The Road to MTN-017

Ross D. Cranston MD FRCP
University of Pittsburgh

Fellow Travellers

MTN Core: Sharon Hillier, Ian McGowan, Beth Galaska Burzuk, Judy Jones, Maria Foster, Cindy Jacobson, Lindsay Kramzer, Ken Ho, Devika Singh **Network Lab**: Charlene Dezzutti, Craig Hendrix, Pam Kunjara, Florian Hladik **DAIDS**: Roberta Black, Jeanna Piper, Cynthia Grossman **BSWG:** Alex Carballo-Dieguez, Rebecca Gigiere, Ivan Balan, Titcha Ho **SCHARP:** Barbra Richardson, Karen Patterson, Marla Husnik, Yevgeny Grigoriev, Karen Liu, Danica Wright, Martha Doyle, Katie Weaver, Lori Filipcic, Della Wilson, Katie Snapinn **FHI:** Sherri Johnson, Kaila Gomez, Stephanie Horn, Jonathan Lucas **CWG:** Jim Pickett **Fenway:** Kenneth Mayer, Lori Panther, Jennifer Mitty, Ami Multani, Marcy Gelman, Ian Lemieux, Jesse Ripton, Amber Rucker, Ralph Mele, Sinclair Lao, Janet Dargon, Julia Gaggin, Erika Woodbury, Jessica LaCroix, Anna Hidalgo, Douglass Krakower, Jake Tinsely, Glory Mercilus, Sachin Jain **Pittsburgh:** Carol Mitchell, Carly Mowrey, Christy Pappalardo, Jennifer van Panhuis, Jonathan Baker, Sharon Riddler, Jim Gavel, Ray Cefola, Carol Oriss, Deborah McMahon, Benard Macatangay, Christine O Neill, Stacy Edick, Randall Brand, Janet Harrison, Richard Duerr **SFDH:** Susan Buchbinder, Albert Liu, Alfonso Diaz, Deawodi Ladzekpo, Elizabeth Faber, Hailey Gilmore, Kerry Murphy, Kimberly Marsh, Ryan Gonzalez, Sally Grant, Zoe Lehman, Tim Matheson, Janie Vinson, Jobert Poblete, Jose Carlos Asencios, Toren Jones, Jenese Jackson, Myra Ozaetz, Monique Biega, Scott Fields, Diana Ng Wong, Yelena Koplo, Chris Quan, Beth Osterbauer, Marcelle Millian, Ian Schneider, Montica Levy, Emily Schaeffer, Alani Kalfayan **San Juan:** Carmen D. Zorrilla, Vivian Tamayo, Irma Febo, Sylvia I. Dávila, Iris García, Sheyla Garced Trado, Claudia Mántaras, Meredith Herrera Roque, Jannette Valentin, Noelia Acevedo, Indira Purcell, Maritza Cruz, Wilmer Torres , Carmen Irizarry ,Viviana Cancel, Olga Mendez, Santiago Marrero, Ana Mosquera, Vilma Corres **Bangkok:** Timothy H. Holtz, Anupong Chitwarakorn, Marcel Curlin, Warunee Thienkrua, Wipas Wimonsate, Sumetha Hengprasert, Chaiwat Ungsedapand, Phunlerd Piyaraj, Boonchai Kowadisaiburana, Supurat Khemnark, Anchalee Varangrat, Tareerat Chemnasiri, Sarika Pattanasin, Patnaree Oungprasertgul, Nichnawee Kamchaithep, Teeraparp Watanatanyaporn, Supaporn Chaikummao, Kanokpan Pancharoen, Anuwat Sriporn, Pikunchai Luechai, Kesinee Satumay, Sirirat Lertpruek, Boonyos Raengsakulrach, Punneeporn Wasinrapee, Wannee Chonwattana, Wanna Leelawiwat, Jaray Tongtoyai, Santi Winaitham, Nutthawoot Promda, Philip Mock, Wichuda Sukwicha, Narongritt Tippanont, Somsak Yafant, Achara Sri-insut, Rinda Wongbenchaporn, Chariya Utenpitak, Pechpailin Khlaimanee, Patcharat Niyamakhom, Chanya Peerapatdit, Sasithorn Surikham, Anucha Munngen, Nawarat Sukfuang, Jirawat Suksamosorn, Kasidech Dechkittikun **Chiang Mai:** Suwat Chariyalertsak, Taweewat Supindham, Natthapol Kosashunhanan, Nuntisa Chotirosniramit, Sunida Thetket, Patcharaphan Sugandhavesa, Darin Ruanpeng, Pongpun Saokhieo, Radchanok Songsupa, Amornrat Yangnoi, Rattanaporn Intarawiwarat, Kachaporn yosbud Pratakpong Wongkiti, Sobhon Bipodhi, Kanokporn Wiboonnatakul, Songkran Waiyo, Benjasin Klaharn, Piya Punyarad, Kanlaya Wongworapat, Warunee Jit-Aree, Sirikwan Dokuta, Chamaiporn Na-Prom, Panida Yodkeeree, Chansom Pantip, Panudda Sothanapaisan, Jeitsada Keitkarn, Kritsadee Laosrivorapan, Thipsuda Krueyot, Kittipong Rungruengthanakit, Chiraphorn Kaewkosaba, Nattanun Suwannamas, Supatcharin Thasook, Thunyaporn Wangtan, Sutisa Tienkanted, Wanwisa Trongarom, Nutchanat Janta, Apsornsuda Tuila, Lar Chandee, Antika, Wongthanee, Suthathip Wongsrithep, Ratchaneekorn Khampan, Jarun Chuayen, Wasun Chanchai, Karand Chunpen, Kannika Jungsathit, Pimpaka Puangpotha, Karnjana Chairungsri, Boonlure Pruenglampoo, Kanjana Jeenaraj, Kannika Boursuk, Nittaya Chuenchop, Supaporn, Sirikunpun, Nataporn Kosachunhanan, Piyathida Sroysuwan, Veruree Manoyos **Cape Town:** Linda-Gail Bekker, Peter Chodacki, Richard Kaplan, Francois Cilliers, Catherine Orrel, Anna Cross, Keren Middelkoop, Nicola Killa, Elize Batist, Christina Hosken, Christie Heiberg , Joan Aploon, Maureen Rattley, Phyllisisty Smith, Anna Witbooi, Brian Kanyemba, Ben Brown, Daniel Ndzuzo, Xolani Mvula, Monica Vogt, Melanie Maclachlan, Lindsay Gwambe **Lima:** Pedro Gonzales, Javier R. Lama, Jorge Sánchez, Rosa Infante, Aldo Lucchetti, Javier Salvatierra , Jorge Vergara, Esmelda Montalban, José Gonzales, Eduardo Sánchez, Manuel Villaran, Fanny Garcia, Jessica Rios, Karen Villanueva, Karina Pareja, Monica Sánchez, Carla Porcile, Carmen Sánchez, Richard Teran, Cecilia Correa, Roberto Facho, Peter Brandes, Eduardo Ruiz, Martín Lacherre, Bertha Talaverano, Eliana Díaz, Carolina Moran, Diana Durand, Silvana Torres, Alberto Rondan, Alejandra Flores, Martín Patiño, Esmellin Perez, Robert De la Grecca, Carmela Ganoza , Lily Ganaha , Cecilia Chang, Ricardo Alfaro, Jesus Jurupe, Maria Suarez, Giovanna Solis, Carmen Salinas, Janet Soto, Ronny Tirado, Sonia Minaya, Gustavo Quispe, Roberto Alcantara, Patricia Segura, Medalith Sulca, Yolanda Vidal, Noelia Niño, Luis Castro, Rafael Rosas, Gonzalo Meneses, Daniel Alva, Christian Keller, David Amiel, Julio Dextre, Hector Salvatierra, Martin Patino, Lourdes Cruzado

MTN-017

- A Phase 2 Randomized Sequence Open Label Expanded Safety and Acceptability Study of Oral Emtricitabine/Tenofovir Disoproxil Fumarate Tablet and Rectally-Applied Tenofovir Reduced-Glycerin 1% Gel

Study Products

- Truvada®

- 1% tenofovir RG Gel

Gilead Sciences (Foster City, CA), CONRAD (Arlington, VA)

iPrEx Study

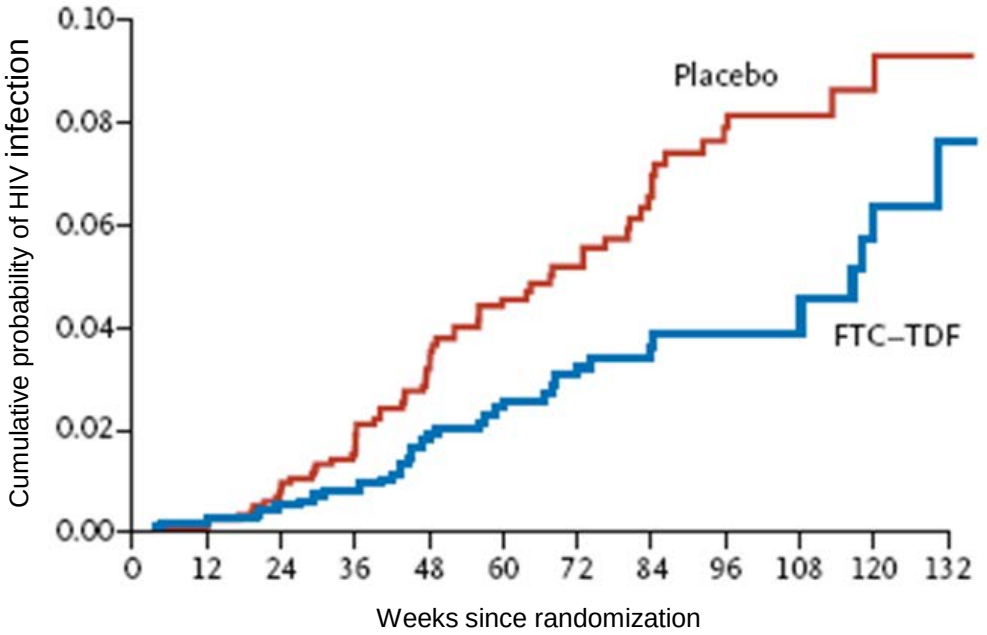
- Phase III multicenter trial of 2499 HIV negative MSM or transgender women randomized to receive placebo vs. FTC/TDF
- Median follow up 1.2 years
- Primary Endpoints:
  - AEs
  - HIV seroconversion

Grant RM, et al. N Engl J Med. 2010

iPrEx: HIV Seroconversion

- 44% effectiveness

  (95% confidence interval, 15 to 63; P=0.005)
- ~50% adherence to product



Grant RM, et al. N Engl J Med. 2010

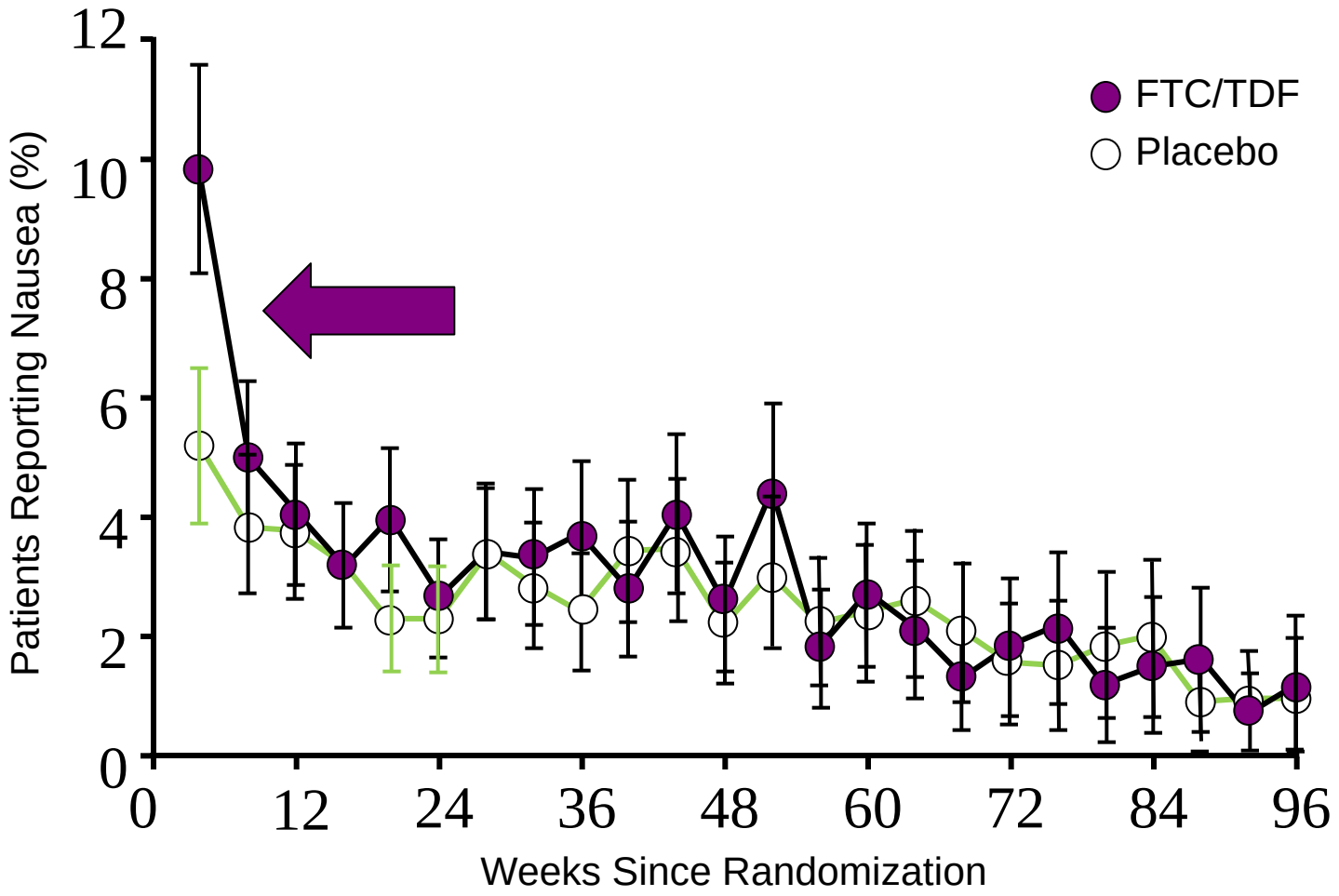
iPrEx: Adverse Events

- No significant differences between active and placebo arms for:
  - Any grade 3/4 event, death, SAE, elevated creatinine, creatinine elevation confirmed on next visit

Adverse Event	FTC/TDF (n = 1251)		Placebo (n = 1248)		P Value
	%	Events	%	Events	
Nausea	2	22	<1	10	0.04
Weight decrease	2	34	1	19	0.04

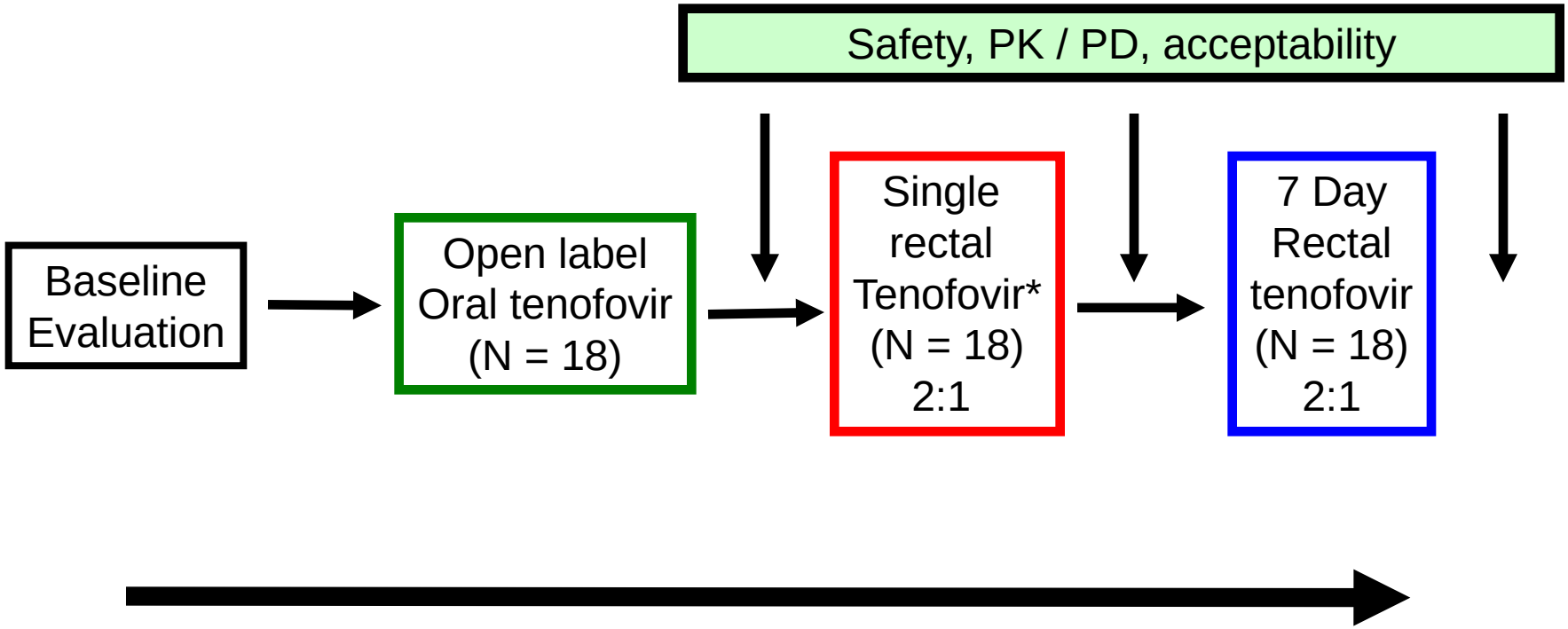
Grant RM, et al. N Engl J Med. 2010

iPrEx: Nausea



Grant RM, et al. N Engl J Med. 2010

RMP-02/MTN-006 Study Design



*1% tenofovir vaginal formulation

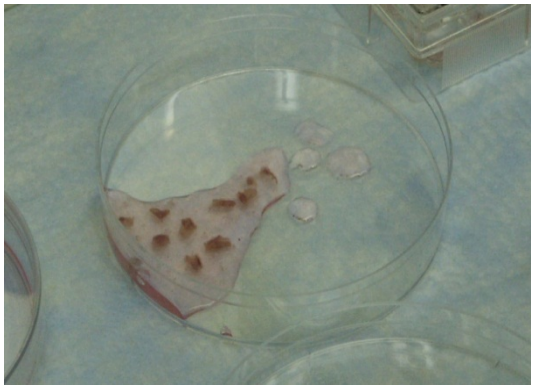
Anton AIDS Res Hum Retroviruses 2012

RMP-02/MTN-006 Adverse Events

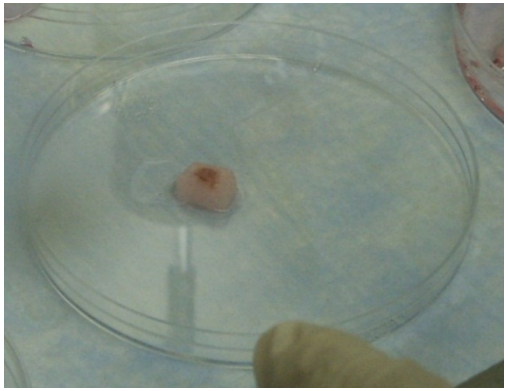
GI Adverse Events in the Tenofovir Arm	RMP-02/MTN-006 (N = 12) Vaginal Formulation	
	N	%
Abdominal pain	6	50%
Rectal urgency	5	42%
Bloating	5	42%
Nausea	4	33%
Diarrhea	7	58%
Flatulence	3	25%
Proctalgia	0	0%
Other	5	42%
Total	35	-

Anton AIDS Res Hum Retroviruses 2012

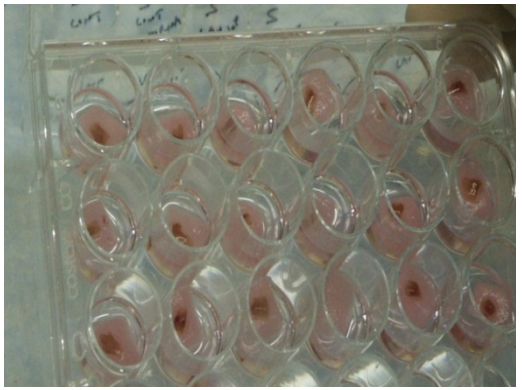
Colorectal Explants



Collect rectal biopsies From ppts previously exposed to Tenofovir gel



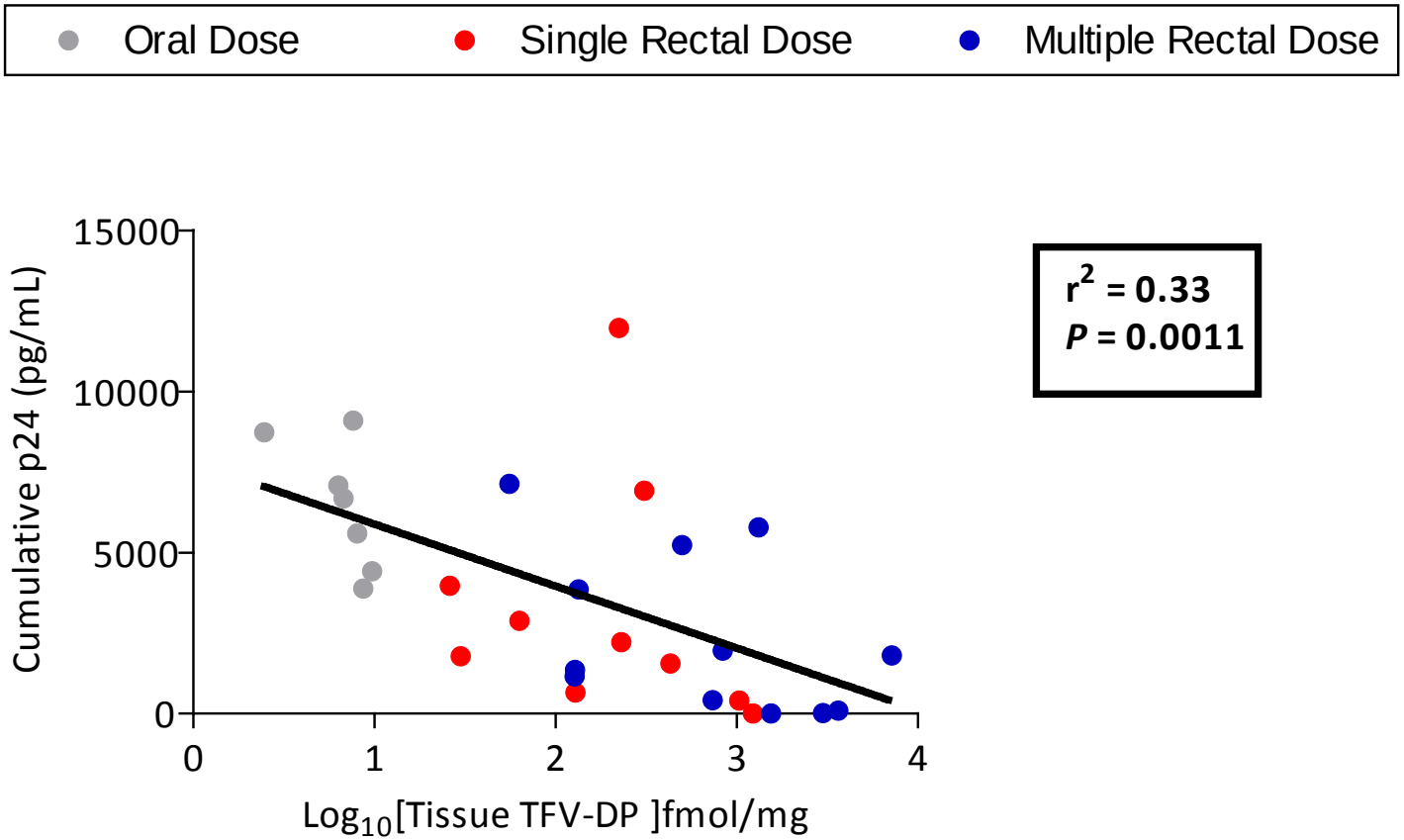
Place biopsy on raft



Expose to HIV and measure sequential p24 levels

Abner SR JID 2005, Watts P, AIDS, 2006

PK/PD Correlation in RMP-02/MTN 006



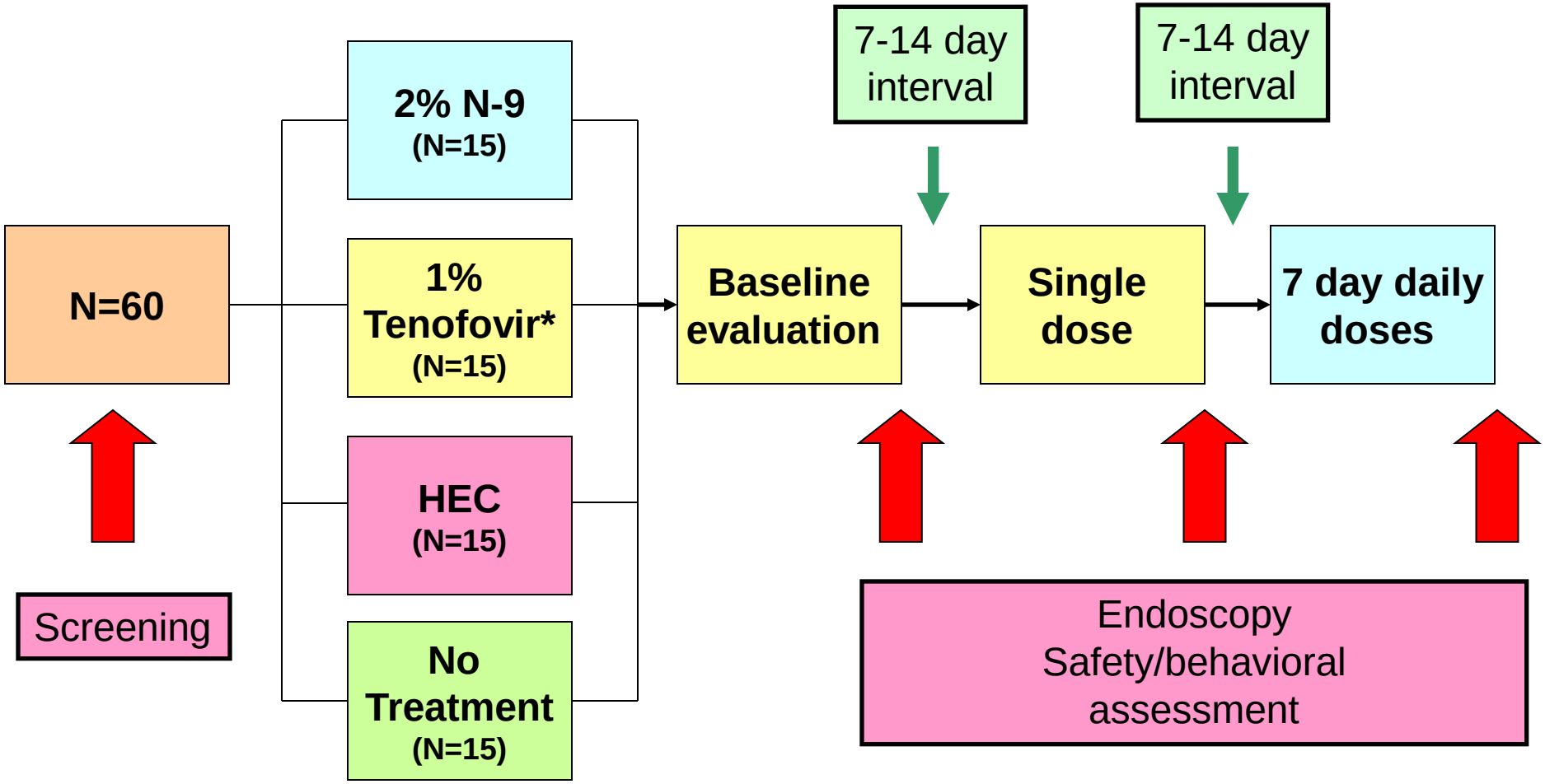
Anton AIDS Res Hum Res 2012

Acceptability

Product (N)	Like very much (%)
Tenofovir 1% gel (12)	25%
HEC Placebo (6)	50%

Anton AIDS Res Hum Retroviruses 2012

MTN-007 Study Design



*1% tenofovir reduced glycerin formulation

McGowan PLoS One 2013

MTN-007 Adverse Events

GI Adverse Events (Tenofovir Arm)	MTN-007 (N = 16) RG Formulation	
	N	%
Abdominal pain	3	16%
Rectal urgency	0	0%
Bloating	0	0%
Nausea	0	0%
Diarrhea	1	6%
Flatulence	6	38%
Proctalgia	1	6%
Other	4	25%
Total	15	-

McGowan PLoS One 2013

Gastrointestinal Adverse Events

GI Adverse Events in the Tenofovir Arm	MTN-007 (N = 16) RG Formulation		RMP-02/MTN-006 (N = 12) Original Formulation	
	N	%	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%

Acceptability

Product (N)	Intention to Use (%)
RG Tenofovir (15)	87%
HEC Placebo (15)	93%
N-9 (16)	63%

McGowan PLoS One 2013

MTN 017

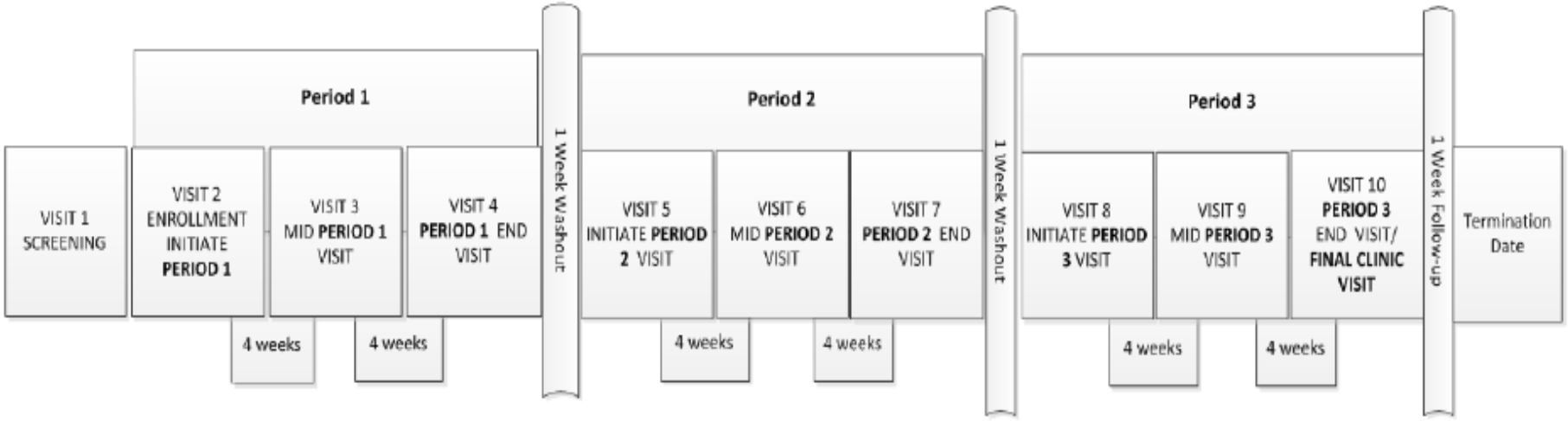
- Study Population
  - Approximately 186 ppts
  - HIV-uninfected
  - MSM or transgender females
  - Reported practicing receptive anal intercourse
  - Age 18 years or older

- Study Duration
  - Follow-up: 27 weeks per participant
  - Accrual: Projected 6-9 calendar months at each site

MTN-017

- Study regimens include:
  - Rectal tenofovir gel used daily
  - Rectal tenofovir gel used before and after sex (BAT 24)
  - Truvada tablets taken daily
- Each participant will follow all of the study regimens for eight weeks, with a weeklong break between regimens when no product will be used
  - The order in which participants follow study regimens will be based on random assignment
- All participants will receive standard HIV prevention package

MTN-017 Study Design



MTN-017 Study Design

Product Sequence	N	Period 1 (8 weeks)	Product Break (1 week)	Period 2 (8 weeks)	Product Break (1 week)	Period 3 (8 weeks)
1	31	Daily Truvada		Daily rectal gel		Rectal gel before and after sex
2	31	Rectal gel before and after sex		Daily Truvada		Daily rectal gel
3	31	Daily rectal gel		Rectal gel before and after sex		Daily Truvada
4	31	Daily rectal gel		Daily Truvada		Rectal gel before and after sex
5	31	Daily Truvada		Rectal gel before and after sex		Daily rectal gel
6	31	Rectal gel before and after sex		Daily Rectal gel		Daily Truvada

MTN
microbicide trials network

Primary Objectives/endpoints

- Safety
  - Compare the safety profiles of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
    - Grade 2 or higher adverse events
- Acceptability
  - To evaluate and compare acceptability of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
    - Participant self-report of ease of use, liking the product, and likelihood of product use if shown to be effective

Secondary Objective/Endpoints #1

- Pharmacokinetics
  - To compare systemic and local pharmacokinetics (PK)
    - Tenofovir concentrations
      - blood plasma, rectal tissue* and rectal fluid
    - Tenofovir-diphosphate concentrations
      - peripheral blood mononuclear cell (PBMC) and rectal tissue*
    - Emtricitabine concentrations
      - blood plasma, rectal tissue* and rectal fluid
    - Emtricitabine-triphosphate concentrations
      - PBMC and rectal tissue*

* Rectal tissue will be collected on a subset of participants taking part in the Rectal Biopsy/Fluid Subset

Secondary Objective/Endpoint #2

- Adherence
  - Compare the safety profiles of rectal tenofovir gel used daily and before and after sex, and Truvada tablets
    - Percentage of prescribed doses taken orally or administered rectally in an 8-week period

Exploratory Objectives

- Characterize pharmacodynamic responses
- Characterize changes in mucosal immunity
- Assess correlation between PK and adherence measures
- Identify factors associated with product adherence and whether they differ by product used
- Examine whether sexual activity or condom use varies by product used
- Determine the level of sharing of study products with non-participants
- Determine the prevalence of behavioral practices associated with anal intercourse that may affect microbicide use

Study Sites


Pittsburgh, PA
Boston, MA
San Juan, Puerto Rico
Chiang Mai, Thailand
Bangkok, Thailand
San Francisco, CA
Lima, Peru
Cape Town, South Africa

Adherence in African PrEP Trials

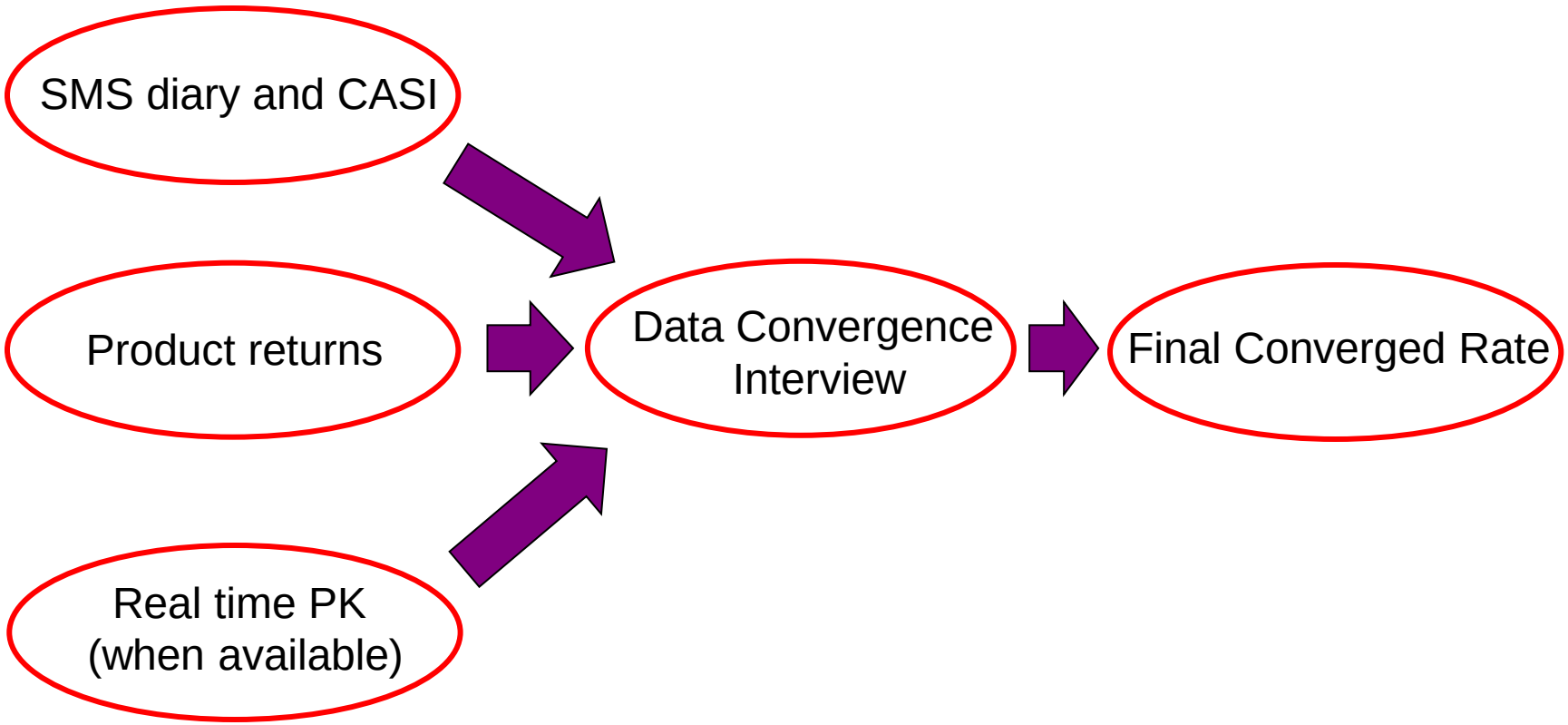
Name	Population	Estimated Adherence		
		Self report	CPC	Drug level (in subset)
TDF2	557 ♀ & 662 ♂	94%	84%	80%
Partners PrEP	4758 sd ♀/♂ couples	98%	97%	82%
Fem-PrEP	2120 ♀	95%	85%	<40%
VOICE	5029 ♀			
• TDF		90%	87%	30%
• Truvada		91%	92%	29%
• TFV gel		91%	86%	25%

Ambia (review) 2013; Baeten (review) 2013; van der Straten 2012; Baeten CROI 2013; Marrazzo CROI 2013

LoA (01-25-13)

- Main items:
  - Inclusion of mid and end period ‘real time’ plasma tenofovir PK (qualitative)
  - Inclusion of language to describe use of mid-period PK in data convergence interview
  - All AEs are reportable by CRF

Measuring Adherence in 017



Adapted from Pool PLoS One 2010

Timelines

- Protocol development:
  - Protocol development meeting 09-28-11
  - Community consultations
    - Cape Town Oct 2011
    - Pittsburgh Dec 2011
    - Bangkok and Chiang Mai Jan 2012
    - Boston Mar 2012
    - Lima Mar 2012
  - PSRC 04-03-12
  - Version 1.0 07-13-12

Site Activation

- Clinical Trial Agreement: 07-11-13
- Sites:
  - Fenway 09-06-13
  - SFDH 09-24-13
  - Pittsburgh* 09-27-13
  - San Juan 11-15-13
  - Chiang Mai 01-06-14
  - Lima 01-15-14
  - Cape Town Expected Feb 2014
  - Bangkok* Expected Apr 2014

*Mucosal immunology subset

017 Activity as of 02-21-14

Site (n)	Screened	Screen Fail	In Screening	Enrolled
Fenway (6)	11	4	0	7*
SFDH (30)	32	19	6	9
Pittsburgh (30)	11	2	3	6
San Juan (24)	6	1	5	3
Chiang Mai (24)	16	6	5	5
Lima (24)	9	1	3	5
Cape Town (24)	-			-
Bangkok (24)	-			-
TOTAL	**85**	**33**	**22**	**35**

* Including 1 replacement ppt

Anticipated Timeline (Approximate)

Topic	Date of completion
Accrual (6-9 months)	February 2015
Follow up (27 weeks)	September 2015
Data Clean up	November 2015
Data lock	December 2015
Primary results	January 2016

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- MTN-017 participants

Thank You!