

## MTN Protocols

Study	Short Title	Countries	Status
MTN-001	Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir	South Africa, Uganda, USA	Primary analysis complete; published
MTN-002	Maternal PK and Placental Transfer of Tenofovir 1% Vaginal Gel	USA	Primary analysis complete; published
MTN-003	Vaginal and Oral Interventions to Control the Epidemic (VOICE)	South Africa, Uganda, Zimbabwe	Primary analysis complete; published
MTN-003B	Bone Mineral Density Substudy of VOICE	Uganda, Zimbabwe	Primary analysis complete; published
MTN-003C	VOICE Community Substudy	South Africa	Primary analysis complete; published
MTN-003D	Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial	South Africa, Uganda, Zimbabwe	Primary analysis complete; published
MTN-003C-01	PREMIS	South Africa	Withdrawn
MTN-003-P01	Wisebag Observational Pilot	South Africa	Primary analysis complete; published
MTN-004	Safety and Acceptability of SPL7013 Gel in Sexually Active Women	USA	Primary analysis complete; published
MTN-005	Safety and Acceptability of a Non-medicated Intravaginal Ring	USA, India	Primary analysis complete
MTN-006	Rectal Safety, Acceptability and PK of Tenofovir 1% Gel	USA	Primary analysis complete; published
MTN-007	Rectal Safety and Acceptability of Reduced Glycerin Tenofovir 1% Gel	USA	Primary analysis complete; published
MTN-008	Expanded Safety of Tenofovir 1% Gel in Pregnancy and Lactation	USA	Primary analysis complete; published
MTN-009	HIV Resistance at Screening for HIV Prevention Trials	South Africa	Primary analysis complete; published
MTN-010	Expanded Safety Study of UC781 Gel	USA	Withdrawn
MTN-011	Coital PK/PD of Tenofovir 1% Gel	USA	Primary analysis complete; published
MTN-012/ IPM 010	Male Tolerance of Dapivirine Gel	USA	Primary analysis complete; published
MTN-013/ IPM 026	Phase 1 Safety and PK/PD of Dapivirine/Maraviroc Vaginal Ring	USA	Primary analysis complete; published
MTN-014	Phase 1 Safety and PK of Reduced Glycerin Tenofovir 1% Gel in the Rectal and Vaginal Compartments	USA	Primary analysis complete
MTN-015	MTN HIV-1 Seroconverter Study	Malawi, South Africa, Uganda, Zimbabwe	<ul style="list-style-type: none"> <li>• HPTN 035 Cohort: primary analysis complete; published</li> <li>• VOICE Cohort: primary analysis complete</li> <li>• ASPIRE Cohort: completed enrollment</li> <li>• HOPE Cohort: open to enrollment</li> </ul>
MTN-016	Prevention Agent Pregnancy Exposure Registry	Malawi, South Africa, Uganda, Zimbabwe, USA	<ul style="list-style-type: none"> <li>• MTN-002, MTN-008, VOICE Cohorts: follow-up completed</li> <li>• ASPIRE Cohort: enrollment completed</li> <li>• HOPE Cohort: open to enrollment</li> </ul>
MTN-017	Safety and Acceptability Study of Oral Truvada® and Reduced Glycerin Tenofovir 1% Gel	South Africa, USA, Thailand, Peru	Primary analysis complete; published
MTN-018	Committed to Having Options for Interventions to Control the Epidemic (CHOICE)	Former VOICE sites	Withdrawn
MTN-018B	CHOICE-B: Breastfeeding Substudy	Former VOICE sites	Withdrawn
MTN-018C	CHOICE-C: Pregnancy Substudy	Former VOICE sites	Withdrawn
MTN-019	Extended Safety of Tenofovir 1% Gel in Pregnancy	Malawi, Uganda, Zimbabwe, USA	Withdrawn
MTN-020	A Study to Prevent Infection with a Ring for Extended Use (ASPIRE)	Malawi, South Africa, Uganda, Zimbabwe	Primary analysis complete; published
MTN-021	Safety and Tolerability of Tenofovir 1% Gel in Adolescent Females	USA	Withdrawn
HVTN 095/ MTN-022	Phase 1 Safety and Immunogenicity of DNA/NYVAC Prime Boost Vaccination With/Without oral Truvada® or vaginal TFV 1% Gel	USA, South Africa	Withdrawn
MTN-023/ IPM 030	Safety Study of Dapivirine Vaginal Ring (VR) in Adolescent Females	USA	Closed to follow-up
MTN-024/ IPM 031	Safety Study of Dapivirine VR in a Post-Menopausal Female Population	USA	Primary analysis complete
MTN-025	HIV Open-label Prevention Extension (HOPE) Trial	Malawi, South Africa, Uganda, Zimbabwe	Enrolling
MTN-026	Safety and PK Study of Rectally-Applied Dapivirine Gel	USA; Thailand	Pending
MTN-027	Safety and PK of IVRs Containing MK-2048/Vicriviroc (MK-4176)/ MK-2048A	USA	Closed to follow-up
MTN-028	PK Trial of Two MK-2048A IVRs of Varying Dose Strengths	USA	Closed to follow-up

MTN-029/ IPM 039	PK Trial of a Dapivirine VR in Lactating Women	USA	Closed to follow-up
MTN-030/ IPM 041	PK and Safety Study of Vaginal Rings Containing Dapivirine and Levonorgestrel	USA	Pending
MTN-031/ IPM 043	Impact of Conditional Incentives on Dapivirine VR Adherence in an Open-Label Trial	Malawi, South Africa	Withdrawn
MTN-032	Assessment of ASPIRE and HOPE Adherence	Malawi, South Africa, Uganda, Zimbabwe	Enrolling (Phase 1 complete)
MTN-033	PK Study of Rectally-Applied Dapivirine Gel	USA	Pending
MTN-034/ IPM 045	Safety of and Adherence to a Dapivirine VR and Oral FTC/TDF in Adolescent Females (REACH)	Kenya, South Africa, Zimbabwe	Pending
MTN-035	Acceptability, Tolerability and Adherence of Two Rectal Placebo Products among HIV Seronegative Men and Transgender Women	TBD	Approved concept
MTN-036/ IPM 047	A Phase 1, Randomized, Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings	USA	In development
MTN-037	Safety and PK Study of PC-1005 in the Rectal Compartment	USA	In development
MTN-038	PK and Safety Study of a 90-Day Intravaginal Ring Containing Tenofovir	USA	In development
MTN-039	Safety and PK Study of TDF and EVG Administered Rectally	USA	Approved concept

With the exception of withdrawn protocols, study descriptions follow this summary table.

## MTN-001

### Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

<b>Protocol Chair:</b>	Craig Hendrix, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Tenofovir Disoproxil Fumarate (TDF) 300 mg Tablet</li><li>• Tenofovir 1% Gel</li></ul>
<b>Date of First Enrollment:</b>	18 July 2008
<b>Closed to Accrual:</b>	6 March 2010
<b>Total Enrolled/Expected:</b>	144 Evaluable (168 Overall)/144 Evaluable
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Compare adherence to and acceptability of three daily regimens of tenofovir (oral, vaginal, and dual use)
- Compare systemic and local pharmacokinetics (PK) among three regimens of tenofovir (oral, vaginal, and dual use) in a subset of participants

**Summary:** MTN-001 was a Phase 2, multi-site, randomized, six-sequence, three-period, open-label crossover study of adherence to and PK of tenofovir disoproxil fumarate (TDF) 300 mg tablet and tenofovir 1% gel. The study population included 18 to 45 year old healthy women who were HIV-uninfected, non-pregnant, sexually active, who used adequate contraception. All participants enrolled at the US study sites underwent more intensive specimen collection for PK analysis. In addition to the primary objectives above, the MTN-001 study characterized the differential safety profiles of the three different daily regimens of tenofovir, and assessed the level of study product sharing with non-participants. This protocol also investigated factors associated with product adherence and potential variations in sexual activity and male condom use associated with the different regimens. An optional procedure for participants at one site - the BLHC CRS in New York - was the collection of rectal swabs to assess tenofovir levels in the rectum following intravaginal administration of tenofovir 1% gel. MTN-001 results were first presented at the 18<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI), February 27-March 3, 2011 in Boston, MA.

**Results:** All three study regimens (TDF 300 mg tablet, tenofovir 1% gel and a combination of TDF 300 mg tablet and tenofovir 1% gel) were well tolerated and acceptable. A statistically significant preference for the oral product was noted ( $p=0.002$ ); this was largely driven by US sites. Self-reported adherence across sites was high (94%). Vaginal tissue levels of tenofovir diphosphate were 100-fold higher after vaginal administration than oral administration.

**Clinical Research Sites:** South Africa Botha's Hill CRS, Umkomaas CRS  
USA Alabama CRS, Bronx-Lebanon Hospital Center CRS (BLHC CRS),  
Case CRS, University of Pittsburgh CRS  
Uganda MUJHU CARE LTD CRS

#### Citations:

1. Hendrix CW, Chen BA, Guddera V, Hoesley C, Justman J, Nakabiito C, Salata R, Soto-Torres L, Patterson K, Minnis AM, Gandham S, Gomez K, Richardson BA, Bumpus NN. MTN-001: randomized pharmacokinetic cross-over study comparing tenofovir vaginal gel and oral tablets in vaginal tissue and other compartments. PLoS One 2013;8(1):e55013. PMID:PMC3559346
2. Minnis AM, Gandham S, Richardson BA, Guddera V, Chen BA, Salata R, Nakabiito C, Hoesley C, Justman J, Soto-Torres L, et al. Adherence and acceptability in MTN 001: a randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. AIDS Behav 2013 Feb;17(2):737-47. PMID:PMC3562423

## MTN-001 (continued)

3. Chaturvedula A, Fossler MJ, Hendrix CW. Estimation of tenofovir's population pharmacokinetic parameters without reliable dosing histories and application to tracing dosing history using simulation strategies. *J Clin Pharmacol* 2014 Feb;54(2):150-160. PMID: PMC5001555
4. Burns RN, Hendrix CW, Chaturvedula A. Population pharmacokinetics of tenofovir and tenofovir-diphosphate in healthy women. *J Clin Pharmacol* 2015 Jun;55(6):629-38.
5. Murphy K, Richardson BA, Dezzutti CS, Marrazzo J, Hillier SL, Hendrix CW, Herold BC. Levels of genital tract defensins and cytokines differ between HIV-uninfected US and African women. *Am J Reprod Immunol* 2015 Oct;74(4):313-22. PMID:PMC4573314
6. Lade JM, To EE, Hendrix CW, Bumpus NN. Discovery of genetic variants of the kinases that activate tenofovir in a compartment-specific manner. *EBioMedicine* 2015;2:1145-52. PMID:PMC4588390
7. Minnis AM, van der Straten A, Salee P, Hendrix CW. Pre-exposure prophylaxis adherence measured by plasma drug level in MTN-001: Comparison between vaginal gel and oral tablets in two geographic regions. *AIDS Behav* 2016 Jul;20(7):1541-8. PMID:PMC4957649.

## MTN-002

### Phase 1 Study of the Maternal Single-Dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel Among Healthy Term Gravidas

<b>Protocol Chair:</b>	Richard Beigi, MD, MSc
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Tenofovir 1% Gel</li></ul>
<b>Date of First Enrollment:</b>	18 August 2008
<b>Closed to Accrual:</b>	22 December 2009
<b>Total Enrolled/Expected:</b>	16 Evaluable (21 Overall)/16 Evaluable
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Assess term pregnancy maternal single-dose pharmacokinetics of tenofovir 1% vaginal gel

**Summary:** MTN-002 was a Phase 1, single-site, open-label study of pharmacokinetic parameters and placental transfer of single-dose of tenofovir 1% gel when administered vaginally to 16 pregnant women at term who were scheduled for elective cesarean delivery. Secondary objectives included the characterization of the systemic safety profile of single-dose tenofovir 1% gel in these women; a comparison of 3<sup>rd</sup> trimester absorption of tenofovir 1% gel to absorption in non-pregnant recent historic controls; and the assessment of amniotic fluid, cord blood, endometrial tissue and placental tissue levels following the observed administration of single-dose tenofovir 1% gel. This protocol was the first study of a candidate microbicide gel in pregnant women and represented an innovative approach to moving products into safety testing in pregnant women, a key recommendation of a 2008 Institute of Medicine report.

This study served as the platform for planning and conducting additional studies of microbicide safety in pregnancy. Along with data derived from MTN-016 (HIV Prevention Agent Pregnancy Exposure Registry), it provides critical new information on the safety of vaginally applied products in pregnant women. MTN-002 results were first presented in 2010 during at the Microbicides 2010 Conference and at the Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) Annual Meeting in 2010.

**Results:** No significant safety concerns were identified. Tenofovir was generally detectable at low levels in maternal and cord blood. In maternal plasma the median  $C_{max}$  after this single dose application of gel was approximately 100-fold lower than the  $C_{max}$  noted after a maternal dose of 600 mg oral TFV used for the prevention of mother to child transmission.

**Clinical Research Site:** USA University of Pittsburgh CRS

#### Citation:

Beigi R, Noguchi L, Parsons T, Macio I, Kunjara Na, Ayudhya RP, Chen J, Hendrix CW, Mâsse B, Valentine M, Piper J, Watts DH. Pharmacokinetics and placental transfer of single-dose tenofovir 1% vaginal gel in term pregnancy. J Infect Dis 2011;204(10):1527-31. PMID:PMC3192189

## MTN-003 (VOICE)

### Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate (TDF) Tablet and TDF-Emtricitabine Tablet for the Prevention of HIV Infection in Women

<b>Protocol Chairs:</b>	Zvavahera Mike Chirenje, MD & Jeanne Marrazzo, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Tenofovir Disoproxil Fumarate (TDF) 300 mg Tablet</li><li>• TDF Placebo Tablet</li><li>• Emtricitabine (FTC)/TDF 200 mg/300 mg Tablet (Truvada)</li><li>• FTC/TDF Placebo Tablet</li><li>• Tenofovir 1% Gel</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel</li></ul>
<b>Date of First Enrollment:</b>	15 September 2009
<b>Closed to Accrual:</b>	6 June 2011
<b>Total Enrolled/Expected:</b>	5029/5000
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among women at risk for sexually transmitted infection (STI)
- Evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection

**Summary:** VOICE was a Phase 2B, multi-site, five-arm, randomized, controlled trial. A total of 5029 women were randomized to five study arms in a 1:1:1:1:1 ratio. Secondary objectives focused on adherence/behavioral factors, HIV-1 drug resistance (among those who become HIV-infected during the study), pharmacokinetic parameters, and the potential for delayed seroconversion during an off-product period scheduled at the end of study participation. Additional objectives included exploring the impact of study products on vaginal microenvironment and assessing potential relationships between method of contraception and HIV seroconversion, product adherence, and adverse events. Version 2.0 of the protocol (dated 31 December 2010) included updates to the sample size, expected length of follow-up on study product, and statistical considerations. The VOICE trial was unique within the HIV prevention field as it was designed to provide parallel comparisons of oral and topically (vaginal) applied antiretroviral strategies for prevention of HIV infection in women. Following the Data and Safety Monitoring Board (DSMB) reviews in September 2011 and November 2011, the oral tenofovir tablet study arms and the vaginal tenofovir gel and corresponding placebo arms were stopped due to futility. Primary results were presented at the 20<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in March 2013.

**Results:** All participants completed study follow-up on 13 August 2012, with an overall study retention rate of 91%. Findings showed that there were no statistically significant differences in rate of new infections when each study product arm was compared to placebo. The results may be due, in part, to the low adherence to study products. Although adherence rates were high by self-report (88-90%) and returned product counts (86%), analysis of plasma drug levels showed that fewer than 30% of women used their assigned study product.

**Clinical Research Sites:** South Africa CAPRISA Aurum CRS, eThekwni CRS; MRC: Botha's Hill CRS, Chatsworth CRS, Isipingo CRS, Overport CRS, Tongaat CRS, Umkomaas CRS, Verulam CRS; Soweto MTN CRS; Wits Reproductive Health and HIV Institute (RHI)

Uganda MUJHU CARE LTD CRS

Zimbabwe Seke South CRS, Spilhaus CRS, Zengeza CRS

## MTN-003 (VOICE) (continued)

### Citations:

1. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodini N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015 Feb 5;372(6):509-18. PMID:PMC4341965
2. White R, Chileshe M, Dawson L, Donnell D, Hillier S, Morar N, Noguchi L, Dixon D. Fostering community understanding of sufficient benefit and early stopping for a phase 2B HIV prevention clinical trial in Africa. *Clin Trials* 2011; 8(1):103-11. PMID:PMC3478774
3. Lanham M, Wilcher R, Montgomery ET, Pool R, Schuler S, Lenzi R, Friedland B. Engaging male partners in women's microbicide use: Evidence from clinical trials and implications for future research and microbicide introduction. *J Int AIDS Soc* 2014 Sep;17(3 Suppl 2):19159. PMID:PMC4163996
4. van der Straten A, Mayo A, Brown ER, Amico KR, Cheng H, Laborde N, Marrazzo J, Torjesen K. Perceptions and experiences with the VOICE Adherence Strengthening Program (VASP) in the MTN-003 Trial. *AIDS Behav* 2015 May;19(5):770-83. PMID:PMC4416998
5. Noguchi LM, Richardson BA, Baeten JM, Hillier SL, Balkus JE, Chirenje ZM, Bunge K, Ramjee G, Nair G, Palanee-Phillips T, et al. Risk of HIV-1 acquisition among women who use different types of injectable progestin contraception in South Africa: a prospective cohort study. *Lancet HIV* 2015 Jul 1;2(7):e279-e287. PMID:PMC4491329
6. Balkus JE, Nair G, Montgomery ET, Mishra A, Palanee-Phillips T, Ramjee G, Panchia R, Selepe P, Richardson BA, Chirenje ZM, et al. Age-disparate partnerships and risk of HIV-1 acquisition among South African women participating in the VOICE Trial. *J Acquir Immune Defic Syndr* 2015 Oct;70(2):212-7. PMID:PMC4573287
7. Dai JY, Hendrix CW, Richardson BA, Kelly C, Marzinke M, Chirenje ZM, Marrazzo JM, Brown ER. Pharmacological measures of treatment adherence and risk of HIV infection in the VOICE Study. *J Infect Dis* 2016 Feb 1;213(3):335-42. PMID:PMC4704663
8. van der Straten A, Brown ER, Marrazzo JM, Chirenje MZ, Liu K, Gomez K, Marzinke MA, Piper JM, Hendrix CW, MTN-003 VOICE Protocol Team for the Microbicide Trials Network. Divergent adherence estimates with pharmacokinetic and behavioural measures in the MTN-003 (VOICE) Study. *J Int AIDS Soc* 2016 Feb 4;19(1):20642. PMID:PMC4744323
9. Mensch BS, Brown ER, Liu K, Marrazzo J, Chirenje ZM, Gomez K, Piper J, Patterson K, van der Straten A. Reporting of adherence in the VOICE trial: Did disclosure of product non-use increase at the termination visit? *AIDS Behav* 2016 Nov;20(11):2654-2661.
10. Balkus JE, Brown E, Palanee T, Nair G, Gafoor Z, Zhang J, Richardson BA, Chirenje ZM, Marrazzo JM, Baeten JM. An empiric HIV risk scoring tool to predict HIV-1 acquisition in African women. *J Acquir Immune Defic Syndr* 2016 Jul 1;72(3):333-43. PMID:PMC4911322
11. Moodley J, Naidoo S, Moodley J, Ramjee G. Sharing of investigational drug among participants in the Voice Trial. *AIDS Behav* 2016 Nov;20(11):2709-2714. PMID:PMC5071120
12. Chirenje ZM, Gundacker, HM, Richardson B, Rabe L, Gaffoor Z, Nair G, Mirembe Gati B, Piper JM, Hillier S, Marrazzo J. Risk factors for incidence of sexually transmitted infections among women in a HIV chemoprevention trial: VOICE (MTN 003). *Sex Transm Dis* 2017 Mar;44(3):135-140.

13. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodhi N, Mirembe BG, Gomez Feliciano K, Horn S, Liu AY, Glidden DV, Grant RM, Benet LZ, Louie A, van der Straten A, Chirenje ZM, Marrazzo JM, Gandhi M. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. *AIDS Res Hum Retroviruses* 2017; Mar 2 [*Epub ahead of print*]
14. Akello CA, Bunge KE, Nakabiito C, Mirembe BG, Fowler MG, Mishra A, Marrazzo J, Chirenje ZM, Celum C, Balkus JE. Contraceptive use and pregnancy incidence among women participating in an HIV prevention trial. *J Womens Health* 2017: *In Press*



## MTN-003B (VOICE-B)

### VOICE Bone Mineral Density (BMD) Substudy

<b>Protocol Chair:</b>	Sharon Riddler, MD, MPH
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	9 November 2009
<b>Closed to Accrual:</b>	13 June 2011
<b>Total Enrolled:</b>	518 Participants
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Compare changes in Bone Mineral Density (BMD) after one year among VOICE participants receiving oral tenofovir disoproxil fumarate (tenofovir or TDF) and emtricitabine (FTC)/TDF (Truvada) compared with oral placebo

**Summary:** The BMD Substudy was an observational substudy of VOICE designed to assess the impact of oral TDF and oral FTC/TDF on bone mineral density. VOICE participants randomized to oral study product at MTN-003B study sites were offered participation in the BMD Substudy (518 of 567 eligible VOICE participants enrolled in MTN-003B). Scheduled follow-up, including nutritional assessment, DXA scan, and blood tests related to bone turnover and metabolism, occurred on a semi-annual basis during VOICE study participation, at the scheduled end of product use visit, and (with the protocol amendment in August 2011) at 6 and 12 months following the discontinuation of an oral study product in VOICE.

A secondary objective of the study was to provide a description of changes over time in nutritional assessment components among eligible VOICE participants. Exploratory objectives include the examination of potential mechanisms of BMD changes among eligible VOICE participants, as well as changes in urinary phosphorous excretion in relation to possible changes in bone density. The potential impact of tenofovir-containing prevention agents on the bone density of healthy women of reproductive age, who may be exposed to other possible stressors on bone health, will be important for the evaluation of the overall safety of these agents for prevention of HIV infection in women.

Primary study results were presented at the HIV Research for Prevention (HIV R4P) meeting held October 28-31, 2014 in Cape Town, South Africa.

**Results:** Small but significant reversible decreases in BMD were observed among young African women with higher adherence on TDF-based oral PrEP. Observed differences were in the range seen in prior studies of HIV-negative men and women. Of 518 women enrolled, 432 had dual-energy x-ray absorptiometry results at baseline and week 48. In the primary analysis, no significant differences in percent BMD change in hip or spine between arms observed, likely because of low product adherence. Among the subset with tenofovir detection in 75%–100% of plasma samples, the mean percent BMD change from baseline to week 48 in the LS was 1.4% lower for TDF or emtricitabine/TDF recipients than for placebo ( $P = 0.002$ ) and TH BMD was 0.9% lower ( $P = 0.018$ ). BMD changes from end of active treatment to 48 weeks were significantly greater in the active arm participants compared with placebo participants with a net difference of approximately +0.9% at the LS ( $P = 0.007$ ) and +0.7% ( $P = 0.003$ ) at the TH.

**Clinical Research Sites:** Uganda MUJHU CARE LTD CRS  
Zimbabwe Seke South CRS, Spilhaus CRS, Zengeza CRS

## MTN-003B (continued)

### Citations:

1. Mirembe BG, Kelly CW, Mgodhi N, Greenspan S, Dai JY, Mayo A, Piper J, Akello CJ, Kiweewa FM, Magure T, et al. Bone mineral changes among young, healthy African women receiving oral tenofovir for HIV pre-exposure prophylaxis. *J Acquir Immune Defic Syndr* 2016;71(3):287–94. PMID:PMC4755358
2. Mgodhi NM, Kelly C, Gati B, Greenspan S, Dai JY, Bragg V, Livant E, Piper JM, Nakabiito C, Magure T, et al. Factors associated with bone mineral density in healthy African women. *Arch Osteoporos* 2015;10(1):206. PMID:PMC4564062

## MTN-003C (VOICE-C)

### VOICE Community Substudy

<b>Protocol Chairs:</b>	Jonathan Stadler, PhD Ariane van der Straten, PhD, MPH
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	27 July 2010
<b>Closed to Accrual:</b>	22 August 2012
<b>Total Enrolled:</b>	175 Participants
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Explore socio-cultural and contextual factors that participants identify as influencing product use (and non-use) in VOICE
- Determine if factors identified by participants as influencing product use (and non-use) are different between those who are randomized to the vaginal product arm vs. oral product
- Elicit Group 1 (VOICE participants at VOICE-C site[s]) participants' perceptions of the importance of adherence and their experiences of barriers and facilitators to adherence

**Summary:** The VOICE Community Substudy was implemented at a single VOICE site in Johannesburg, South Africa. VOICE-C assessed the impact of household factors and community perspectives on reported product adherence by women, utilizing both behavioral research and ethnographic approaches. The VOICE-C study collected data from VOICE participants, male partners of participants, members of the site's Community Advisory Boards (CABs), and key community stakeholders. Study staff members solicited the input of external stakeholders on developing and implementing strategies to improve product adherence in the trial, and collected feedback on participants' experiences with implementation strategies via exit focus group discussions.

The use of qualitative methods in VOICE-C provided insight into the context in which women were asked by VOICE researchers to use their study products. The study also provided information on the complex relationships among those who conduct clinical research, participate in the research, and live in the communities where clinical research takes place. The VOICE-C primary results were first presented at the International Conference on HIV Treatment and Prevention Adherence conference in Miami, FL on June 3, 2013.

**Results:** While many participants acknowledged missing occasional doses of investigational product, few reported long periods of non-use. Employment reportedly had the greatest impact on non-use, causing missed visits and thus time without product. Stigma related to associating products, mostly tablets, with antiretroviral drugs and HIV was pervasive. Other barriers to product use included travel, concerns regarding privacy (for gel users), and side effects (for tablet users). Factors that were reported to facilitate adherence included support from staff and significant others, ancillary benefits of products (e.g. enhanced sexual experience or cleansing properties of gel), feeling protected by the product and altruism.

**Clinical Research Site:** South Africa Wits RHI CRS

#### Citations:

1. van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathebula F, Schwartz K, Laborde N, Soto-Torres L. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLoS One 2014;9(2):e89118. PMID:PMC3931679

## MTN-003C (continued)

2. Magazi B, Stadler J, Delany-Moretlwe S, Montgomery E, Mathebula F, Hartmann M, van der Straten A. Influences on visit retention in clinical trials: insights from qualitative research during the VOICE trial in Johannesburg, South Africa. *BMC Womens Health* 2014;14:88. PMID:PMC4115485
3. Lanham M, Wilcher R, Montgomery ET, Pool R, Schuler S, Lenzi R, Friedland B. Engaging male partners in women's microbicide use: evidence from clinical trials and implications for future research and microbicide introduction. *J Int AIDS Soc* 2014;17(3 Suppl 2):19159. PMID:PMC4163996
4. van der Straten A, Stadler J, Luecke E, Laborde N, Hartmann M, Montgomery ET, on behalf of the VOICE-C Study Team. Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: the VOICE-C qualitative study in Johannesburg, South Africa. *J Int AIDS Soc* 2014, 17(Suppl 2):19146. PMID:PMC4163995
5. Montgomery ET, van der Straten A, Stadler J, Hartmann M, Magazi B, Mathebula F, Laborde N, Soto-Torres L. Male partner influence on women's HIV prevention trial participation and use of pre-exposure prophylaxis: The importance of "understanding". *AIDS Behav* 2015 May;19(5):784-93. PMID:PMC4416996
6. Stadler J, Scorgie F, van der Straten A, Saethre E. Adherence and the lie in a HIV prevention clinical trial. *Med Anthropol* 2016 Nov-Dec;35(6):503-516. PMID: PMC4977196
7. Hartmann M, Montgomery E, Stadler J, Laborde N, Magazi B, Mathebula F, van der Straten A. Negotiating the use of female-initiated HIV prevention methods in a context of gender-based violence: The narrative of rape. *Cult Health Sex* 2016 Jun;18(6):611-24. PMID:PMC4845669

## MTN-003D

### An Exploratory Study of Potential Sources of Efficacy Dilution in VOICE Trial

<b>Protocol Chair:</b>	Ariane van der Straten, PhD, MPH
<b>Protocol Co-Chairs:</b>	Barbara Mensch, PhD Elizabeth Montgomery, PhD
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	11 December 2012
<b>Closed to Accrual:</b>	27 March 2014
<b>Total Enrolled/Expected:</b>	Stage 1 – 88/88 Participants (complete) Stage 2 – 131/108-144 Participants (complete)
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants' actual and reported product use.
- Explore the reasons, motivations and context of engaging in receptive anal intercourse, (and rectal use of gel among VOICE participants in the gel group).

**Summary:** MTN-003D was a VOICE protocol substudy, in which a subset of former participants was asked to complete one or two additional visits after their participation in the VOICE trial. If participants agreed to participate in the MTN-003D substudy, they completed an in-depth interview (IDI) and/or participated in a focus group discussion (FGD). MTN-003D investigated the factors influencing VOICE participants' actual versus reported study product use and explored receptive anal intercourse (AI) behavior. In addition, motivations to join the trial, and risk perception in particular, were explored as one of the explanatory factors contributing to sub-optimal adherence. In Stage 2 of MTN-003D, participants were presented with their drug levels from blood samples collected during participation in VOICE. The drug levels were used as a tool to further explore product non-adherence and related behaviors.

The study was completed 28 March 2014 and primary results presented at HIV Research for Prevention (HIV R4P) in October 2014.

**Results:** Provision of PK results to a sample of VOICE participants (South Africa, Zimbabwe, Uganda) seemingly promoted candid discussions around poor adherence and experience with products in VOICE. Analyses of transcripts demonstrated PK results' elicited reactions and adherence challenges reported by each PK group.

**Clinical Research Sites:** Uganda MU-JHU Research Collaboration CRS  
Zimbabwe Seke South CRS, Zengeza CRS  
South Africa MRC: Isipingo CRS, Overport CRS

#### Citations:

1. van der Straten A, Montgomery ET, Musara P, Etima J, Naidoo S, Laborde N, Hartmann M, Levy L, Bennie T, Cheng H, et al. Disclosure of pharmacokinetic drug results to understand non-adherence. *AIDS* 2015 Oct;29(16):2161-71. PMID:PMC4638164
2. Duby Z, Hartmann M, Mahaka I, Munaiwa O, Nabukeera J, Vilakazi N, Mthembu F, Colvin CJ, Mensch B, van der Straten A. Lost in translation: Language, terminology and understanding of penile-anal intercourse in an HIV prevention trial in South Africa, Uganda and Zimbabwe. *J Sex Res* 2016; Nov-Dec 53(9):1096-1106. PMID: PMC4961617

### MTN-003D (continued)

3. DUBY Z, Hartmann M, Montgomery ET, Colvin CJ, Mensch B, van der Straten A. Sexual scripting of heterosexual penile-anal intercourse amongst participants in an HIV prevention trial in South Africa, Uganda and Zimbabwe. *Culture Health Sex* 2016 Jan;18(1):30-44. PMID:PMC4659730
4. DUBY Z, Hartmann M, Montgomery ET, Colvin CJ, Mensch B, van der Straten A. Condoms, lubricants and rectal cleansing: Practices associated with heterosexual penile-anal intercourse amongst participants in an HIV prevention trial in South Africa, Uganda and Zimbabwe. *AIDS Behav* 2016 Apr;20(4):754-62. PMID:PMC4698090
5. Luecke EH, Cheng H, Woeber K, Nakyanzi T, Mudekanye-Mahaka IC, van der Straten A, MTN-003D Study Team. Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study. *J Int AIDS Soc* 2016 May 30;19(1):20875. PMID:PMC4887458
6. Montgomery ET, Mensch B, Musara P, Hartmann M, Woeber K, Etima J, van der Straten A. Misreporting of Product adherence in the MTN-003/VOICE Trial for HIV prevention in Africa: participants' explanations for dishonesty. *AIDS Behav* 2017 Feb;21(2):481-491.
7. Musara P, Montgomery ET, Mgodini NM, Woeber K, Akello CA, Hartmann M, Cheng H, Levy L, Katz A, Grossman CI, Chirenje ZM, van der Straten A, Mensch B; Microbicide Trials Network-003D Study Team. How presentation of drug detection results changed reports of product adherence in South Africa, Uganda and Zimbabwe. *AIDS Behav* 2017 Jan 21 [*Epub ahead of print*]
8. DUBY Z, Mensch B, Hartmann M, Montgomery E, Mahaka I, Bekker L, van der Straten A. Achieving the optimal vaginal state: the use of vaginal products and study gels in Uganda, Zimbabwe and South Africa. *Int Perspect Sex Reprod Health* 2017; *In Press*.

**The Wisebag Observational Pilot Study: Feasibility, Acceptability and Performance of an Electronic Event-based Monitoring System (Wisebag)**

<b>Protocol Chairs:</b>	Ariane van der Straten, PhD, MPH Elizabeth Montgomery, PhD
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	27 July 2011
<b>Closed to Accrual:</b>	9 September 2011
<b>Total Enrolled/Expected:</b>	50/50
<b>Current Status:</b>	Primary Analysis Complete; Published

**Primary Objectives:**

- Compare the on-site technical performance of the “offline” and “online” functionalities of Wisebag
- Assess the success of attempted blinding of the “dummy” vs. active (“online” or “offline”) Wisebag
- Measure the concordance between Wisebag opening-event data (both “online” and “offline”) and self-reported data
- Explore the feasibility and acceptability of Wisebag use by participants

**Summary:** The objectives of the study were based on the assumption that the “active” Wisebags will: 1) successfully and accurately record opening events; 2) will be acceptable for use by women in the study; 3) women will not be able to distinguish between an active and dummy Wisebag.

It is widely accepted that self-reporting of adherence yields inaccurate results, most often inflation, of product use. Adherence, however, is one of the most important components of testing whether or not a study product is effective. The Wisebag™ is a lunch bag-style container with an electronic events-monitoring system. This opening event-monitoring bag is a promising technology that could provide objective measures of the days and times that women retrieve gel applicators for use. However, the functionality of Wisebag when used daily and in “offline” mode had never been tested, and required piloting prior to its use in larger-scale studies. The MTN-003-P01 study results were first presented at the Microbicides 2012 Conference.

**Results:** In the two-week pilot study, women found the bags acceptable for use. Blinding between the different WB/devices types (online/offline/dummy) was successful. Agreement between Wisebag opening data and clinic-based observation was high. During home use, however, moderate concordance was found between Wisebag opening data and the diary card. Adherence reporting was higher by self-report (diary card or CRF at study exit) compared to Wisebag. Many participants reported protocol non-adherence, including non-use and over-use of the Wisebag.

**Clinical Research Site:** South Africa eThekweni CRS

**Citation:**

van der Straten A, Elizabeth Montgomery, Pillay D, Cheng H, Naidoo A, Cele Z, Naidoo K, Hartmann M, Piper J, Nair G. Feasibility, performance, and acceptability of the Wisebag™ for potential monitoring of daily gel applicator use in Durban, South Africa. AIDS Behav 2013;17(2):640-8. PMID: PMC3562379

## MTN-004

### Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

<b>Protocol Chair:</b>	Ian McGowan, MD, PhD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• VivaGel® (SPL7013 Gel)</li><li>• VivaGel® Placebo Gel</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel</li></ul>
<b>Date of First Enrollment:</b>	21 August 2007
<b>Closed to Accrual:</b>	14 October 2009
<b>Total Enrolled/Expected:</b>	61/61
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Assess the safety of VivaGel® when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18-24 years

**Summary:** MTN-004 was a double-blind, placebo-controlled study investigating the safety, tolerability, and systemic absorption of 3% VivaGel® when administered vaginally twice daily for 14 consecutive days in healthy, sexually active, HIV-negative young women. This study was a collaborative effort between the MTN and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Participants were to be randomized to either 3% w/w VivaGel® or VivaGel® placebo in a 1:1 ratio.

Enrollment into this study began in July 2007 and was paused in October 2007 for a review of adverse event data. An interim blinded review of laboratory and clinical data on the seven enrolled women took place and confirmed that the study could continue. The protocol was revised and a third treatment arm was added to the study, a universal hydroxyethylcellulose (HEC) placebo gel arm to allow for a comparison of the safety of VivaGel®, VivaGel® placebo and the HEC placebo gel in sexually active young women. Results were first presented at the Microbicides 2010 conference.

**Results:** MTN-004 demonstrated that VivaGel was generally well tolerated and comparable with the VivaGel placebo, although there was lower adherence and acceptability and a higher incidence of related genital adverse events compared to the HEC placebo gel.

#### Clinical Research Sites: USA

University of Pittsburgh CRS  
University of Puerto Rico, San Juan, Puerto Rico  
Univ. of S. Florida, Div. of Adolescent Medicine

#### Citations:

1. McGowan I, Gomez K, Bruder K, Febo I, Chen BA, Richardson BA, Husnik M, Livant E, Price C, Jacobson C. Phase 1 randomized trial of the vaginal safety and acceptability of SPL7013 gel (VivaGel) in sexually active young women (MTN-004). *AIDS* 2011 May 15;25(8):1057-64. PMID: PMC3103767
2. Carballo-Dieguez A, Giguere R, Dolezal C, Chen BA, Kahn J, Zimet G, Mabragana M, Leu CS, McGowan I. "Tell Juliana": acceptability of the candidate microbicide VivaGel(R) and two placebo gels among ethnically diverse, sexually active young women participating in a phase 1 microbicide study. *AIDS Behav* 2012 Oct;16(7):1761-74. PMID: PMC3272128



### MTN-004 (continued)

3. Giguere R, Carballo-Diequez A, Ventuneac A, Mabragana M, Dolezal C, Chen BA, Kahn JA, Zimet GD, McGowan I. Variations in microbicide gel acceptability among young women in the USA and Puerto Rico. *Cult Health Sex* 2012;14(2):151-66. PMID:PMC3265079
4. Gigure R, Zimet GD, Kahn JA, Dolezal C, Leu CS, Mabragana M, McGowan I, Carballo-Diequez A. The motivations and experiences of young women in a microbicide trial in the USA and Puerto Rico. *World J AIDS* 2013 Sep;3(3). PMID:PMC3855411
5. Mabragana M, Carballo-Diequez A, Giguere R. Young women's experience with using videoconferencing for the assessment of sexual behavior and microbicide use. *Telemed J E Health* 2013 Nov;19(11):866-71. PMID:PMC3810614
6. Pellett Madan R, Dezzutti CS, Rabe L, Hillier SL, Marrazzo J, McGowan I, Richardson BA, Herold BC. Soluble immune mediators and vaginal bacteria impact innate genital mucosal antimicrobial activity in young women. *Am J Reprod Immunol* 2015 Oct;74(4): 323-32. PMID:PMC4573238

## MTN-005

### Expanded Safety and Adherence Study of a Non-Medicated Intravaginal Ring

<b>Protocol Chair:</b>	Craig Hoesley, MD
<b>Study Product:</b>	Non-medicated Intravaginal Ring
<b>Date of First Enrollment:</b>	15 June 2011
<b>Closed to Accrual:</b>	20 September 2012
<b>Total Enrolled/Expected:</b>	195/252
<b>Current Status:</b>	Primary Analysis Complete

#### Primary Objectives:

- Evaluate adherence to the study intravaginal ring in HIV-uninfected women over 12 weeks of use
- Evaluate the safety of the study intravaginal ring in HIV-uninfected women over 12 weeks of use

**Summary:** MTN-005 was a multi-site, randomized, open-label, two-arm, controlled trial of a non-medicated intravaginal ring. A vaginal ring delivery system for microbicides has the potential to minimize adherence problems found with the use of daily or coitally-dependent dosing regimens. This study evaluated the safety and adherence to intravaginal ring use in women in the U.S. and India. Currently published data on the use of contraceptive or hormonal intravaginal rings among women in India is limited. The study population included healthy 18 to 45 year-old women who were HIV-uninfected, sexually-active, and using adequate contraception. Participants at two sites in the USA and a single site in India were randomized to one of two study arms: intravaginal ring use or no ring.

MTN-005 also examined the impact of 12 weeks of intravaginal ring use on vaginal flora. Studies have shown that the presence of H<sub>2</sub>O<sub>2</sub>-producing vaginal lactobacilli offers a protective effect against sexually transmitted infections. There were no previously published data on the impact of intravaginal ring use on quantitative measures of vaginal flora.

**Clinical Research Sites:** India National AIDS Research Institute (NARI) Arogya Aadhar Clinic CRS  
USA Alabama CRS  
Bronx-Lebanon Hospital Center CRS (BLHC CRS)

## RMP-02/MTN-006

### A Two-Site, Phase 1, Partially-Blinded, Placebo-Controlled Safety, Acceptability and Pharmacokinetic Trial of Topical, Vaginally Formulated Tenofovir 1% Gel Applied Rectally Compared With Oral 300 mg Tenofovir Disoproxil Fumarate in HIV-1 Seronegative Adults

<b>Protocol Chair:</b>	Peter Anton, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Tenofovir 1% Gel</li><li>• Tenofovir Disoproxil Fumarate (TDF) (TDF) 300 mg Tablet</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel</li></ul>
<b>Date of First Enrollment:</b>	7 October 2009
<b>Closed to Accrual:</b>	12 May 2010
<b>Total Enrolled/Expected:</b>	18 Evaluable (22 Overall)/18 Evaluable
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Evaluate the systemic safety of vaginally-formulated tenofovir 1% gel

**Summary:** RMP-02/MTN-006 was a Phase 1, partially-blinded, placebo-controlled trial designed to evaluate the safety, acceptability, pharmacokinetics and pharmacodynamics of rectal administration of tenofovir 1% vaginally formulated gel and oral tenofovir (TDF) in healthy men and women. This tenofovir gel formulation was originally designed for vaginal use. The primary objective of this trial was to evaluate the systemic safety profile of vaginally formulated tenofovir 1% gel, applied rectally, during a single exposure, followed by once-daily rectal administration for 7 days, as compared to a single oral dose of tenofovir. In addition to acceptability, RMP-02/MTN-006 assessed concentrations of tenofovir in tissue, rectal fluid, intracellular (both peripheral blood mononuclear cells (PBMC)) and mucosal mononuclear cells (MMC), and plasma.

Determining whether the intracellular levels of tenofovir diphosphate concentrations in presumptive mucosal target cells are similar using topical or oral formulations will impact clinical trials and drug development plans for prevention of HIV among populations for whom receptive anal intercourse is a route of HIV exposure. This was a joint project of the MTN and the Integrated Preclinical Clinical Program (IPCP) in Topical Microbicides funded by the Division of AIDS. This study was the first MTN trial to leverage the IPCP in Topical Microbicides through collaboration with the UCLA IPCP on rectal microbicides (Peter Anton, PI). The MTN partnered with the IPCP to provide CORE resources, laboratory support, and CRS support for the study. Preliminary results were reported at annual Conference on Retroviruses and opportunistic Infections (CROI) in held on February 27-March 2, 2011 in Boston, MA.

**Results:** Rectal dosing with the vaginal formulation of 1% TFV was found to be neither entirely safe nor fully acceptable. A regimen of 7 rectally applied daily doses of TFV resulted in significant inhibition of *ex vivo* HIV infection. However, neither single dosing of oral (TDF), nor rectal (TFV) dosing significantly inhibited biopsy infection.

**Clinical Research Sites:** USA University of Pittsburgh CRS  
UCLA Ctr. for Prevention Research

#### Citations:

1. Anton PA, Cranston RD, Kashuba A, Hendrix CW, Bumpus NN, Richardson-Harman N, Elliott J, Janocko L, Khanukhova E, Dennis R, et al. RMP-02/MTN-006: A phase 1 rectal safety, acceptability, pharmacokinetic, and pharmacodynamic study of tenofovir 1% gel compared with oral tenofovir disoproxil fumarate. *AIDS Res Hum Retroviruses* 2012 Nov;28(11):1412-21. PMID:PMC3484811

## RMP-02/MTN-006 (continued)

2. Richardson-Harman N, Hendrix CW, Bumpus NN, Mauck C, Cranston RD, Yang K, Elliott J, Tanner K, McGowan I, Kashuba A, et al. Correlation between compartmental tenofovir concentrations and an *ex vivo* rectal biopsy model of tissue infectibility in the RMP-02/MTN-006 Phase 1 Study. PLoS One 2014;9(10):e111507. PMID:PMC4211741
3. Yang KH, Hendrix C, Bumpus N, Elliott J, Tanner K, Mauck C, Cranston R, McGowan I, Richardson-Harman N, Anton PA, et al. A multi-compartment single and multiple dose pharmacokinetic comparison of rectally applied tenofovir 1% gel and oral tenofovir disoproxil fumarate. PLoS One 2014;9(10):e106196. PMID:PMC4211672

## MTN-007

### Phase 1 Randomized, Blinded, Placebo-Controlled Safety and Acceptability Study of Tenofovir 1% Gel

<b>Protocol Chair:</b>	Ian McGowan, MD, PhD
<b>Protocol Co-Chair:</b>	Kenneth Mayer, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Reduced Glycerin (RG) Tenofovir 1% Gel</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel</li><li>• 2% Nonoxynol-9 Gel</li></ul>
<b>Date of First Enrollment:</b>	28 October 2010
<b>Closed to Accrual:</b>	13 July 2011
<b>Total Enrolled/Expected:</b>	60 Evaluable (65 Total)/60 Evaluable
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Evaluate the safety of reduced glycerin (RG) tenofovir 1% gel when applied rectally

**Summary:** MTN-007 was a Phase 1, randomized, blinded, placebo-controlled safety and acceptability study of RG tenofovir 1% gel when applied rectally. This study also examined whether rectal use of RG tenofovir 1% gel was associated with rectal mucosal damage using a broad range of immunological safety biomarkers. Nonoxynol-9 (N-9) 2% gel was used as a positive control for mucosal damage as rectal application of 2% N-9 was previously shown to cause mild but transient mucosal damage. Other secondary objectives included evaluations of the acceptability of rectal administration of tenofovir RG 1% gel as well as the safety of HEC placebo gel when applied rectally.

Recruitment began in late 2010 and completed in July 2011 with 60 evaluable participants enrolled. Participants were randomized to receive a single dose of RG tenofovir 1% gel, 2% N-9 gel, placebo gel, or no treatment, to be self-administered under observation. Within approximately 30 minutes, lavage, stool, and rectal biopsy specimens were collected. After a one-week recovery period, participants returned to the clinic for assessment. If no significant adverse events (AEs) were reported, participants began to self-administer once-daily doses of the study gel for 7 days on an outpatient basis. Participants returned to the clinic for evaluation and specimen collection after completion of 7 days of daily dosing. MTN-007 results were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI) held on March 5-8, 2012 in Seattle, WA.

**Results:** Reduced Glycerin tenofovir 1% gel was found to be safe and well tolerated. There was no significant difference in the prevalence of adverse events across study arms. Likelihood of future product use (acceptability) was 86.7% (tenofovir gel), 93.3% (HEC gel), and 62.5% (N-9 gel). The mucosal safety data indicated the most significant irritation occurred in the N-9 arm.

**Clinical Research Sites:** USA  
Alabama CRS  
University of Pittsburgh CRS  
The Fenway Institute CRS

#### Citations:

1. McGowan I, Hoesley C, Cranston RD, Andrew P, Janocko L, Dai JY, Carballo-Diequez A, Ayudhya RK, Piper J, Hladik F, et al. A phase 1 randomized, double blind, placebo controlled rectal safety and acceptability study of tenofovir 1% gel (MTN-007). PLoS One 2013;8(4):e60147. PMID:PMC3616022
2. Leu CS, Mabragana M, Giguere R, Dolezal C, Carballo-Diequez A, McGowan I. Use of a novel technology to track adherence to product use in a microbicide trial of short duration (MTN-007). AIDS Behav 2013 Nov;17(9):3101-7. PMID:PMC4157755

3. Hladik F, Burgener A, Ballweber L, Gottardo R, Vojtech L, Fourati S, Dai JY, Cameron MJ, Strobl J, Hughes SM, et al. Mucosal effects of tenofovir 1% gel. *eLife Sciences* 2015 Feb 3;4. PMID:PMC4391502

## Expanded Safety Investigation of Tenofovir 1% Gel in Pregnancy and Lactation

<b>Protocol Chair:</b>	Richard Beigi, MD, MSc
<b>Study Product:</b>	<ul style="list-style-type: none"> <li>• Tenofovir 1% Gel</li> <li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel (Pregnancy Cohort Only)</li> </ul>
<b>Date of First Enrollment:</b>	21 April 2011
<b>Closed to Accrual:</b>	25 July 2013
<b>Total Enrolled/Expected:</b>	Lactation Cohort- 17/16 Mother-Infant Pairs Pregnancy Cohort- Group 1: 52/45; Group 2: 47/46
<b>Current Status:</b>	Primary Analysis Complete; Published

**Primary Objectives:**

- Assess the safety and tolerability of tenofovir 1% gel used daily for 7 days in third trimester pregnancy and lactation
- Assess the pharmacokinetics (PK) of tenofovir 1% gel used daily for 7 days in third trimester pregnancy and lactation

**Summary:** MTN-008 was the first study of repeat dosing of tenofovir 1% gel in pregnant and lactating women. Consistent with recommendations of the Institute of Medicine, the MTN-008 mother-infant pair study pursued critically valuable safety and PK data for microbicide use in HIV-uninfected women during pregnancy and breastfeeding, who represent a uniquely susceptible population of women in terms of HIV acquisition risk. The protocol assessed the presence of tenofovir in the blood of infants of women who enrolled in the Pregnancy and Lactation Cohorts, and examined the impact of tenofovir 1% gel exposure on the presence of select organisms in the vagina. Follow-up for all participants completed in 2013. Results for the Lactation Cohort were first presented at Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) 2013 and results for the Pregnancy Cohort were first presented at IDSOG the following year.

**Results: Lactation Cohort:** Seventeen healthy HIV-uninfected women who were breastfeeding (BF) a healthy infant between 4 and 24 weeks of age were enrolled. Serum tenofovir (TFV) was detectable in all women, with median  $C_{max}$  of 7.5 ng/mL after dose 1 and 5.6 ng/mL after dose 7. Breast milk TFV was quantifiable in 4 (25%) of 16 women after dose 1, and in 6 (37.5%) of 16 after dose 7. Infant serum TFV was quantifiable in 6 infants (37.5%) at 6 hours after dose 1 and in 12 infants (75%) after dose 7. Nine (53%) of 17 mothers had one or more adverse events (AEs). All maternal AEs were mild and over half (60%) were deemed unrelated. Four of 17 infants had one or more AEs for a total of 8, all of which were mild and typical for infancy. In summary, maternal PK values were similar to steady-state values in previous studies of observed dosing in non-lactating women. Tenofovir did not accumulate in breast milk following multi-day vaginal dosing and absorption of TFV in infants was low overall.

**Pregnancy Cohort:** Ninety-eight healthy pregnant women were successfully and sequentially enrolled (first cohort at term, second cohort at late preterm) into a 2:1 randomized, placebo-controlled trial of Tenofovir (TFV) 1% vaginal gel versus HEC placebo gel. Most (>85%) maternal and neonatal AEs were low grade in nature, with no higher grade AEs related to study product, and occurred at statistically equal rates in both gestational age cohorts and in both product arms. All maternal and neonatal primary endpoints also occurred in statistically equivalent proportions between the two study arms. All women randomized to TFV gel in both gestational age cohorts had detectable serum TFV, with low overall median drug levels consistent with non-pregnant women. Overall, 16% of women and 25% of neonates had low but detectable TFV at delivery. In summary, daily use of TFV 1% vaginal gel in term and late

## MTN-008 (continued)

preterm pregnancy is well tolerated, demonstrates a favorable safety profile, and produces low serum levels consistent with those in non-pregnant women.

**Clinical Research Sites:** USA      Alabama CRS  
University of Pittsburgh CRS

### Citations:

1. Noguchi LM, Montgomery ET, Biggio JR, Hendrix CW, Bogen DL, Hillier SL, Dai JY, Piper JM, Marzinke MA, Dezzutti CS, Isaacs SK, Schwartz JL, Watts DH, Beigi RH. Detectable tenofovir levels in breastfeeding infants of mothers exposed to topical tenofovir. *Antimicrob Agents Chemother* 2016; Aug 22;60(9):5616-9. PMID: PMC4997886
2. Beigi RH, Noguchi L, Montgomery E, Biggio J, Hendrix CW, Marzinke M, Dai JY, Pan J, Kunjara Na Ayudhya R, Schwartz J, Isaacs K, Piper JM, Watts DH. A randomized safety and pharmacokinetic trial of daily tenofovir 1% gel in term and near-term pregnancy. *J Int AIDS Soc* 2016 Sep 21;19(1):20990. PMID: PMC5034095



## MTN-009

### HIV-1 Resistance at Screening for HIV Prevention Studies

<b>Protocol Chair:</b>	Urvi Parikh, PhD
<b>Protocol Co-Chair:</b>	Photini Kiepiela, PhD
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	30 August 2010
<b>Closed to Accrual:</b>	24 March 2011
<b>Total Enrolled/Expected:</b>	1074 Total Participants; 401 HIV-Infected Participants/ 350 Evaluable HIV-positive Women
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objective:

- Assess the frequency of HIV drug resistance mutations among women who test HIV-positive when presenting to screen for participation in HIV prevention trials

**Summary:** MTN-009 was a multi-site, cross-sectional study that provided an estimate of the prevalence of antiretroviral (ARV) drug resistance mutations in the population of women who present to study sites to be pre-screened or screened for participation in an HIV prevention trial. Limited data exist on the prevalence of HIV infection or HIV drug resistance among individuals who are potential users of ARV-based prevention products. Secondary objectives included: 1) the identification and evaluation of behavioral indicators including self or sexual partner(s) exposures to ARV drugs as risk factors for drug resistant HIV infection; and 2) characterization of the degree of immunodeficiency and risk of disease progression by quantifying plasma HIV-1 RNA and CD4-positive T cells among women who test HIV-positive when presenting to screen for participation in an HIV prevention trial. Exploratory objectives included the identification of polymorphic or subtype-specific sequence changes in HIV-1 that may impact susceptibility to ARVs and the estimation of the proportion of HIV-positive women who have chronic versus recent HIV infection. Preliminary results were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI), March 5-8, 2012 in Seattle, WA.

**Results:** Of the 1073 evaluable women enrolled in MTN-009, 400 (37%) had confirmed HIV infection. Of those, 91% (365/400) had detectable plasma HIV-1 RNA (>40 copies/ml). 156 women (39%) were eligible for antiretroviral therapy (CD4<350 cells/mm<sup>3</sup>) and 50 (13%) met criteria for AIDS (CD4<200 cells/mm<sup>3</sup>). Of 352 plasma samples analyzed for drug resistance, 26 (7.4%) had nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) drug resistance mutations. Effective screening to exclude HIV infection among women interested in uptake of ARV based HIV prevention will be essential in limiting the spread of HIV drug resistance.

**Clinical Research Sites:** South Africa Botha's Hill CRS, Chatsworth CRS, Isipingo CRS, Overport CRS, Tongaat CRS, Umkomaas CRS, Verulam CRS

#### Citations:

1. Parikh UM, Kiepiela P, Ganesh S, Gomez K, Horn S, Eskay K, Kelly CI, Mensch B, Gorbach P, Soto-Torres L, Ramjee G, Mellors J, on behalf of the MTN-009 Protocol Team. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009); PLoS ONE. 2013; 8(4): e59787. PMID:PMC3621758
2. Mensch BS, Gorbach PM, Kelly C, Kiepiela P, Gomez K, Ramjee G, Ganesh S, Morar N, Soto-Torres L, Parikh UM. Characteristics associated with HIV drug resistance among women screening for an HIV prevention trial in KwaZulu-Natal, South Africa. AIDS Behav 2015 Nov;19(11):2076-86. PMID:PMC4600421

## MTN-011

### Evaluation of the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Coitus

<b>Protocol Chair:</b>	Betsy Herold, MD
<b>Study Product:</b>	Tenofovir 1% Gel
<b>Date of First Enrollment:</b>	21 December 2012
<b>Closed to Accrual:</b>	28 February 2014
<b>Total Evaluable/Expected:</b>	Group 1: 24/20 Couples in -1hr cohort; 22/20 Couples in -24 hr Cohort; 23/20 Couples in BAT Cohort; Group 2: Study closed prior to completing; 5 enrolled
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Assess the impact of coitus (and semen) on the pharmacokinetics (PK) of tenofovir 1% gel in female genital and rectal tract secretions and tissue
- Assess the impact of coitus (and semen) on pharmacodynamics (PD) of luminal drug by measuring the anti-HIV-1 activity in CVL samples

**Summary:** MTN-011 was a Phase 1 study that evaluated the effect of coitus on the PK and PD of tenofovir 1% gel following pericoital or daily gel dosing. The study enrolled heterosexual, sexually active monogamous couples, in which both individuals were healthy and HIV-negative. This Phase 1 expanded safety study assessed tenofovir PK in genital tract secretions (CVL), rectal (rectal sponge) and both intracellular and extracellular genital tissue compartments (vaginal and cervical biopsies) in the absence of, or following coitus. PD (i.e., antiviral activity) was also assessed in CVL samples. Group 1 examined PK/PD following a single dose of gel applied 1 hour prior, 24 hours prior, or 1 hour before and 1 hour after (BAT) sex. The single or BAT dosing regimens provide PK/PD data in the absence of any tissue reservoir. It was determined that Group 2 which aimed to examine PK/PD following seven daily doses of gel with the last dose applied 1 hour or 72 hours prior to sex would not proceed. Group 1 completed follow-up on June 9, 2014, and preliminary results were reported at the HIV Research for Prevention (HIV R4P) meeting in October 2014.

**Results:** BAT dosing achieved the highest TFV levels (CVL:  $3.5 \times 10^5$  ng/mL; cervical: 129 ng/mg; vaginal: 258 ng/mg) and -24 h + sex the lowest TFV levels (CVL:  $2.9 \times 10^3$  ng/mL; cervical: 1.46 ng/mg; vaginal: 5.3 ng/mg). Compared to dosing without sex, mean TFV levels after sex decreased 42% and 78% ( $1.33 \times 10^5$  ng/mL,  $p=0.005$  and  $8.53 \times 10^3$  ng/mL,  $p<0.001$ ) in CVL and decreased 74% and 55% (13.92 ng/mg,  $p=0.04$  and 2.64 ng/mg,  $p<0.001$ ) in cervical tissue with -1 h and -24 h dosing, respectively. Vaginal tissue decreases were even greater. In contrast, mean plasma TFV was 128% higher (1.61 ng/mL,  $p<0.01$ ) following sex with -1 h dosing, presumably reflecting greater absorption. Postcoital CVL anti-HIV activity increased significantly from a median [IQR] baseline of 55[54]% in the absence of gel to 99[7], 77[57], and 100[0.4] with -1, -24, or BAT dosing, respectively. The antiviral activity of CVL correlated significantly with drug level. These data suggest that timing of dosing relative to sex impacts TFV gel PK/PD. Pericoital dosing or sustained delivery may be optimal for PrEP, particularly with poor adherence.

**Clinical Research Sites:** [USA](#) Case CRS, University of Pittsburgh CRS

#### Citation:

Herold BC, Chen BA, Salata RA, Marzinke MA, Kelly CW, Dezzutti CS, McGowan I, Galaska B, Levy L, Piper JM, et al. Impact of sex on the pharmacokinetics and pharmacodynamics of 1% tenofovir gel. Clin Infect Dis 2016 Feb;62(3):375-82. PMID:PMC4706638

**Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures**

<b>Protocol Chair:</b>	Ross Cranston, MD, FRCP
<b>Study Product:</b>	<ul style="list-style-type: none"> <li>• Dapivirine 0.05% Gel</li> <li>• Matched Placebo Gel</li> <li>• Universal Hydroxycellulose (HEC) Placebo Gel</li> </ul>
<b>Date of First Enrollment:</b>	11 April 2011
<b>Closed to Accrual:</b>	7 July 2011
<b>Total Enrolled/Expected:</b>	48/48
<b>Current Status:</b>	Primary Analysis Complete; Published

**Primary Objective:**

- Determine the genitourinary safety of dapivirine gel (0.05%) compared to matched placebo gel and universal placebo gel following seven once daily penile applications

**Summary:** MTN-012/IPM 010 was a Phase 1 male tolerance trial that studied the safety of dapivirine gel (0.05%), among 48 (24 circumcised and 24 uncircumcised) sexually abstinent, HIV-negative males. Each participant was asked to apply study gel to his penis prior to his longest period of rest for 7 consecutive days. The pre-filled applicators contained dapivirine 0.05% gel, a matched placebo gel, or the universal HEC placebo gel. This study was conducted to determine if dapivirine 0.05% gel was safe and well-tolerated by circumcised and uncircumcised men.

This Phase 1 trial adds valuable data to the development portfolio of dapivirine gel (0.05%) as a microbicide. The inclusion of a vehicle placebo arm (matched placebo gel) allows for an assessment of whether any adverse events are associated with the gel formulation as opposed to the active ingredient in the gel. The inclusion of a HEC placebo gel arm provides data regarding male tolerance of this widely used microbicide trial control. Results were first presented at the Microbicides 2012 Conference.

**Results:** Cumulatively, 13 adverse events (AEs) were reported (12 Grade 1 and 1 Grade 2). A total of 7 AEs were reported in the dapivirine 0.05% gel arm, 4/7 were judged to be related to study product. These included increased alanine aminotransferase, increased aspartate aminotransferase, application site paresthesia and inflamed sebaceous gland. The PK analysis resulted in detectable dapivirine levels in plasma of all participants who completed their final clinic visit (23 men), with geometric mean level of 343 pg/mL (95% confidence interval: 229-458 pg/mL). Acceptability of the product was high, with 72% of men reporting that they would be ‘very likely’ to use the gel in the future.

**Clinical Research Sites:** USA Alabama CRS, University of Pittsburgh CRS

**Citation:**

Cranston R, Hoesley C, Carballo-Diequez A, Hendrix C, Husnik M, Levy L, Hall W, Soto-Torres L, Nel A. A randomized male tolerance study of dapivirine gel following multiple topical penile exposures (MTN 012/IPM 010). AIDS Res Hum Retroviruses 2014;30(2):184-9. PMID:PMC3910451



## MTN-013/IPM 026

### Phase 1 Safety and Pharmacokinetics/Pharmacodynamics of Dapivirine/Maraviroc Intravaginal Ring

<b>Protocol Chair:</b>	Beatrice Chen, MD, MPH
<b>Protocol Co-Chair:</b>	Lori Panther, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring (VR)</li><li>• Maraviroc (100 mg) VR</li><li>• Dapivirine/Maraviroc VR</li><li>• Placebo VR</li></ul>
<b>Date of First Enrollment:</b>	15 November 2011
<b>Closed to Accrual:</b>	10 July 2012
<b>Total Enrolled/Expected:</b>	48/48
<b>Current Status:</b>	Primary Analysis Complete, Published

#### Primary Objectives:

- Assess and compare the safety of vaginal rings (VRs) containing 25 mg dapivirine, 100 mg maraviroc, or the combination of 25 mg dapivirine + 100 mg maraviroc, when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with the placebo vaginal ring
- Examine the systemic and local pharmacokinetics (PK) of dapivirine and maraviroc in vaginal fluid, plasma and tissue during and after 28 days' continuous use of a matrix vaginal ring containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc

**Summary:** MTN-013/IPM 026 was a Phase 1 safety and PK study of 48 healthy, HIV-uninfected, sexually abstinent, 18-40 year old women. Participants were randomized to receive one of four study VRs (containing 25 mg dapivirine, 100 mg maraviroc, 25 mg dapivirine + 100 mg maraviroc, or placebo) in a 1:1:1:1 ratio. The VR was to be used continuously for approximately 28 consecutive days. Safety assessments were conducted with special consideration for monitoring systemic toxicity and intensive PK assessments were conducted at multiple time points.

MTN-013/IPM 026 was the first clinical trial that evaluated a VR containing maraviroc and a VR containing the combination of antiretroviral agents. The design of MTN-013/IPM 026 allowed for a comparison of the safety of each study VR to a placebo VR and provided data regarding the absorption and distribution of the drug(s) administered. Primary study results were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI) held on March 3-6, 2014, in Boston.

**Results:** All four study VRs were safe and well tolerated. Dapivirine was consistently detected in plasma, cervicovaginal fluid (CVF) and cervical tissue; maraviroc was consistently detected only in CVF. Dapivirine levels in cervical tissue were about 10,000-fold higher than in plasma and 10-fold lower than in CVF for both dapivirine only and combination VR study arms. Dapivirine, but not maraviroc, demonstrated concentration-dependent inhibition of HIV-1 infection in cervical tissue.

#### Clinical Research Sites: USA

Alabama CRS  
The Fenway Institute CRS  
University of Pittsburgh CRS

**Citations:**

1. Chen BA, Panther L, Marzinke MA, Hendrix CW, Hoesley CJ, van der Straten A, Husnik MJ, Soto-Torres L, Nel A, Johnson S, et al. Phase 1 safety, pharmacokinetics, and pharmacodynamics of dapivirine and maraviroc vaginal rings: a double-blind randomized trial. *J Acquir Immune Defic Syndr* 2015 Nov;70(3):242-9.PMCID:PMC4607587
2. van der Straten A, Panther L, Laborde N, Hoesley CJ, Cheng H, Husnik MJ, Horn S, Nel A, Soto-Torres L, Chen BA. Adherence and acceptability of a multidrug vaginal ring for HIV prevention in a phase I study in the United States. *AIDS Behav* 2016;20(11):2644-2653. PMCID: PMC4970965.
3. Dezzutti CS, Richardson-Harman N, Rohan LC, Marzinke MA, Hoesley CJ, Panther L, Johnson S, Nuttall JP, Nel A, Chen BA; Microbicide Trials Network, MTN-013/IPM 026 Protocol Team. Pharmacodynamic correlations using fresh and cryopreserved tissue following use of vaginal rings containing dapivirine and/or maraviroc in a randomized, placebo controlled trial. *Medicine (Baltimore)* 2016 Jul;95(28):e4174. PMCID:PMC4956805
4. Richardson-Harman N, Parody R, Anton P, McGowan I, Doncel G, Ries Thurman A, Herrera C, Kordy K, Fox J, Tanner K, Swartz G, Dezzutti C. Analytical advances in the ex vivo challenge efficacy assay. *AIDS Res Hum Retroviruses* 2016;Dec 16 [*Epub ahead of print*]

## MTN-014

### A Phase 1 Crossover Trial Evaluating the Pharmacokinetics and Safety of Reduced Glycerin Tenofovir 1% Gel in the Rectal and Vaginal Compartments in Sexually-Active Women

<b>Protocol Chair:</b>	Gonasagrie Nair, MBChB
<b>Protocol Co-Chair:</b>	Jessica Justman, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Reduced-Glycerin (RG) Tenofovir 1% gel</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo gel</li></ul>
<b>Date of First Enrollment:</b>	19 May 2014
<b>Closed to Accrual:</b>	10 October 2014
<b>Total Enrolled/Expected:</b>	14/14
<b>Current Status:</b>	Primary Analysis Complete

#### Primary Objective:

- Compare local and systemic pharmacokinetics (PK) of reduced-glycerin tenofovir 1% gel after 2 weeks of daily rectal use and after 2 weeks of daily vaginal use

**Summary:** This Phase 1, two-arm, crossover, randomized trial in healthy, HIV-negative, sexually-active women aged 21 to 45 (inclusive) years assessed the level of tenofovir in both the rectal and vaginal compartments after the rectal and vaginal application of RG tenofovir 1% gel. Women were randomized to the sequence of vaginal or rectal RG tenofovir 1% gel application for two weeks. Blood, vaginal and rectal samples, including tissue, were collected to assess the PK endpoints at the end of the first period of product use. Following a minimum 6-week washout period, women who initially applied the product vaginally were crossed-over to apply product rectally and vice versa. Secondary objectives of MTN-014 study included safety assessment of RG tenofovir 1% gel after 2 weeks of rectal and after 2 weeks of vaginal use. The protocol was amended in May 2013 to incorporate directly observed dosing (DOD) to ensure complete compliance to the study product regimen, critical for this Phase 1 PK clinical trial. Results were presented at the International AIDS Conference (IAS) (HIV Pathogenesis Treatment and Prevention), July 19-22, 2015, Vancouver, Canada. The primary manuscript is in preparation and is planned to be submitted for publication in Q2 2017.

**Results:** A total of 14 women were enrolled into the study; 13 completed all study procedures. Of the 392 expected doses, 358 (91%) were directly observed, two were missed doses and the remaining 32 doses were reported by participants to have been administered. Mean plasma concentrations of tenofovir (TFV) were similar after 14 days of dosing via either compartment. After vaginal dosing, rectal concentrations of TFV were detectable in only 1 of 13 tissue samples and tenofovir diphosphate (TFV-DP) levels were detectable in only 2 of 13 tissue samples. After rectal dosing, vaginal concentrations of TFV and TFV-DP were detectable in 6 of 14 and 3 of 14 tissue samples, respectively. Rectal and vaginal dosing phases each resulted in markedly lower levels of tissue TFV and TFV-DP concentrations in the opposite compartment, with at least 1.7 log<sub>10</sub> differences between mean concentrations in the two compartments. After vaginal dosing, inhibition of HIV increased by 42% in vaginal fluid, but no change was found in rectal fluid. After rectal dosing, no change in HIV inhibition was noted in either vaginal fluid or rectal fluid.

**Clinical Research Sites:** [USA](#) Bronx Prevention Center CRS

#### Citation:

Nair G, Justman JE, Piper J, Marzinke M, Hendrix C, Dai J, Pan J, Galaska B, Levy L, Schwartz J, Dezzutti C. Pharmacokinetics and pharmacodynamics of tenofovir reduced-glycerin 1% gel in the rectal and vaginal compartments in women: a cross-compartmental study with directly observed dosing. IAS conference on HIV Pathogenesis Treatment and Prevention, July 19-22, 2015, Vancouver, Canada. Abstract # TUAC0206LB

## MTN-015

### An Observational Cohort Study of Women Following HIV-1 Seroconversion in Microbicide Trials

<b>Protocol Chair:</b>	Sharon Riddler, MD, MPH
<b>Study Product:</b>	Not applicable
<b>Target Sample Size:</b>	Approximately 500
<b>Date of First Enrollment:</b>	25 August 2008
<b>Enrolled:</b>	Not provided so as not to disclose parent protocol endpoints
<b>Current Status:</b>	Enrolling

#### Primary Objective:

- Compare HIV disease progression twelve months post seroconversion among participants assigned to an active agent compared to placebo/control participants

**Summary:** MTN-015 is a multi-site, prospective, observational cohort study of women following HIV-1 seroconversion in microbicide trials of ARV-based microbicides or oral pre-exposure prophylaxis (PrEP). It is anticipated that approximately 500 women will be enrolled in this study. Further comparisons between participants assigned to an agent and participants assigned to a placebo include HIV disease progression over the total duration of follow-up, virologic and immunologic responses following initiation of ART, HIV-1 drug resistance profile among ART recipients at the time of virologic failure. This study will also describe post-seroconversion changes in participant sexual behaviors and partnership status.

MTN-015 is designed to capture extensive prospective data on the clinical progression of HIV disease and the prevalence of drug resistance mutations among seroconverters from studies examining various formulations of microbicides (such as a gel or vaginal ring), as well as orally administered antiretroviral agents for HIV prevention.

The protocol was amended in May 2013 to clarify that participants will remain on-study for a minimum of 12 months after HIV-1 seroconversion and that follow-up may continue as long as funding resources permit or as determined by MTN leadership. The status of MTN-015 participants enrolled from the following parent protocols is as follows:

- HPTN 035 protocol cohort completed follow-up on 31 May 2013
- MTN-003 protocol cohort completed follow-up on 30 June 2014
- MTN-020 protocol cohort in follow-up
- MTN-025 open to enrollment

**Results:** Results for the subset of HIV seroconverters from the HPTN-035 trial were published in HIV Clinical Trials in September 2016. Of 194 seroconverters in HPTN 035, 186 were eligible to enroll in MTN-015 and 100 (72%) were enrolled into MTN-015. The median time from HIV detection to enrollment in MTN-015 was 18.2 months (range 5.0–45.7). As a result of the enrollment time frame, the analysis of HIV disease progression 12 months after seroconversion could not be performed for the HPTN 035 subset. The median follow-up time was 48 months from enrollment. The median age at enrollment was 27 years (range 20–45). The majority (n=82) were enrolled prior to initiating ART. In ART-naïve participants, the median CD4+ was 405 cells/mm<sup>3</sup> (interquartile range [IQR] 273, 657) and median plasma HIV-1 RNA was 3.9 log<sub>10</sub> copies/ml (IQR 3.3, 4.6). ART was initiated prior to or during the trial in 68/100 (68%) participants. Combination ART regimens (≥3 medications) were used in 54/68 participants and were most commonly non-nucleoside reverse transcriptase (NNRTI)-based regimen. HIV genotypic resistance test results were available for 85/100 participants: 84 were infected with Subtype C HIV-1 virus. Several resistance-associated polymorphisms were identified including F77F/L, V90I/V, E138E/A,

## MTN-015 (continued)

and V179A/D/T in reverse transcriptase and M46I/L in protease. However, none were associated with reductions in susceptibility to ART.

Results for HIV seroconverters from the VOICE trial were presented at HIV Research for Prevention (R4P) in 2014. MTN-015 enrolled 255/356 (72%) of VOICE seroconverters; 93% were from South Africa. Median age at MTN-015 enrollment was 23 years; median time from detection of HIV infection to enrollment was 2.1 months. At enrollment, median CD4+ and HIV-1 RNA were 539 cells/mm<sup>3</sup> and 4.4 log<sub>10</sub> copies/ml. No significant difference by VOICE study arm with regard to time to CD4< 350, ART initiation, or AIDS-defining events was observed. ART was initiated by 49 women (3 prior to MTN-015 enrollment); 82% met local CD4 guidelines for ART initiation and 16% started ART due to pregnancy. Initial ART regimens were NNRTI based most commonly (61%). AIDS-defining events occurred in 11 (4%) women.

**Clinical Research Sites:**

<u>Malawi</u>	Blantyre CRS, Malawi (Lilongwe) CRS
<u>South Africa</u>	CAPRISA Aurum CRS, eThekweni CRS; MRC: Botha's Hill CRS, Chatsworth CRS, Isipingo CRS, Overport CRS, Tongaat CRS, Umkomaas CRS, Verulam CRS, Soweto MTN CRS; Wits RHI CRS Emavundleni CRS
<u>Uganda</u>	MU-JHU Research Collaboration CRS
<u>Zambia</u>	Kamwala Clinic CRS
<u>Zimbabwe</u>	Seke South CRS, Spilhaus CRS, Zengeza CRS

### Citations:

1. Riddler SA, Husnik M, Gorbach PM, Levy L, Parikh U, Livant E, Pather A, Makanani B, Mhlanga F, Kasaro M, Martinson F, Elharrar V, Balkus JE. Long-term follow-up of HIV seroconverters in microbicide trials – Rationale, study design, and challenges in MTN-015. HIV Clin Trials 2016 Sep;17(5):204-11. PMID:PMC5002236
2. Etter P, Landovitz R, Sibeko S, Sobieszczyk ME, Riddler SA, Karg C, Tsibris A, Schouten J. Recommendations for the follow-up of study participants with breakthrough HIV infections during HIV/AIDS biomedical prevention studies. AIDS 2013 Apr; 27(7):1119-28. PMID:PMC4286368

### Abstracts:

Riddler S, Wang L, Ganesh S, Mhlanga F, Makanani B, Martinson F, Kasaro M, Ou SS, Levy L, Eskay K, Parikh U. Long-term Follow up of HIV Seroconverters in Microbicide Trials MTN 015. Microbicides 2010, May 22-25, 2010, Pittsburgh, PA. Abstract# P01.02

Kasaro M, Mhlanga F, Wang L, Ou SS, Coumi N, Makanani B, Martinson F, Guffey MB, Riddler S. Recent HIV Seroconverters Are at High Risk for Sexually Transmitted Infections. Microbicides 2010, May 22-25, 2010, Pittsburgh, PA. Abstract# 309

Msiska Z, Mngonywa N, Parikh U, Gordon K, Kiepiela P, Ganesh S, Ramjee G. Case Report of a Possible Elite Controller Identified in MTN 015 in Durban, South Africa. Microbicides 2010, May 22-25, 2010, Pittsburgh, PA. Abstract# 470

Riddler S, Husnik M, Pather A, Palanee T, Nair G, Mhlanga F, Taljaard M, Nakabiito C, Premraj A, Levy L, Elharrar V, Ramjee G, Balkus J. Long-term Follow up of HIV Seroconverters from the VOICE Trial - An Analysis of Data from MTN-015. HIV Research for Prevention (HIVR4P), October 28-31, 2014, Cape Town, South Africa. Abstract # P01.02



## MTN-015 (continued)

Balkus JE, Husnik M, Palanee-Phillips T, Panchia R, Harkoo I, Pather A, Govender V, Taljaard M, Gorbach P, Riddler SA. Incidence of Curable Sexually Transmitted Infections Among South African Women Recently Infected with HIV. Conference on Retroviruses and Opportunistic Infections (CROI), February 23-26, 2015, Seattle, WA. Abstract # 1033

Caplan MR, McKenney J, Landovitz R, Palanee-Phillips T, Nair G, Mhlanga F, Balkus JE, Riddler S, Gorbach PM. Correlates of Injectable Contraceptive Discontinuation Following HIV-1 Seroconversion. Conference on Retroviruses and Opportunistic Infections (CROI), February 22-25, 2016, Boston, MA.

Pather A, Noguchi L, Oromendia C, Ramjee G, Palanee T, Nair G, Premrajh A, Riddler S, Balkus J. Assessing the effect of depot medroxyprogesterone acetate (DMPA) versus norethisterone enanthate (NET-EN) on HIV disease progression among recently infected South African women. International AIDS Conference (AIDS 2016), July 17-22, 2016, Durban, South Africa. Abstract #WEPEB121

Riddler SA, Balkus J, Mellors J, Parikh U, Akello C, Dadabhai S, Mhlanga F, O'Rourke C, Baeten J, MTN-015 and MTN-020/ASPIRE study teams. NNRTI-containing ART is Effective for Dapivirine Ring Breakthrough HIV-1 Infection. Conference on Retroviruses and Opportunistic Infections (CROI), Feb 13-17, 2017, Seattle, WA. Abstract # 952.

## MTN-016

### Prevention Agent Pregnancy Exposure Registry

<b>Protocol Chairs:</b>	Richard Beigi, MD, MSc Samuel Kabwigu, MBChB, MMedr
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	1 October 2009
<b>Total Enrolled/Expected:</b>	422/550 Women as of 1 February 2017 381/400 Infants as of 1 February 2017
<b>Current Status:</b>	Enrolling

#### Primary Objectives:

- Compare adverse pregnancy and delivery outcomes between participant mothers assigned to an active agent with those of mothers assigned to placebo/control
- Compare prevalence of major malformations identified in the first year of life between infants of mothers assigned to an active agent with those of infants of mothers assigned to placebo/control

**Summary:** The Prevention Agent Pregnancy Exposure Registry, also known as EMBRACE (Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure) is a prospective observational cohort study of maternal exposures to investigational HIV prevention agents. Approximately 550 pregnant participants and 400 live infants will be offered enrollment. Participants are enrolled as early in pregnancy as possible to maximize data validity. The study population will consist of current or recent female participants identified as becoming pregnant during MTN microbicide or PrEP trials, or who have had planned exposures in pregnancy safety studies. This study includes infants resulting from those pregnancies. This protocol monitors for adverse pregnancy outcomes, evaluate growth parameters of infants during the first year of life, and collect information on the prevalence of major malformations in infants during the first year of life. The study will also evaluate the prevalence and persistence of HIV drug resistance mutations in plasma among HIV-infected infants and provide a cohort of infants not exposed to active study agents during pregnancy. The protocol was amended in February 2014 with modifications made to the anticipated sample size, study duration, study objectives, and endpoints.

The status of MTN-016 participants enrolled from MTN-002, MTN-008, MTN-003, and MTN-020 have completed follow-up. MTN-016 is open to enrollment for participants in MTN-025 and their infants.

**Results:** Results of obstetric and infant outcomes from MTN-016 participants who had been participants in either parent protocol (MTN-002 or MTN-008) were presented at HIV Research for Prevention (HIVR4P) in 2014. All 16 MTN-002 and 90% (88/98) of MTN-008 mothers were registered, with 25% (n=4) of MTN-002 and 97% (n=86) of MTN-008 participants enrolling prior to known pregnancy outcome. Demographics were similar for MTN-008 enrollees and non-enrollees in the registry. Infant retention at 12 months was 88% (MTN-002) and 80% (MTN-008). One defect (ear canal) was noted in MTN-002, a rate (6%) comparable to the 3% US background rate for malformations ( $p=0.51$ ); no defects were noted in infants from MTN-008. Compared to placebo (n=30), TFV gel (n=58) was not associated with preterm delivery (1/58 (2%) vs. 2/30 (7%),  $p=0.27$ ), postpartum hemorrhage (11/58 (19%) vs. 3/30 (10%),  $p=0.36$ ), non-reassuring fetal status (3/58 (5%) vs. 1/30 (3%),  $p=1.0$ ), chorioamnionitis (1/58 (2%) vs. 2/30 (7%),  $p=0.27$ ), gestational diabetes (0/58 (0%) vs. 1/30 (3%),  $p=0.34$ ), or abnormal infant physical exam findings in the first year of life (14/58 (24%) vs. 8 (27%),  $p=1.0$ ).

Pregnancy incidence and outcomes from the MTN-003 (VOICE) trial were presented at IAS in 2015. A total of 452 pregnancies occurred among 428 women who became pregnant while enrolled in VOICE (overall incidence of 8.2 per 100 person years). The median age at pregnancy was 23 years. Among those who became pregnant, 1 (0.2%) was using an IUD, 289 (67.5%) were using oral contraceptives,

## MTN-016 (continued)

129 (30.1%) were using injectable contraceptives, and 11 (2.6%) were using implants. Small for gestational age or intrauterine growth restriction occurred in 10 out of 172 (5.8%) infants for whom classification was available. There were 263 (59%) full term live births, 22 (5%) premature births, 14 (3%) still births, 83 (19%) spontaneous abortions, 3 (1%) ectopic pregnancies, 60 (13%) elective abortions, and 3 (1%) other. Pregnancy rates and outcomes were equally distributed between study arms, but drug detection at visits associated with pregnancy diagnosis was too low to analyze pregnancy outcomes based on exposure.

Data regarding growth and development of MTN-016 infants born to VOICE/MTN-016 participant mothers was presented at the HIV R4P conference (Chicago, IL, USA) in October 2016. Of 199 live births in VOICE study participants, 185 (93%) were enrolled in MTN-016, of whom 14 (7.6%) were premature at birth and 6 (3.2%) died during follow-up. The majority of infants (88%) were evaluated within 10 days of birth and, of those enrolled, 87%, 93% and 89% completed visits at 1, 6 and 12 months respectively. After adjusting for pre-term gestation, there were no differences in growth over the first year among infants whose mothers were enrolled in study arms evaluating antiretroviral agents compared to placebos. Indications of developmental delay were rare: Denver II Screening results of “delay” or “caution” at 12 months were infrequent (2.5% gross motor, 0.6% fine motor, 1.9% language and 2.5% personal-social).

Pregnancy incidence and outcomes from the MTN-020 (ASPIRE) trial were presented recently at the Conference on Retroviruses and Opportunistic Infections (CROI) (Seattle, WA, USA) in February 2017. Of 2629 women enrolled in ASPIRE, 2551 were available for analysis (78 reported prior history of tubal ligation). A total of 179 pregnancies were detected in 169 women, resulting in 180 pregnancy outcomes (dapivirine arm, n=86; placebo arm, n=94). Pregnancy incidence in the dapivirine arm was 4.0 per 100 person-years (95% CI 3.1-5.1) versus 4.3 per 100 person-years (95% CI 3.4-5.5) in the placebo arm (HR=0.93, 95% CI 0.68-1.26). Pregnancy outcomes were similar by arm. Among 114 pregnancies that resulted in live births, data on potential congenital anomalies were available for 107, with any anomaly seen in 4 (8%) in the dapivirine arm versus 4 (7%) in the placebo arm and no pattern of anomalies for those assigned to dapivirine. Pregnancy rates did not differ between women randomized to dapivirine ring versus placebo in the ASPIRE trial. Pregnancy outcomes and the frequency of site-identified congenital anomalies were also similar by arm, suggesting that dapivirine use in the periconception period is not associated with adverse effects on pregnancy.

**Clinical Research Sites:** Malawi Blantyre CRS, Malawi CRS  
South Africa CAPRISA Aurum CRS, eThekweni CRS; MRC: Botha's Hill CRS, Chatsworth CRS, Isipingo CRS, Overport CRS, Tongaat CRS, Umkomaas CRS, Verulam CRS; Soweto MTN CRS; Wits RHI CRS; Emavundleni CRS  
USA Alabama CRS, University of Pittsburgh CRS  
Uganda MU-JHU Research Collaboration CRS  
Zimbabwe Seke South CRS, Spilhaus CRS, Zengeza CRS

### Abstracts:

Kabwigu S, Noguchi L, Moodley J, Palanee T, Kintu K, Nair G, Panchia R, et al. The MTN-016 Pregnancy Registry: Baseline Characteristics of Enrollees from the VOICE Study and Reasons for Non-enrollment of Eligible Women. HIV Research for Prevention (HIVR4P), October 28-31, 2014, Cape Town, South Africa. Abstract # P45.05

## MTN-016 (continued)

Noguchi LM, Biggio J, Bunge K, Dai J, Isaacs K, Torjesen K, Kabwigu S, Schwartz J, Vargas J, Scaglia F, Jacobson C, Watts DH, Piper J, Beigi RH. Obstetric and Infant Outcomes Following Maternal Third Trimester Exposure to Tenofovir 1% Vaginal Gel. HIV Research for Prevention (HIVR4P), October 28-31, 2014, Cape Town, South Africa. Abstract # P45.07

Bunge K, Balkus J, Noguchi L, Pan J, Piper J, Marrazzo J, Chirenje M, Kabwigu S, Richardson B, Hendrix C, et al. Pregnancy Incidence and Outcomes in Women Receiving Tenofovir-based PrEP in the VOICE Trial. International AIDS Society (IAS), July 19-22, 2015, Vancouver, Canada. Abstract # MOPEC480

Scheckter R, McKinstry LA, Balkus JE, Beigi R, Kabwigu S, Noguchi LM, Ndase P, Panchia R, Kintu K, Taljaard M, Mhlanga F, Nair G, Palanee T, Moodley J, Piper JM, Watts H, Pan Z, Torjesen K. Growth and development of infants born to women enrolled in a clinical trial of tenofovir-based pre-exposure prophylaxis for HIV prevention. HIV Research for Prevention - HIVR4P, Oct 17-21, 2016, Chicago, IL. Abstract #P25.13

Makanani B, Balkus JE, Palanee-Philips T, Mbilizi Y, Piper J, Kintu K, Tembo T, Noguchi L, Rees H, Baeten JM, for the MTN-020/ASPIRE Team. Pregnancy incidence and outcomes among women using the dapivirine vaginal ring in ASPIRE . Conference on Retroviruses and Opportunistic Infections (CROI), Feb 13-17, 2017, Seattle, WA. Abstract #638

## MTN-017

### A Phase 2 Randomized Expanded Safety and Acceptability Study of Rectally-Applied Reduced-Glycerin Formulation Tenofovir 1% Gel and Oral Truvada®

<b>Protocol Chair:</b>	Ross D. Cranston, MD, FRCP
<b>Protocol Co-Chair:</b>	Javier Lama, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Reduced Glycerin (RG) Tenofovir 1% Gel</li><li>• Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)</li></ul>
<b>Date of First Enrollment:</b>	25 September 2013
<b>Closed to Accrual:</b>	18 November 2014
<b>Total Enrolled/Expected:</b>	187 Evaluable (195 Total; includes replacement participants)
<b>Current Status:</b>	Primary analysis complete, published

#### Primary Objectives:

- Compare the safety profiles of Truvada®, daily RG tenofovir 1% gel, and receptive anal intercourse (RAI)-associated RG tenofovir 1% gel
- Evaluate and compare acceptability of Truvada®, daily RG tenofovir 1% gel, and RAI-associated RG tenofovir 1% gel

**Summary:** MTN-017 was a Phase 2, multi-site, six-sequence, three-period, open label, crossover, randomized study examining the effects of oral FTC/TDF (Truvada®) and RG tenofovir 1% gel used as a rectal microbicide. The study enrolled 195 sexually active, HIV-uninfected males or transgender women (TGW) at least 18 years of age who also reported a history of RAI in the past 3 months. Participants were randomized equally across the 6 sequences and followed for approximately 27 weeks (>6 months). Study product use periods included three 8-week sessions with 1-week washout periods between each. One week following the third 8-week session, a follow-up visit occurred. To assess acceptability, participants self-reported ease of use, liking the product, and likelihood of product use if shown to be effective. Each of the study product regimens offered different advantages to participants seeking an effective HIV prevention agent, and this study examined how these relative advantages compared in terms of safety, acceptability, systemic and local absorption, and adherence.

**Results:** One hundred eighty-seven evaluable participants were recruited from the US (42%), Thailand (29%), Peru (19%), and South Africa (10%) with mean age of 31.1 years (range 18-64). Twelve percent were transgender women by self-report and 80% had a college education. Participants were seen every 4 weeks. High product adherence was defined as >80% of expected doses taken, assessed by convergence scoring of daily texts and study product returns. Qualitative plasma TFV testing was also performed, with results provided to participants at their next clinic visit. Generalized estimating equation models with exchangeable correlation structures and robust errors were used to compare safety, acceptability, and adherence between the three regimens. There were no differences in Grade 2 or higher adverse event rates in participants using daily gel (incidence rate ratio [IRR]: 1.03, p=0.88) or RAI gel (IRR: 0.88, p=0.43) compared to FTC/TDF. High adherence was less likely during the daily gel regimen (odds ratio [OR]: 0.35, p<0.001) and participants reported they would be less likely to use the daily gel regimen for HIV protection compared to FTC/TDF (OR: 0.38, p<0.001). Adherence to gel use at least twice weekly (RAI regimen) was similar to FTC/TDF (p=0.7) with no difference in intention to use product for HIV prevention (p=0.2). Rectal application of RG TFV gel was safe in men who have sex with men (MSM) and TGW. Similar adherence and intention to use product for HIV prevention was seen with gel applied at least twice weekly and FTC/TDF. Primary results were presented at the 2016 annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

## MTN-017 (continued)

<b>Clinical Research Sites:</b> <u>USA:</u>	The Fenway Institute CRS University of Pittsburgh CRS Puerto Rico CEMI CRS Bridge HIV CRS
<u>Thailand:</u>	Chiang Mai University HIV Prevention CRS Silom Community Clinic CRS
<u>South Africa:</u>	Groote Schuur HIV CRS
<u>Peru:</u>	San Miguel CRS

### Citations:

1. Cranston RD, Lama JR, Richardson BA, Carballo-Diéguez A, Kunjara Na Ayudhya RP, Liu K, Patterson KB, Leu C, Galaska B, Jacobson CE, Parikh UM, Marzinke MA, Hendrix CW, Johnson S, Piper JM, Grossman C, Ho KS, Lucas J, Pickett J, Bekker L, Chariyalertsak S, Chitwarakorn A, Gonzales P, Holtz TH, Liu AY, Mayer KH, Zorrilla C, McGowan I, the MTN-017 Protocol Team. MTN-017: A Rectal Phase 2 Extended Safety and Acceptability Study of Tenofovir Reduced-Glycerin 1% Gel. Clin Infect Dis 2016; Dec 16(pii: ciw832) [*Epub ahead of print*]

## MTN-020 (ASPIRE)

### A Phase 3 Safety and Efficacy Trial of a Vaginal Matrix Ring with Dapivirine for the Prevention of HIV-1 Infection in Women

<b>Protocol Chair:</b>	Jared Baeten, MD, PhD
<b>Protocol Co-Chair:</b>	Thesla Palanee, PhD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring (VR)</li><li>• Placebo VR</li></ul>
<b>Date of First Enrollment:</b>	21 August 2012
<b>Closed to Accrual:</b>	12 June 2014
<b>Total Enrolled/Expected:</b>	2629/2629
<b>Current Status:</b>	Primary Analysis Complete; Published

#### Primary Objectives:

- Determine the effectiveness of dapivirine (25 mg) administered in a silicone elastomer matrix vaginal ring (VR), when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-uninfected women
- Assess the safety of dapivirine (25 mg) administered in a silicone elastomer matrix VR compared to placebo VR, when inserted once every 4 weeks over the investigational product use period

**Summary:** Use of a VR to provide sustained delivery of microbicides is a novel investigational method for prevention of heterosexual transmission of HIV in women. This drug delivery method may circumvent potential difficulties related to adherence to daily or coitally-dependent uses of microbicide regimens.

MTN-020 (ASPIRE) was a Phase 3, multi-site, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the safety and efficacy of the dapivirine VR (25 mg) for the prevention of HIV-1 infection in healthy, sexually active, HIV-negative women. The study enrolled 2,629 participants who were randomized to receive either the 25 mg dapivirine VR or a placebo VR. Participants used the investigational VRs until 120 events (HIV-1 seroconversions) were observed in the trial. It was anticipated that participants would use the study product for a minimum of 12 months. Following VR use discontinuation, participants had an additional 4 weeks of follow-up to identify HIV-1 seroconversions not detected during the product-use period. MTN-020 (ASPIRE) closed to follow-up on 25 June 2015. Results were presented in February at CROI 2016.

**Results:** Follow-up completed June 25, 2015. Participants attended 91% of scheduled study visits and 97% after accounting for early withdrawals from the study. Results of ASPIRE demonstrated that the monthly dapivirine vaginal ring was safe and effective for HIV prevention. There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms, and incident sexually transmitted infections occurred at a similar rate in the two study arms. A total of 168 incident HIV-1 infections occurred during the product use period: 71 in the dapivirine ring arm and 97 in the placebo arm, indicating a 27% relative reduction in the rate of HIV-1 acquisition due to the dapivirine vaginal ring (95% confidence interval [CI] 1-46%,  $p=0.05$ ). In as-randomized subgroup analyses, HIV-1 protection was generally similar to that seen overall. However, HIV-1 protection differed significantly by age, with women  $\geq 25$  years of age demonstrating 61% HIV-1 protection (95% CI 32-77%,  $p<0.001$ ) while those  $< 25$  years of age had no statistically significant reduction in HIV-1 incidence (10% HIV-1 protection effectiveness, 95% CI -41-43%,  $p=0.64$ ). Further analyses found that lack of HIV-1 protection, along with lower adherence, was limited to those  $\leq 21$  years of age; for those  $> 21$  years of age, HIV-1 protection effectiveness was 56% (95%CI 31-71%,  $p<0.001$ ). The rate of adverse medical events was similar between study arms as was the frequency of antiretroviral resistance in those who acquired HIV-1. In summary, a monthly vaginal ring containing dapivirine provided protection against HIV-1 in African women; HIV-1 protection was greater in subgroups with evidence of better adherence to ring use.

## MTN-020 (continued)

**Clinical Research Sites:** Malawi Blantyre CRS, Malawi CRS  
South Africa eThekweni CRS; Emavundleni CRS; MRC: Botha's Hill CRS,  
Chatsworth CRS, Isipingo CRS, Tongaat CRS, Umkomaas CRS,  
Verulam CRS; Wits RHI CRS  
Uganda MU-JHU Research Collaboration CRS  
Zimbabwe Seke South CRS, Spilhaus CRS, Zengeza CRS

### Citations:

1. Palanee-Phillips T, Schwartz K, Brown ER, Govender V, Mgodhi N, Kiweewa FM, Nair G, Mhlanga F, Siva S, Bekker LG, et al. Characteristics of women enrolled into a randomized clinical trial of dapivirine vaginal ring for HIV-1 prevention. PLoS ONE 2015 Jun;10(6):e0128857. PMID:PMC4489588
2. Baeten J, Palanee-Phillips T, Brown E, Schwartz K, Soto-Torres L, Govender V, Mgodhi N, Matovu Kiweewa F, Nair G, Mhlanga F, et al. for the MTN-020/ASPIRE Study Team. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016 Dec 1; 375(22):2121-2132. PMID: PMC4993693
3. Montgomery ET, van der Straten A, Chitukuta M, Reddy K, Woeber K, Atujuna M, Bekker L, Etima J, Nakyanzi T, Mayo A, Katz A, Laborde N, Grossman CI, Soto-Torres L, Palanee-Phillips T, Baeten JM, on behalf of the MTN-020/ ASPIRE team. "It's inside my body and it's mine": Acceptability and use of a dapivirine vaginal ring in a phase III trial. AIDS 2017: *In Press*.



## MTN-023/IPM 030

### Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in Adolescent Females

<b>Protocol Chair:</b>	Kathleen E. Squires, MD
<b>Protocol Co-Chair:</b>	Katherine Bunge, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring (VR)</li><li>• Placebo VR</li></ul>
<b>Date First Enrollment:</b>	9 July 2014
<b>Closed to Accrual:</b>	11 January 2016
<b>Total Enrolled/Expected:</b>	96/96 participants
<b>Current Status:</b>	Closed to follow-up

#### Primary Objective:

- Assess safety of dapivirine (25 mg) administered via silicone vaginal ring (VR) in HIV-uninfected adolescent females, when inserted once every 4 weeks during 24 weeks of study product use

**Summary:** MTN-023/IPM 030 was a multi-center, two-arm, randomized, double-blind, placebo-controlled Phase 2a trial. The study enrolled 96 healthy, HIV-uninfected adolescent females, 15 - 17 years old (inclusive). Participants were randomized in a 3:1 ratio to one of the following study groups: dapivirine (25 mg) VR or placebo VR. Each participant was followed for approximately 25 weeks (24 weeks on study product and a final phone call one week after end of study product use). Secondary objectives of the trial included evaluating acceptability and adherence to a dapivirine (25 mg) VR when inserted once every 4 weeks for a 24-week period in HIV uninfected adolescent females, and to evaluate local and systemic dapivirine exposure.

The dapivirine (25 mg) VR was evaluated in ASPIRE and other studies in women who are 18 to 40 years of age. The FDA requested additional safety data in adolescent females and MTN-023/IPM 030 along with MTN-034/IPM 045 will provide safety and acceptability data in adolescent females.

This study was a collaborative effort between the MTN and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

Follow-up of all participants was completed July 5, 2016, and results are expected to be available in Q3 2017.

#### Clinical Research Sites: USA

Alabama CRS  
Montefiore Medical Center  
The Fenway Institute  
The University of Colorado, Children's Hospital Colorado  
University of Pittsburgh CRS  
St. Jude Children's Research Hospital

## MTN-024/IPM 031

### Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

<b>Protocol Chair:</b>	Beatrice Chen, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring (VR)</li><li>• Placebo VR</li></ul>
<b>Date of First Enrollment:</b>	23 December 2013
<b>Closed to Accrual:</b>	28 January 2015
<b>Total Enrolled/Expected:</b>	96/96 Participants
<b>Current Status:</b>	Primary analysis complete

#### Primary Objective:

- Assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring (VR) in HIV-uninfected postmenopausal women, when inserted once every 4 weeks during 12 weeks of study product use

**Summary:** MTN-024/IPM 031 was a multi-center, two-arm, randomized, double blind, placebo-controlled Phase 2a trial. The study enrolled 96 healthy, HIV-uninfected, post-menopausal females, 45-65 (inclusive) years of age. Participants were randomized in a 3:1 ratio to one of two study groups: placebo VR or dapivirine (25 mg) VR. Each enrolled participant was followed for approximately 13 weeks (12 weeks on study product and a final phone call one week after end of study product use). In addition to the primary objective stated above, the MTN-024/IPM 031 trial evaluated additional secondary objectives including acceptability of and adherence to a dapivirine (25 mg) VR when inserted once every 4 weeks for a 12-week period in HIV uninfected postmenopausal women, as well as local and systemic dapivirine exposure.

The dapivirine (25 mg) VR was evaluated in ASPIRE and other studies in women who are 18 to 40 years of age. MTN-024/IPM 031 will fill a gap in the dapivirine VR research portfolio, by providing the necessary safety and acceptability data in sexually-active, postmenopausal females. Primary results were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2016 and the preparation of a primary manuscript is in progress.

**Results:** Dapivirine VRs were safe and well tolerated in postmenopausal women. The mean age of the 96 enrolled participants was 56.8 years (range 46-65); 66% were white, 31% were black, and 3% were of other race. Retention was 97%. There was no difference in the incidence of related Grade 2 or higher genital, genitourinary, or reproductive system AEs in the dapivirine vs placebo arms (6/72 (8%) vs 3/24 (13%),  $p=.69$ ) and no difference in Grade 3 or higher AEs in the dapivirine vs placebo arms (4/72 (6%) vs 0/24 (0%),  $p=.57$ ). Plasma dapivirine levels in postmenopausal women were similar to those in women of reproductive age when compared to published data on dapivirine VR use in reproductive-age women that found mean plasma dapivirine levels of 217.5 pg/mL.

**Clinical Research Sites:** USA  
Alabama CRS  
Case CRS  
University of Pittsburgh CRS

#### Abstracts:

Chen BA, Hoesley C, Salata RA, Zhang J, van der Straten A, Soto-Torres LE, Nel AM, Johnson S, Dezzutti CS, Marzinke M, MTN-024/IPM 031 Protocol Team. Safety and pharmacokinetics of dapivirine vaginal rings in postmenopausal U.S. women. Conference on Retroviruses and Opportunistic Infections (CROI), February 22-25, 2016, Boston, MA. Abstract #872

## MTN-024/IPM 031 (continued)

van der Straten A, Laborde N, Cheng H, Hoesley C, Salata RA, Johnson S, Nel A, Soto-Torres L, Chen BA. Adherence and Acceptability of a Dapivirine vaginal ring in postmenopausal U.S. women. Conference on Retroviruses and Opportunistic Infections (CROI), February 22-25, 2016, Boston, MA. Abstract #873

Laborde N, Shapely-Quinn M, van der Straten A. Keeping safe and keeping it up: HIV risk and prevention among post-menopausal women in a US vaginal ring trial. Annual Meeting of the Society for Applied Anthropology, Mar 29- Apr 2, 2016, Vancouver, Canada.

Avolia HA, Rabe LK, Meyn L, Chen BA, Salata RA, Hoesley CJ, Hillier SL . Effects of a Vaginal ring containing dapivirine worn for 12 weeks on the vaginal microbiota of postmenopausal women. HIV Research for Prevention - HIVR4P, Oct 17-21, 2016, Chicago, IL, USA; Abstract #P14.02

## MTN-025 (HOPE)

### A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

<b>Protocol Chair:</b>	Jared Baeten, MD, PhD
<b>Protocol Co-Chairs:</b>	Nyaradzo M. Mgodl, MBChB, MMed Thesla Palanee-Phillips, PhD
<b>Study Product:</b>	Dapivirine (25 mg) Vaginal Ring (VR)
<b>Target Sample Size:</b>	All Eligible Participants from the ASPIRE Trial
<b>Date of First Enrollment:</b>	15 August 2016
<b>Total Enrolled:</b>	465 (+13 in Decliner Population) as of 2/7/17
<b>Current Status:</b>	Enrolling

#### Primary Objectives:

- Characterize the safety profile associated with the open label use of the dapivirine (25 mg) vaginal matrix ring (VR) in women
- Characterize adherence to the open label use of the dapivirine VR (25 mg) in women

**Summary:** MTN-025, the HIV Open-label Prevention Extension (HOPE) trial, is a multi-site, open-label, Phase 3B trial. Eligible HIV-uninfected former ASPIRE participants will be offered a silicone elastomer VR containing 25 mg of dapivirine. Participants may choose not to accept study product at any time and still take part in the study. Study follow-up visits will occur monthly for the first 3 months and quarterly thereafter for 12 months, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). The study will compare the safety of and adherence to dapivirine (25 mg) in a silicone elastomer VR. Former ASPIRE participants who choose not to take part in MTN-025 will have the option of completing behavioral questionnaires and may be selected for qualitative evaluation assessing reasons for non-interest in enrolling. The HOPE sample size will be contingent upon the number of former ASPIRE participants who are eligible and interested in enrolling.

The first participant was enrolled August 15, 2016. All sites were activated for recruitment as of December 2016. Approximately 13 months of follow-up per participant is planned.

**Clinical Research Sites:**

<u>Malawi</u>	Blantyre CRS, Malawi (Lilongwe) CRS
<u>South Africa</u>	eThekweni CRS; Emavundleni CRS; MRC: Botha's Hill CRS, Chatsworth CRS, Isipingo CRS, Tongaat CRS, Verulam CRS; Wits RHI CRS
<u>Uganda</u>	MU-JHU Research Collaboration CRS
<u>Zimbabwe</u>	Seke South CRS, Spilhaus CRS, Zengeza CRS

## MTN-026

### A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

<b>Protocol Chair:</b>	Ross D. Cranston, MD, FRCP
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine Gel (0.05%)</li><li>• Universal Hydroxyethylcellulose (HEC) Placebo Gel</li></ul>
<b>Target Sample Size:</b>	Approximately 27 evaluable participants
<b>Current Status:</b>	Pending

#### Primary Objectives:

- To evaluate the safety of dapivirine gel formulation when applied rectally.
- To characterize the systemic and compartmental pharmacokinetics of dapivirine gel following rectal application.

**Summary:** MTN-026 is a Phase 1, randomized (2:1), double-blind, multi-site, placebo-controlled trial designed to evaluate the safety and pharmacokinetics of dapivirine gel (0.05%) when administered rectally to healthy, HIV-1 uninfected men and women. MTN-026 will enroll a total of approximately 27 evaluable participants between the ages of 18 and 45 years (inclusive). Participants will be randomized to receive either a single dose of dapivirine gel (0.05%) or universal HEC placebo gel rectally, followed by 7 daily doses of the same product to be administered under direct observation in the clinic. Specimens will be collected at multiple time points to assess drug concentrations, HIV explant infection and mucosal safety.

MTN-026 will be the first clinical trial to collect safety and pharmacokinetic data on the rectal application of dapivirine gel (0.05%) in a cohort of HIV-uninfected adults.

**Clinical Research Sites:** USA Alabama CRS  
University of Pittsburgh CRS  
Thailand Silom Community Clinic CRS

## MTN-027

### Phase 1 Safety and Pharmacokinetics Study of MK-2048/Vicriviroc (MK-4176)/MK-2048A Intravaginal Rings

<b>Protocol Chair:</b>	Craig Hoesley, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Vicriviroc (MK-4176) Intravaginal Ring (IVR) containing 182 mg of vicriviroc (MK-4176)</li><li>• MK-2048 IVR containing 30 mg MK-2048</li><li>• MK-2048A IVR containing the combination of vicriviroc (MK-4176) (182 mg) and MK-2048 (30 mg)</li><li>• Placebo IVR</li></ul>
<b>Date of First Enrollment:</b>	8 June 2015
<b>Closed to Accrual:</b>	1 February 2016
<b>Total Enrolled/Expected:</b>	48/48 participants
<b>Current Status:</b>	Closed to follow-up

#### Primary Objectives:

- Assess and compare the safety of ethylene-vinyl acetate (EVA) IVRs containing 182 mg vicriviroc (MK-4176), or 30 mg MK-2048, or 182 mg vicriviroc (MK-4176) + 30 mg MK-2048 (MK-2048A), when used continuously for 28 days by healthy, HIV-uninfected, sexually abstinent women, as compared with the placebo IVR
- Examine systemic and local pharmacokinetics (PK) of vicriviroc (MK-4176) and MK-2048 in vaginal fluid, plasma and cervical tissue during and after 28 days continuous use of an IVR containing 182 mg vicriviroc (MK-4176), or 30 mg MK-2048, or 182 mg vicriviroc (MK-4176) + 30 mg MK-2048 (MK-2048A)

**Summary:** MTN-027 was a multi-site, single-blind, four-arm, randomized, placebo-controlled Phase 1 safety and PK trial of the vicriviroc (MK-4176) IVR, containing 182 mg vicriviroc (MK-4176); the MK-2048 IVR, containing 30 mg MK-2048; the MK-2048A IVR, containing 182 mg vicriviroc (MK-4176) and 30 mg MK-2048; and the Placebo VR. The combination IVR (MK-2048A IVR) combines two different classes of antiretroviral agents - a CCR5-receptor antagonist, VCV (MK-4176), with an integrase inhibitor, MK-2048. The study enrolled 48 healthy, 18-45 year old women who were HIV-uninfected, non-pregnant, sexually abstinent, and using adequate contraception. Women were randomized to one of four study regimens in a 1:1:1:1 ratio. The IVR was used continuously for approximately 28 consecutive days.

The design of MTN-027 allows for safety comparisons of each study product to a placebo and may provide data on relative safety among active products. Additionally, data related to the absorption and distribution of the drug(s) were collected. MTN-027 and MTN-028 were the first clinical trials to test an integrase inhibitor as a microbicide.

Follow-up of all participants was completed March 7, 2016; preparation of the primary manuscript is in progress.

**Clinical Research Sites:** USA Alabama CRS, University of Pittsburgh CRS

## MTN-028

### Phase 1 Pharmacokinetic Trial of Two Intravaginal Rings (IVRs) Containing Different Dose Strengths of Vicriviroc (MK-4176) and MK-2048

<b>Protocol Chair:</b>	Albert Liu, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Formulation A (Low dose): MK-2048A intravaginal ring (IVR) containing the combination of vicriviroc (MK-4176) (91 mg) + MK-2048 (10 mg)</li><li>• Formulation B (Original dose): MK-2048A intravaginal ring (IVR) containing the combination of vicriviroc (MK-4176) (182 mg) + MK-2048 (30 mg)</li></ul>
<b>Date of First Enrollment:</b>	13 July 2015
<b>Closed to Accrual:</b>	16 February 2016
<b>Total Enrolled/Expected:</b>	18/18 evaluable participants
<b>Current Status:</b>	Closed to follow-up

#### Primary Objective:

- Assess local pharmacokinetics (PK) of vicriviroc (MK-4176) and MK-2048 during and after 28-days of continuous use of two MK-2048A IVRs containing different dose strengths

**Summary:** MTN-028 was a single-site, single-blind, two-arm, randomized Phase 1 safety and PK trial of two IVRs containing a combination of a CCR5-receptor antagonist, VCV (MK-4176), with an integrase inhibitor, MK-2048. The two rings tested in MTN-028 were formulated with different dose strengths:

1. Formulation A (Low dose): IVR containing 91 mg of VCV (MK-4176) and 10 mg of MK-2048
2. Formulation B (Original dose): IVR containing 182 mg VCV (MK-4176) 30 mg MK-2048

The study enrolled 18 evaluable healthy, 18-45 year old HIV-uninfected, non-pregnant, sexually abstinent women who were using adequate contraception. Women were randomized to one of two study regimens in a 2:1 ratio (low dose: original dose). The IVR was used continuously for approximately 28 consecutive days.

Based on *in vitro*, *in vivo*, and *ex vivo* studies, VCV (MK-4176) and MK-2048 show promise as topically-applied microbicides. The safety and acceptability of these agents alone and in combination is being evaluated in the MTN-027 trial; however, the optimal dose of MK-4176 and MK-2048 to achieve sufficient vaginal fluid concentrations for antiviral activity is unknown. Two different formulations of the MK-2048A combination IVR were developed and are being evaluated in MTN-028 in an effort to inform *in vitro* and *in vivo* modeling to further optimize the drug release profiles of an IVR containing VCV and MK-2048 for use in future studies, including the potential development of a combination antiretroviral/contraceptive ring. MTN-027 and MTN-028 were the first clinical trials to test an integrase inhibitor as a microbicide.

Follow-up of all participants was completed March 22, 2016; preparation of the primary manuscript is in progress.

**Clinical Research Sites:** [USA](#) Bridge HIV CRS

## MTN-029/IPM 039

### Phase 1 Pharmacokinetic Study of the Dapivirine Vaginal Ring in Lactating Women

<b>Protocol Chair:</b>	Lisa Noguchi, PhD, CNM
<b>Protocol Co-Chair:</b>	Richard Beigi, MD, MSc
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring (VR-004)</li></ul>
<b>Date of First Enrollment:</b>	16 March 2016
<b>Closed to Accrual</b>	15 February 2017
<b>Total Enrolled/Expected</b>	16/16
<b>Current Status:</b>	Closed to follow-up

#### Primary Objective:

- To assess the pharmacokinetics of dapivirine vaginal ring used for 14 consecutive days in lactating women

**Summary:** MTN-029/IPM 039 is a Phase I, open-label study that is designed to assess the presence of dapivirine in blood, breast milk, and cervicovaginal fluid when delivered via a vaginal ring used continuously for 14 days. The trial will also evaluate the safety and tolerability of the dapivirine vaginal ring when used for 14 consecutive days in lactating women. Further, the trial will assess adherence to dapivirine vaginal ring use in lactating women. The study enrolled 16 healthy, HIV-negative women, aged 18 years or older, at least 6 weeks postpartum, who were lactating but not breastfeeding, at two U.S. sites. Accrual for MTN-029 was completed on 15 February 2017 and it is anticipated that follow-up for this study will be completed in early March 2017.

**Clinical Research Sites:** USA Alabama CRS, University of Pittsburgh CRS



## MTN-030/IPM 041

### A Phase 1, Randomized, Double-Blind Pharmacokinetic and Safety Study of Dapivirine/Levonorgestrel Vaginal Rings

<b>Protocol Chair:</b>	Sharon L. Achilles, MD, PhD
<b>Protocol Co-Chair:</b>	Beatrice A. Chen, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Vaginal ring (VR) containing 200 mg of DPV (Ring-104)</li><li>• VR containing 200 mg of DPV + 320 mg LNG (Ring-102)</li></ul>
<b>Target Sample Size:</b>	Approximately 24 participants
<b>Current Status:</b>	Pending

#### Primary Objectives:

- To characterize the local and systemic pharmacokinetics of a DPV vaginal ring formulation and a DPV-LNG vaginal ring formulation used continuously for 14 days
- To evaluate the safety of a DPV vaginal ring formulation and a DPV-LNG vaginal ring formulation used continuously for 14 days

**Summary:** MTN-030/IPM 041 is a multi-site, randomized (1:1), double blind Phase 1 trial. The study will assess the pharmacokinetics and safety of two silicone elastomer vaginal matrix rings containing either 200 mg of dapivirine alone or 200 mg of dapivirine and 320 mg of levonorgestrel. The MTN-030/IPM 041 study population will consist of healthy, HIV-uninfected, non-pregnant women between 18-45 years of age. It is anticipated that this study will take approximately 6-8 months to enroll the target sample size. Participants will use one of the two vaginal rings for a period of approximately 14 days, and will be followed up for a total duration of approximately 16 days.

The primary focus of MTN-030/IPM 041 is the collection of pharmacokinetic and safety data on rings containing either dapivirine alone or a combination of dapivirine and levonorgestrel, formulated with higher dapivirine dose strengths than previously evaluated in Phase 3 trials. Furthermore, MTN-030/IPM 041 will examine the effects, if any, the study product has on vaginal bleeding patterns. MTN-030/IPM 041 will also investigate the acceptability of and adherence to this biomedical HIV prevention-plus-contraception method, and will evaluate the vaginal microenvironment (microflora and biomarkers) during 14 days of continuous study product use. MTN-030/IPM 041 is the first in human study of a vaginal ring containing a combination of dapivirine and levonorgestrel.

**Clinical Research Sites:** USA Alabama CRS, University of Pittsburgh CRS

## MTN-032

### Assessment of ASPIRE and HOPE Adherence

<b>Protocol Chair:</b>	Elizabeth Montgomery, PhD, MHS
<b>Protocol Co-Chairs:</b>	Sarita Naidoo, PhD and Jonathan Stadler, PhD, MA
<b>Study Product:</b>	Not Applicable
<b>Date of First Enrollment:</b>	13 June 2016
<b>Target Sample Size:</b>	Phase 1 – Up to 192 former ASPIRE participants Phase 2 – Approximately 84 former HOPE participants who have completed Phase 1
<b>Total Enrolled/Expected:</b>	Phase 1 – 187 participants enrolled as of 28 October 2016 Phase 2 – (Pending)
<b>Current Status:</b>	Phase 1 complete Phase 2 expected to begin enrollment Q4 2017/Q1 2018

#### Primary Objective:

- To explore socio-contextual and trial specific issues, which affected participants' adherence to the dapivirine vaginal ring (VR)

**Summary:** In the first phase of MTN-032, 187 ASPIRE participants with varying levels of adherence to the dapivirine vaginal ring were enrolled. Based upon participants' ASPIRE plasma dapivirine levels and residual drug levels from returned vaginal rings, participants were pre-selected and approached for study participation. Enrolled participants were categorized into one of the following groups (with final group designation dependent on adequate sample size): consistently low adherence, inconsistent adherence, or consistently high adherence.

After being presented their ASPIRE ring adherence results (PK and residual drug level results), participants were asked to complete a single in-depth interview (IDI) or a focus group discussion (e.g., with other participants with similar adherence levels) where factors influencing adherence, as well as strategies used to overcome adherence challenges, were explored. Intermittent and strategic use around study visits were also discussed.

The second phase of MTN-032 will examine the effect of known efficacy level on adherence in participants who take part in HOPE, an open label extension trial to ASPIRE. A single IDI will be conducted during the second phase of this study to explore:

- Motivations for participant enrollment into HOPE among participants with varying levels of adherence in ASPIRE
- What effect, if any, knowledge of the ring's efficacy had on adherence behavior
- Motivation for continued study participation among those participants who were inconsistently or not adherent
- VR uptake, marketing and other product roll-out issues

Phase 1 results have been submitted for presentation at the July 2017 IAS Conference on HIV Science meeting.

**Clinical Research Sites:** Malawi Malawi CRS  
South Africa eThekweni CRS, Botha's Hill CRS, Wits RHI CRS  
Uganda MU-JHU Research Collaboration CRS  
Zimbabwe Spilhaus CRS, Zengeza CRS

## MTN-033

### An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults

<b>Protocol Chair:</b>	Ken Ho, MD
<b>Protocol Co-Chair:</b>	Ian McGowan, MD, PhD, FRCP
<b>Study Product:</b>	<ul style="list-style-type: none"><li>Dapivirine Gel (0.05%)</li></ul>
<b>Target Sample Size:</b>	16 Evaluable Participants
<b>Current Status:</b>	Pending

#### Primary Objective:

- To characterize the systemic and compartmental pharmacokinetics of dapivirine 0.05% gel applied rectally by two different methods

**Summary:** Intermittent dosing of a rectal microbicide gel associated with sexual activity may be a more feasible strategy for long-term usage. Data are needed on the pharmacokinetics, safety, and acceptability of applying dapivirine gel as a lubricant in at-risk men who have sex with men (MSM) and transgender females who have sex with men.

MTN-033 participants will administer a single dose of dapivirine gel (DPV 0.05%) in each study sequence. Participants will be randomized to one of two product application sequences. Product sequences include the application of a single dose of study product via applicator (2.5 g) and administration of up to 10 g of dapivirine gel applied via a coital simulation device (to simulate receptive anal intercourse); order of administration will be randomly selected. A washout period is planned between each product application visit. This design allows for the collection of valuable pharmacokinetic (PK) data from those exposed to a single dose of dapivirine gel rectally (which may be representative of episodic or coital dosing) with and without the use of a coital simulation device. The ideal coital-dosing regimens for dapivirine gel applied rectally are not yet known. It is anticipated that this study will take approximately 6-8 months to enroll the target sample size.

**Clinical Research Site:** USA University of Pittsburgh CRS

## MTN-034/IPM 045

### A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

<b>Protocol Chair:</b>	Gonasagrie Nair, MBChB, MPH
<b>Protocol Co-Chairs:</b>	Connie Celum, MD, MPH and Kenneth Ngunjiri, PhD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring</li><li>• Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)</li></ul>
<b>Target Sample Size:</b>	300 Evaluable Participants
<b>Current Status:</b>	Pending

#### Primary Objectives:

- To compare and describe the safety profiles of FTC/TDF oral tablet administered daily and dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring inserted once every 4 weeks in an adolescent female population
- To compare adherence to the FTC/TDF oral tablet administered daily to the dapivirine (25 mg) silicone elastomer vaginal matrix ring inserted once every 4 weeks in an adolescent female population
- To compare variation in adherence when participants choose to take/use FTC/TDF oral tablet or dapivirine (25 mg) silicone elastomer vaginal matrix ring

**Summary:** The dapivirine vaginal ring has been shown to be a safe and effective HIV prevention product in adult women in two Phase 3 trials, ASPIRE and The Ring Study (Baeten, NEJM 2016; Nel, NEJM 2016). Multiple studies have demonstrated the safety and effectiveness of oral PrEP (FTC/TDF) and WHO recommends that oral PrEP be considered for people at substantial risk of acquiring HIV. HIV continues to be the leading cause of death among adolescents between the ages of 10-19 in the WHO African Region, and the second most common cause of death among adolescents globally (WHO Progress Report, 2015). Adolescent girls and young women aged 15-24 are a vulnerable population disproportionately affected by HIV (WHO Progress Report, 2016). Data regarding product preferences of adolescent and young woman, their adherence to the products, and additional safety data in this vulnerable population are needed.

The primary purpose of MTN-034/IPM 045 is to collect safety and adherence data for these two study products in an adolescent population, and to provide important information regarding individual preference for the products. This trial will enroll healthy, HIV-uninfected, adolescent females, between the ages of 16 - 21 years old (inclusive). Participants will be randomized (1:1) to one of two study product application sequences: (a) use of a VR containing 25 mg dapivirine to be inserted monthly for a total duration of 24 weeks, followed by oral tablets containing 200 mg emtricitabine/300 mg tenofovir disoproxil (FTC/TDF) to be taken daily for a total duration of 24 weeks; or (b) take the FTC/TDF oral tablets daily for 24 weeks, followed by use of the dapivirine VR inserted monthly for 24 weeks. After completing the randomized sequence of two study product use periods, participants will then select one of the study products (or neither) to use in the third and final 24 weeks of the trial. It is anticipated that sites will be activated to enroll participants in Q3-Q4 2017.

**Clinical Research Sites:** Kenya Kisumu CRS  
South Africa Emavundleni CRS; Wits RHI CRS  
Zimbabwe Spilhaus CRS

## MTN-035

### Acceptability, Tolerability and Adherence of Two Rectal Placebo Products among HIV Seronegative Men and Transgender Women

<b>Protocol Chair:</b>	TBD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• CONRAD Placebo Rectal Insert</li><li>• Normal saline rectal douche</li></ul>
<b>Target Sample Size:</b>	Approximately 150 participants
<b>Current Status:</b>	Concept Approved for Development

#### Primary Objectives:

- To evaluate the acceptability and tolerability of a placebo insert when applied rectally and used pericoitally prior to receptive anal intercourse (RAI)
- To evaluate the acceptability and tolerability of a placebo rectal douche when used pericoitally prior to RAI
- To evaluate the adherence to a placebo rectal insert prior to RAI over a 4-week-long period
- To evaluate the adherence to a placebo rectal douche prior to RAI over a 4-week-long period

**Summary:** MTN-035 is a multi-site, randomized (1:1), open label crossover study. The study will evaluate the acceptability of and adherence to a placebo rectal insert and to a placebo rectal douche when each is used pericoitally prior to RAI over a 4-week-long period. The study population will consist of healthy, HIV-uninfected men who are 18-29 years of age and have sex with men (MSM) and healthy, HIV-uninfected transgender women who are 18-29 years of age who engage in RAI. Participants will be randomized to use either a rectal insert or a rectal douche during the first 4 weeks before switching to the other product for another 4 weeks. It is hypothesized that both the placebo rectal insert and the placebo rectal douche will be acceptable and that adherence will be high.

## MTN-036/IPM 047

### A Phase 1, Randomized, Pharmacokinetics and Safety Study of Extended Duration Dapivirine Vaginal Rings

<b>Protocol Chair:</b>	Albert Liu, MD, MPH
<b>Study Products:</b>	<ul style="list-style-type: none"><li>• Dapivirine (25 mg) Vaginal Ring</li><li>• Dapivirine (100 mg) Vaginal Ring</li><li>• Dapivirine (200 mg) Vaginal Ring</li></ul>
<b>Target Sample Size:</b>	48 Evaluable Participants
<b>Current Status:</b>	In Development

#### Primary Objectives:

- To compare the local and systemic pharmacokinetics (PK) of two extended duration dapivirine (DPV) vaginal rings (VRs) (100 mg and 200 mg) used continuously for 13 weeks to the monthly 25 mg DPV VR to be replaced at weeks 4 and 8 (with the third ring worn for 5 weeks to total 13 weeks of use)
- To assess the safety of two extended duration DPV vaginal ring formulations and the current 25 mg DPV VR used continuously for 13 weeks

**Summary:** It is likely that microbicidal products that can be applied less frequently or products that can remain *in situ* for an extended duration will be more acceptable and will achieve better adherence. Vaginal rings that need to be replaced monthly or less frequently may have benefits over microbicidal products that need to be applied more frequently. The safety and efficacy of the DPV-only 25 mg VR (Ring-004) replaced monthly was tested in two Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study). MTN-036/IPM 047 is a Phase 1, three-arm, open label, multi-site, randomized (1:1:1) trial designed to yield data on the PK and safety profile of DPV when administered via silicone elastomer VR containing the active ingredient at three dosage strengths:

- 25 mg DPV (IPM Ring-004) [Comparator VR]
- 100 mg DPV (IPM Ring-008)
- 200 mg DPV (IPM Ring-006)

Approximately 48 healthy, HIV-uninfected women ages 18-45 will be enrolled in MTN-036/IPM 047. The study will evaluate DPV levels in plasma, vaginal fluid, and cervical tissue. The anticipated exposure from the release of the 200 mg dapivirine VR (Ring-006) is anticipated to fall within pre-established preclinical and clinical safety margins for which vaginally-administered data exist. The study design includes frequent collection of corresponding blood and vaginal samples following insertion of the VR to allow for detection of burst release. PK parameters of DPV will be calculated for blood plasma, vaginal fluid, and cervical tissue. It is hypothesized that plasma, cervicovaginal fluid and cervical tissue DPV levels will be measurable in all women randomized to DPV VRs, that continuous exposure to DPV via VR for 13 weeks will be safe, and that dose-proportionality will be demonstrated in tissue and systemic PK. It is anticipated that this study will take approximately 6-9 months to enroll the target sample size, and that total study duration for participants will be approximately 94 days.

**Clinical Research Sites:** [USA](#) Alabama CRS; Bridge HIV CRS

## MTN-037

### A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults

<b>Protocol Chair:</b>	Craig Hendrix, MD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>PC-1005 Rectal Gel (0.002%MIV-150/0.3% Zinc Acetate [ZA] in 3.0% Carrageenan [CG] gel)</li></ul>
<b>Target Sample Size:</b>	12 Evaluable Participants
<b>Current Status:</b>	In Development

#### Primary Objectives:

- To evaluate the safety of PC-1005 gel formulation (0.002%MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) when applied rectally
- To characterize the systemic and compartmental pharmacokinetics of MIV-150 following rectal application

**Summary:** MTN-037 is a Phase 1, open label, sequential dose/volume escalation study designed to evaluate the safety and pharmacokinetics of PC-1005 (MIV-150/zinc acetate/carrageenan gel) when administered rectally. Approximately 12 healthy, HIV-uninfected men and women (cis or transgender) who are 18 years of age or older and who have a history of consensual receptive anal intercourse (RAI) will be enrolled in MTN-037. PC-1005 was designed to be a dual compartment gel (vaginal or rectal use), with potential activity against HIV-1, herpes simplex virus type 2 (HSV-2), and human papilloma virus (HPV).

Study product will be rectally administered by clinic staff at the clinic. Each participant will receive a total of three doses of PC-1005 (1<sup>st</sup> dose = 4mL, 2<sup>nd</sup> dose = 16mL, and 3<sup>rd</sup> dose = 32mL), with a 2-6 week washout period between each dose. Study endpoint assessments will be performed within 24-48 hours of each of the three product applications. It is hypothesized that PC-1005 gel will be safe when applied to the rectum and well-tolerated. It is anticipated that this study will take approximately 6-8 months to enroll the target sample size, and that total study duration for participants will be approximately 3-5 months.

MTN-037 is the first study to assess the safety and PK of PC-1005 gel applied rectally.

**Clinical Research Sites:** [USA](#) Alabama CRS; University of Pittsburgh CRS

## MTN-038

### PROTOCOL CONCEPT

#### A Phase 1, Randomized, Double-Blind Pharmacokinetic and Safety Study of a 90 Day Intravaginal Ring Containing Tenofovir

<b>Protocol Chair:</b>	TBD
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Tenofovir Intravaginal Ring</li><li>• Placebo Intravaginal Ring</li></ul>
<b>Target Sample Size:</b>	Approximately 48 participants
<b>Current Status:</b>	In Development

#### Primary Objectives:

- To characterize the local and systemic pharmacokinetics (PK) of one tenofovir (TFV) intravaginal ring (IVR) used continuously for 90 days
- To evaluate the safety of one TFV IVR used continuously for 90 days

**Summary:** MTN-038 is a Phase 1, two-arm, double-blind, multi-site, randomized (2:1), placebo-controlled trial. The study will evaluate the safety and PK of a 90-day TFV IVR. The study population will consist of healthy, HIV-uninfected women ages 18-45. Participants will be randomized (2:1) to TFV IVR or placebo, and will use the assigned IVR for approximately 90 days. It is anticipated that this study will take approximately 6-9 months to enroll the target sample size, and that total study duration for participants will be approximately 13 weeks. It is hypothesized that the TFV IVR will be safe and well-tolerated among healthy adult females when a single IVR is used continuously for 90 days.

**Clinical Research Sites:** USA Bridge HIV CRS; University of Pittsburgh CRS



PROTOCOL CONCEPT

**A Randomized, Double Blind, Phase 1 Safety and Pharmacokinetic Study of Rectal Tenofovir Disoproxil Fumarate (TDF) 8 mg and Elvitegravir (EVG) 8 mg Delivered Using an Insert Administered Rectally to HIV-1 Seronegative Adults**

<b>Protocol Chair:</b>	Sharon Riddler, MD, MPH
<b>Study Product:</b>	<ul style="list-style-type: none"><li>• Elvitegravir (EVG) 8 mg Insert</li><li>• Tenofovir Disoproxil Fumarate (TDF) 8 mg + Elvitegravir (EVG) 8 mg Insert</li></ul>
<b>Target Sample Size:</b>	Approximately 30 participants
<b>Current Status:</b>	Concept Approved for Development

**Primary Objective:**

- To evaluate the safety of EVG (8 mg) and TDF (8 mg) + EVG (8 mg) when applied rectally using an insert.

**Summary:** MTN-039 is a Phase 1, double-blind, multi-site trial to evaluate the safety and pharmacokinetics (PK) of two rectally-administered inserts, one containing elvitegravir (EVG) 8 mg alone and another containing the combination of tenofovir disoproxil fumarate (TDF) 8 mg + EVG 8 mg. Approximately 30 healthy, HIV-uninfected men and women (cis or transgender) who are 18-45 years of age and who have a history of consensual receptive anal intercourse (RAI) will be enrolled in MTN-039. Participants will receive a single dose of one rectal insert, followed by a single dose of the other rectal insert after a washout period. Participants will be randomized to sequence of study product application (EVG alone then TDF/EVG, or TDF/EVG then EVG alone) and to timing of PK/pharmacodynamic sampling (2, 24, 48, or 72 hours after product application). It is anticipated that this study will take approximately 6-8 months to enroll the target sample size, and that total study duration for participants will be approximately one month. It is hypothesized that the EVG and TDF/EVG inserts will be safe and well-tolerated among healthy men and women, when a single dose of either study product is administered rectally under direct observation in the clinic.

**Clinical Research Sites:** USA Alabama CRS, University of Pittsburgh CRS