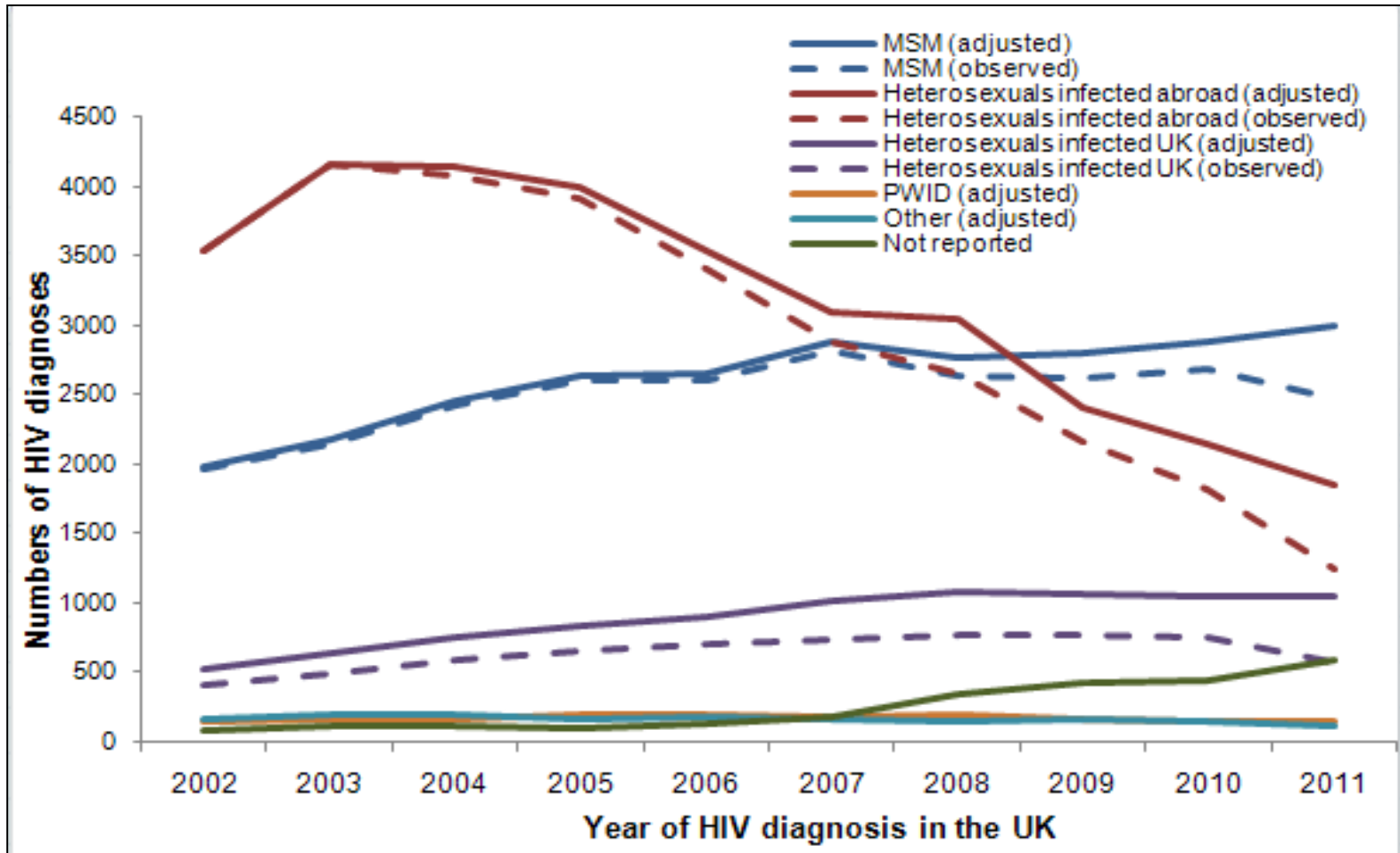


Do we Need Rectal Microbicides?

- HIV incidence rates in MSM remain stable or are increasing around the world as our anorectal STIs
- Unprotected receptive anal sex is extremely common
- Few MSM have access to PreP
- US uptake of PreP is so far very limited
- People need choices



HIV Infection in UK MSM



<http://www.hpa.org.uk>



Rectal Microbicide Research A Brief Update



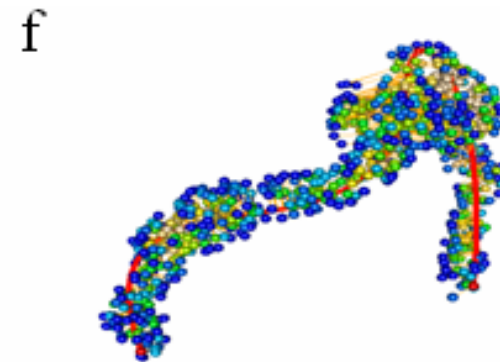
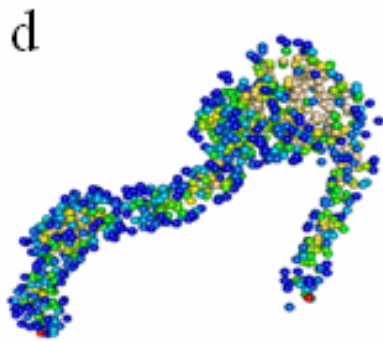
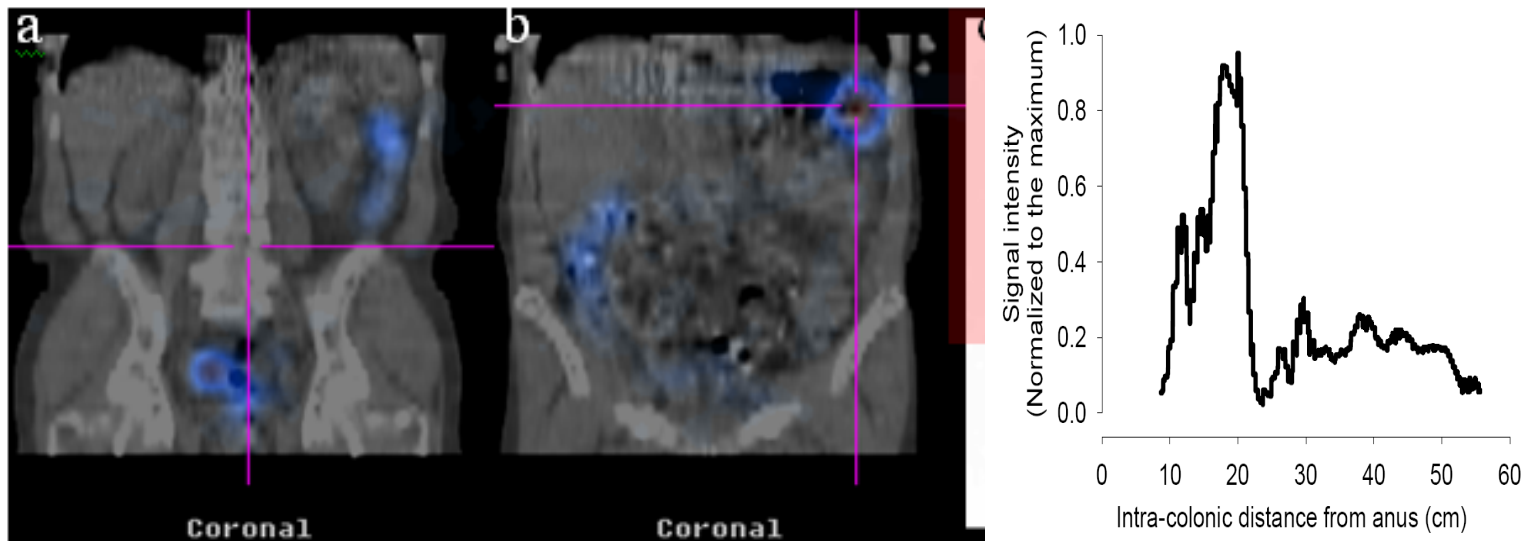
Non Human Primate Studies



- 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



Product Distribution Studies



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



Phase 1 Development

- 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



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
 - Applicator / pill count
 - Acceptability
 - PK/PD
 - Tissue subset

PI: Ross Cranston



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)



VOICE - What are the
Implications for Phase 2
Rectal Microbicide Research?



Questions for the Field

- How do we provide relevant education and messaging in the community about trials/adherence?
- How do we create desire about products and about studies?
- Who are the best participants for RM studies and how do we identify them?
- How do we monitor adherence on studies?



Education



<http://www.tinyurl.com/RectalRevEnglish>



Creating Desire



The Right Participants

The eligibility criteria for ASPIRE set the minimum standards for study participation. Just because a woman meets the eligibility criteria does not mean she is a 'good fit' for ASPIRE.

Taking a participant-centered approach to who is enrolled in the study may ultimately improve adherence. Ask yourself:

Is ASPIRE a good fit for this participant?



ASPIRE
A Study to Prevent Infection
with a Ring for Extended Use



Be a Hero



Para disfrutar primero
te lo debes aplicar

SOY GELLUX

Y traigo una nueva opción
que nos podría ayudar a
prevenir el VIH...

Los Microbicidas Rectales

herqes

Ser Voluntario

Impacta

INFÓRMATE MÁS LLAMANDO
AL 0-800-1-7432

f Gellux.Impacta

To enjoy (the gel)
first you need
to use it



Optimizing Adherence

- Select the right participants
- Provide adherence counseling
 - All counselors trained and monitored for quality
- Monitor adherence
 - Methods triangulation method
 - SMS, CASI, and applicator/pill counts
 - Data convergence interview
 - Real time PK monitoring



Real Time PK in MTN-017

- All participants will be informed that we will be monitoring PK every 4 weeks
- PK data will be shared with participants as part of the Product adherence / counseling sessions
- Sessions will be audiotaped (with consent) to allow quality of counseling to be assessed



VOICE - What are the
Implications for Phase 3
Rectal Microbicide Research?



Initial Steps

- Successful completion of MTN-017
 - High participant retention
 - Objective (PK) data supporting high product use
- Development of trial design scenarios
 - Community engagement and discussion
- Protocol development with ongoing community involvement
- Social mobilization and support



Phase 3 Design Strategies

- Classical placebo controlled study
 - Enhanced prevention package (PrEP)
 - Open-label run in to assess adherence
- Direct comparison of active agents
 - Truvada versus tenofovir gel
- Deferred design
 - UK PROUD study



Rectal Microbicide Timeline*

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Phase 1	→								
Phase 2				→					
Phase 2B/3						→			
Review								→	
Available									→

*An approximation based on tenofovir 1% gel



Summary

- Antiretroviral PreP has the potential to be highly effective in populations who adhere to product use
- Failure to demonstrate high levels of product adherence in MTN-017 may jeopardize the opportunity to conduct Phase 3 rectal microbicide trials in the future
- We need community support to design and execute these challenging trials



Thank You

