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	An 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MTN-003C-01	PREMIS	South Africa	Withdrawn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 Pilot Study	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 (IVR)	USA, India	Primary analysis complete
MTN-006	Phase 1 Rectal Microbicide Safety and Acceptability of Tenofovir Compared with Oral Tablet	USA	Primary analysis complete; published
MTN-007	Tenofovir Rectal Safety Study	USA	Primary analysis complete; published
MTN-008	Tenofovir Gel in Pregnancy and Lactation	USA	Primary analysis complete; published
MTN-009	HIV-1 Drug Resistance Study	South Africa	Primary analysis complete; published
MTN-010	Expanded Safety Study of UC781 Gel	USA	Withdrawn
MTN-011	Coital PK/PD of Tenofovir Gel	USA	Primary analysis complete; published
MTN-012/ IPM 010	Male Tolerance of Dapivirine Gel	USA	Primary analysis complete; published
MTN-013/ IPM 026	Safety and PK of Dapivirine/Maraviroc VR	USA	Primary analysis complete; published
MTN-014	Tenofovir Levels Following Local Application of Tenofovir Reduced-Glycerin 1% Gel	USA	Primary analysis complete; published
MTN-015	MTN HIV-1 Seroconverter Study	Malawi, South Africa, Uganda, Zimbabwe	• HPTN 035, VOICE, and ASPIRE Cohorts: Primary analysis complete; published • HOPE and ASPIRE Cohorts: Study exit visits ongoing
MTN-016	EMBRACE (Evaluation of Maternal and Baby Outcome Registry after Chemoprophylactic Exposure)	Malawi, South Africa, Uganda, Zimbabwe, USA	• MTN-002, MTN-008 Cohorts: Primary analysis complete, published • VOICE Cohort: Primary analysis complete • ASPIRE Cohorts: Primary analysis complete; published • HOPE Cohort: Enrolling
MTN-017	Safety and Acceptability Study of Oral Truvada® and Rectally-Applied Tenofovir Reduced Glycerin 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	Phase 2 Study of Tenofovir 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	Study of Dapivirine Vaginal Ring (VR) in Adolescent Females	USA	Primary analysis complete
MTN-024/ IPM 031	Study of Dapivirine VR in a Post-Menopausal Female Population	USA	Primary analysis complete; published
MTN-025	HIV Open-label Prevention Extension (HOPE)	Malawi, South Africa, Uganda, Zimbabwe	Closed to follow-up
MTN-026	Dapivirine Gel Rectal Safety and PK Study	USA; Thailand	Closed to follow-up
MTN-027	Safety and PK of IVRs Containing VCV (MK-4176) and/or MK-2048	USA	Primary analysis complete; published
MTN-028	PK Trial of Two MK-2048A IVRs of Varying Dose Strengths	USA	Primary analysis complete; published

MTN-029/ IPM 039	Phase 1 PK Study of the Dapivirine Vaginal Ring in Lactating Women	USA	Primary analysis complete; manuscript; published
MTN-030/ IPM 041	PK and Safety Study of Vaginal Rings Containing Dapivirine and Levonorgestrel	USA	Closed to follow-up
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	Phase 1: Primary analysis complete; published Phase 2: Enrolling (pending management decision regarding additional FGDs)
MTN-033	Rectal PK Study of Dapivirine (DPV) Gel	USA	Closed to follow-up
MTN-034	Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)	Kenya, South Africa, Zimbabwe, Uganda	Open to accrual
MTN-035	Rectal Microbicide Acceptability, Tolerability, and Adherence	USA, Malawi, South Africa, Thailand, Peru	Pending
MTN-036/ IPM 047	PK and Safety Study of Extended Duration DPV VRs	USA	Closed to follow-up
MTN-037	Safety and PK Study of PC-1005 Applied Rectally	USA	Closed to accrual
MTN-038	PK and Safety Study of a 90-Day Vaginal Ring Containing Tenofovir	USA	Enrolling
MTN-039	Safety and PK Study of TAF/EVG Administered Rectally	USA	In development
MTN-040	Phase 2A Study of Dapivirine 0.05% Gel Applied Rectally in HIV-1 Seronegative Adults	Multiple	Withdrawn
MTN-041	Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa (MAMMA)	Malawi, South Africa, Uganda, Zimbabwe	Closed to follow-up
MTN-042	Deliver: A Study of the Dapivirine Ring and PrEP in Pregnant Women	Malawi, South Africa, Uganda, Zimbabwe	In development
MTN-042B	Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa	Malawi, South Africa, Uganda, Zimbabwe	Pending
MTN-043	Mother-infant Pair Study of Dapivirine Ring and PrEP in Breastfeeding (B-PROTECTED)	Malawi, South Africa, Uganda, Zimbabwe	In development
MTN-044/ IPM 053/ CCN019	PK Study of 90-Day Use of Vaginal Rings Containing Dapivirine and Levonorgestrel	USA	Enrolling
MTN-045	Couple User Preferences in Dual Purpose Prevention Products (CUPID)	Uganda, Zimbabwe	In development

Except for protocols listed as *withdrawn*, study descriptions follow this summary table.

MTN-001

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

Protocol Chair:	Craig Hendrix, MD
Study Product:	• Tenofovir Disoproxil Fumarate (TDF) 300 mg Tablet • Tenofovir 1% Gel
Date of First Enrollment:	18 July 2008
Closed to Accrual:	6 March 2010
Total Enrolled/Expected:	144 Evaluable (168 Overall)/144 Evaluable
Current Status:	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 18th 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. PMCID: 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. PMCID: PMC3562423

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. PMCID: 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. PMCID: 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. PMCID: 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. PMCID: PMC4957649.

MTN-002

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

Protocol Chair:	Richard Beigi, MD, MSc
Study Product:	• Tenofovir 1% Gel
Date of First Enrollment:	18 August 2008
Closed to Accrual:	22 December 2009
Total Enrolled/Expected:	16 Evaluable (21 Overall)/16 Evaluable
Current Status:	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 3rd 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 (IOM) 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 2010 Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) Annual Meeting.

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. PMCID: 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

Protocol Chairs:	Zvavahera Mike Chirenje, MD & Jeanne Marrazzo, MD, MPH
Study Product:	• Tenofovir Disoproxil Fumarate (TDF) 300 mg Tablet • TDF Placebo Tablet • Emtricitabine (FTC)/TDF 200 mg/300 mg Tablet (Truvada) • FTC/TDF Placebo Tablet • Tenofovir 1% Gel • Universal Hydroxyethylcellulose (HEC) Placebo Gel
Date of First Enrollment:	15 September 2009
Closed to Accrual:	6 June 2011
Total Enrolled/Expected:	5029/5000
Current Status:	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. The primary results were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI) held on March 3-6, 2013 in Atlanta, GA.

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

Citations:

1. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi 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. PMCID: 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. PMCID: PMC3478774

3. 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. PMCID: PMC4416998

4. 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. PMCID: PMC4491329

5. 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. PMCID: PMC4573287

6. 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. PMCID: PMC4704663

7. 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. PMCID: PMC4744323

8. 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. PMCID: PMC5354168

9. 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. PMCID: PMC4911322

10. 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. PMCID: PMC5071120

11. 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. PMCID: PMC5535309

12. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodi 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 Aug 1; 33(8): 778-783. PMCID: PMC5564054

13. 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 (Larchmt) 2017;26(6):670-676. PMCID: PMC5512296

14. Livant E, Heaps A, Kelly C, Maharaj R, Samsunder N, Nhlangulela L, Karugaba P, Panchia R, Marrazzo J, Chirenje ZM, Parikh UM; VOICE Study Team. The fourth generation AlereTM HIV Combo rapid test improves detection of acute infection in MTN-003 (VOICE) samples. J Clin Virol 2017 Sep; 94:15-21. PMCID: PMC5790424

15. Abbai N, Nyirenda M, Naidoo S, Ramjee G. Prevalent Herpes Simplex Virus-2 increases the risk of incident bacterial vaginosis infections in women from South Africa. AIDS Behav 2018 July; 22(7): 2172-2180. PMCID: PMC5871553

16. Wynne J, Muwawu R, Mubiru MC, Kamira B, Kemigisha D, Nakyanzi T, Kabwigu S, Nakabiito C, Kiweewa Matovu F; VOICE Team. Maximizing participant retention in a phase 2B HIV prevention trial in Kampala, Uganda: The MTN-003 (VOICE) Study. HIV Clin Trials 2018 Oct 27:1-7 [Epub ahead of print]

MTN-003B (VOICE-B)

VOICE Bone Mineral Density (BMD) Substudy

Protocol Chair:	Sharon Riddler, MD, MPH
Study Product:	Not Applicable
Date of First Enrollment:	9 November 2009
Closed to Accrual:	13 June 2011
Total Enrolled:	518 Participants
Current Status:	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

Citations:

1. Mirembe BG, Kelly CW, Mgodi 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. PMCID: PMC4755358

2. Mgodi 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. PMCID: PMC4564062

MTN-003C (VOICE-C)

VOICE Community Substudy

Protocol Chairs:	Jonathan Stadler, PhD Ariane van der Straten, PhD, MPH
Study Product:	Not Applicable
Date of First Enrollment:	27 July 2010
Closed to Accrual:	22 August 2012
Total Enrolled:	175 Participants
Current Status:	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. PMCID: PMC3931679

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. PMCID: 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. PMCID: 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. PMCID: 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. PMCID: 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. PMCID: 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. PMCID: PMC4845669

MTN-003D

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

Protocol Chair:	Ariane van der Straten, PhD, MPH
Protocol Co-Chairs:	Barbara Mensch, PhD Elizabeth Montgomery, PhD
Study Product:	Not Applicable
Date of First Enrollment:	11 December 2012
Closed to Accrual:	27 March 2014
Total Enrolled/Expected:	Stage 1 – 88/88 Participants (complete) Stage 2 – 131/108-144 Participants (complete)
Current Status:	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 in particular, risk perceptions 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. PMCID: 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. PMCID: PMC4961617

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. PMCID: 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. PMCID: PMC4698090

5. Luecke EH, Cheng H, Woeber K, Nakyanzi T, Mudekunye-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. PMCID: 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. PMCID: PMC5290166

7. 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;29(3):247-257. PMCID: PMC6276804

8. Musara P, Montgomery ET, Mgodi 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 2018 Mar;22(3):877-886. PMCID: PMC5587392

9. Simoni JM, Beima-Sofie K, Amico KR, Hosek SG, Johnson MO, Mensch BS. "Debrief Reports" to expedite the impact of qualitative data on clinical trials: Do they accurately capture data from in-depth interviews? AIDS Behav 2019; *In Press*

MTN-003-P01

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

Protocol Chairs:	Ariane van der Straten, PhD, MPH Elizabeth Montgomery, PhD
Study Product:	Not Applicable
Date of First Enrollment:	27 July 2011
Closed to Accrual:	9 September 2011
Total Enrolled/Expected:	50/50
Current Status:	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 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 2012 Microbicides 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 eThekwini 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 WisebagTM for potential monitoring of daily gel applicator use in Durban, South Africa. AIDS Behav 2013;17(2):640-8. PMCID: 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

Protocol Chair:	Ian McGowan, MD, PhD
Study Product:	• VivaGel® (SPL7013 Gel) • VivaGel® Placebo Gel • Universal Hydroxyethylcellulose (HEC) Placebo Gel
Date of First Enrollment:	21 August 2007
Closed to Accrual:	14 October 2009
Total Enrolled/Expected:	61/61
Current Status:	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 2010 Microbicides 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. PMCID: 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. PMCID: PMC3272128

3. Giguere R, Carballo-Dieguez 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. PMCID: PMC3265079

4. Gigure R, Zimet GD, Kahn JA, Dolezal C, Leu CS, Mabragana M, McGowan I, Carballo-Dieguez 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). PMCID: PMC3855411

5. Mabragana M, Carballo-Dieguez 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. PMCID: 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. PMCID: PMC4573238

MTN-005

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

Protocol Chair:	Craig Hoesley, MD
Study Product:	Non-medicated Intravaginal Ring
Date of First Enrollment:	15 June 2011
Closed to Accrual:	20 September 2012
Total Enrolled/Expected:	195/252
Current Status:	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_2O_2-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

Protocol Chair:	Peter Anton, MD
Study Product:	• Tenofovir 1% Gel • Tenofovir Disoproxil Fumarate (TDF) (TDF) 300 mg Tablet • Universal Hydroxyethylcellulose (HEC) Placebo Gel
Date of First Enrollment:	7 October 2009
Closed to Accrual:	12 May 2010
Total Enrolled/Expected:	18 Evaluable (22 Overall)/18 Evaluable
Current Status:	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 the annual Conference on Retroviruses and opportunistic Infections (CROI) 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. PMCID: PMC3484811

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. PMCID: 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. PMCID: PMC4211672

MTN-007

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

Protocol Chair:	Ian McGowan, MD, PhD
Protocol Co-Chair:	Kenneth Mayer, MD
Study Product:	• Reduced Glycerin (RG) Tenofovir 1% Gel • Universal Hydroxyethylcellulose (HEC) Placebo Gel • 2% Nonoxynol-9 Gel
Date of First Enrollment:	28 October 2010
Closed to Accrual:	13 July 2011
Total Enrolled/Expected:	60 Evaluable (65 Total)/60 Evaluable
Current Status:	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, HEC 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 study gel for seven days on an outpatient basis. Participants returned to the clinic for evaluation and specimen collection after completion of seven 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 placebo 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-Dieguez 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. PMCID: PMC3616022

2. Leu CS, Mabragana M, Giguere R, Dolezal C, Carballo-Dieguez 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. PMCID: 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. PMCID: PMC4391502

MTN-008

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

Protocol Chair:	Richard Beigi, MD, MSc
Study Product:	• Tenofovir 1% Gel • Universal Hydroxyethylcellulose (HEC) Placebo Gel (Pregnancy Cohort Only)
Date of First Enrollment:	21 April 2011
Closed to Accrual:	25 July 2013
Total Enrolled/Expected:	Lactation Cohort- 17/16 Mother-Infant Pairs Pregnancy Cohort- Group 1: 52/45; Group 2: 47/46
Current Status:	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 was completed in 2013. Results for the Lactation Cohort were first presented at the annual meeting of the 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 a healthy infant between 4 and 24 weeks of age were enrolled. Serum tenofovir was detectable in all mothers, with median C_{max} of 7.5 ng/mL after dose 1 and 5.6 ng/mL after dose 7. Breast milk tenofovir was quantifiable in 4 (4/16; 25%) mothers after dose 1, and in 6 (6/16; 37.5%) women after dose 7. Infant serum tenofovir was quantifiable in 6 infants (37.5%) at 6 hours after dose 1 and in 12 infants (75%) after dose 7. Nine (9/17; 53%) 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 AEs, 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 tenofovir 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) in a 2:1 ratio to tenofovir 1% vaginal gel versus HEC placebo gel. Most (>85%) maternal and neonatal AEs were low grade AEs, 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 tenofovir gel in both gestational age cohorts had detectable serum tenofovir, 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 tenofovir 1% vaginal gel in term and late preterm pregnancy was well-tolerated,

demonstrated a favorable safety profile and produced 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. PMCID: 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. PMCID: PMC5034095

3. Montgomery ET, Noguchi LM, Dai JY, Pan J, Biggio J, Hendrix C, Isaacs K, Watts DH, Schwartz JL, Piper J, Beigi R. Acceptability of and Adherence to an Antiretroviral-Based Vaginal Microbicide among Pregnant Women in the United States. AIDS Behav 2018 Feb;22(2):402-411. PMCID: PMC5702586

MTN-009

HIV-1 Resistance at Screening for HIV Prevention Studies

Protocol Chair:	Urvi Parikh, PhD
Protocol Co-Chair:	Photini Kiepiela, PhD
Study Product:	Not Applicable
Date of First Enrollment:	30 August 2010
Closed to Accrual:	24 March 2011
Total Enrolled/Expected:	400 HIV-infected participants (1073 Evaluable)/350
Current Status:	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 2012 Retroviruses and Opportunistic Infections (CROI) Annual Conference.

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^3) and 50 (13%) met criteria for AIDS (CD4<200 cells/mm^3). 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. PMCID: 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. PMCID: PMC4600421

MTN-011

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

Protocol Chair:	Betsy Herold, MD
Study Product:	Tenofovir 1% Gel
Date of First Enrollment:	21 December 2012
Closed to Accrual:	28 February 2014
Total Evaluable/Expected:	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
Current Status:	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 October 28-31, 2014, in Cape Town, South Africa.

Results: BAT dosing achieved the highest TFV levels (CVL: 3.5×10^5 ng/mL; cervical: 129 ng/mg; vaginal: 258 ng/mg) and -24 h + sex the lowest TFV levels (CVL: 2.9×10^3 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% ($1.33x10^5$ ng/mL, p=0.005 and $8.53x10^3$ 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. PMCID: PMC4706638

MTN-012/IPM 010

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

Protocol Chair:	Ross Cranston, MD, FRCP
Study Product:	• Dapivirine 0.05% Gel • Matched Placebo Gel • Universal Hydroxycellulose (HEC) Placebo Gel
Date of First Enrollment:	11 April 2011
Closed to Accrual:	7 July 2011
Total Enrolled/Expected:	48/48
Current Status:	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 seven 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 seven 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-Dieguez 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. PMCID: PMC3910451

MTN-013/IPM 026

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

Protocol Chair:	Beatrice Chen, MD, MPH
Protocol Co-Chair:	Lori Panther, MD, MPH
Study Product:	• Dapivirine (25 mg) Vaginal Ring (VR) • Maraviroc (100 mg) VR • Dapivirine/Maraviroc VR • Placebo VR
Date of First Enrollment:	15 November 2011
Closed to Accrual:	10 July 2012
Total Enrolled/Expected:	48/48
Current Status:	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- to 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 Conference on Retroviruses and Opportunistic Infections (CROI), March 3-6, 2014 in Boston, MA..

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 2017 Apr;33(4):395-403. PMCID: PMC5372762

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

Protocol Chair:	Gonasagrie Nair, MBChB
Protocol Co-Chair:	Jessica Justman, MD
Study Product:	• Reduced-Glycerin (RG) Tenofovir 1% gel • Universal Hydroxyethylcellulose (HEC) Placebo gel
Date of First Enrollment:	19 May 2014
Closed to Accrual:	10 October 2014
Total Enrolled/Expected:	14/14
Current Status:	Primary Analysis Complete; Published

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, in Vancouver, Canada.

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 vaginally or rectally. 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.

Clinical Research Sites: USA Bronx Prevention Center CRS

Citation:

Justman JE, Nair G, Hendrix CW, Piper JM, Marzinke MA, Dai JY, Pan Z, Galaska B, Levy L, Schwartz JL; Balar B, Kunjara Na Ayudhya RP, Mushamiri I, McGowan I, Dezzutti CS, for the MTN-014 Study Team. 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. J Acquir Immune Defic Syndr 2018 June 1;78(2):175-182. PMCID: PMC5963717

MTN-015

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

Protocol Chair:	Sharon Riddler, MD, MPH
Study Product:	Not applicable
Target Sample Size:	Approximately 500
Date of First Enrollment:	25 August 2008
Enrolled:	Not provided so as not to disclose parent protocol endpoints
Current Status:	HPTN 035 Cohort – Primary analysis complete; published VOICE Cohort – Primary analysis complete; published ASPIRE Cohort – Primary analysis complete; published HOPE and ASPIRE Cohorts – Study exit visits ongoing

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). MTN-015 is designed to capture extensive prospective data on the clinical progression of HIV disease, virologic and immunologic responses following initiation of ART, and 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. 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 completed follow-up on 06 October 2017
- MTN-025 and MTN-020 study exit visits ongoing, to complete no later than 30 June 2019

Results: MTN-015/HPTN-035 cohort results were presented at the Microbicides 2010 meeting and published in *HIV Clinical Trials* in September 2016. Of 194 HIV-infected women in HPTN 035, 186 were eligible to enroll in MTN-015 and 100 (72%) were enrolled. The median time from HIV detection to enrollment in MTN-015 was 18.2 months (range 5.0–45.7). There was a delay in enrollment that occurred because of the implementation timeline of MTN-015 during HPTN 035. Due to the enrollment timeframe, 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 antiretroviral therapy (ART). In ART-naïve participants, the median CD4+ was 405 cells/mm^3 (interquartile range [IQR] 273, 657) and median plasma HIV-1 RNA was 3.9 $\log_{10}$ 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 regimens. HIV genotypic resistance test results were available for 85/100 participants: 84 were infected with clade C virus. Several resistance-associated polymorphisms were identified including F77F/L, V90I/V, E138E/A, and V179A/D/T in reverse transcriptase and M46I/L in protease. However, none were associated with reductions in susceptibility to ART.

MTN-015/VOICE Cohort results were presented at HIV R4P 2016 meeting and were published in *PLoS One* in June 2017. Of 312 women that were HIV-infected during VOICE, 229 (73%) were enrolled in MTN-015 and 224/229 had subsequent follow-up visits and were include in the analysis. Median age at enrollment was 24 years; the majority (93%) were from South Africa and majority (94%) had clade C virus. No

significant differences for HIV RNA at steady state or the trajectory at 12 months were observed for each active study arm (oral or vaginal tenofovir-based regimen) as compared to placebo. With a median follow-up of 31 months, no significant differences were observed for time to CD4 count ≤ 350 cells/mm^3, or the composite endpoint of CD4 cells ≤ 350 cells/mm^3, ART initiation, or death for each active arm compared to placebo. In conclusion, no clinically significantly impact was shown following use of tenofovir-based for HIV prevention on subsequent HIV disease parameters in HIV-infected women from the VOICE trial.

MTN-015/ASPIRE cohort results were presented at Conference on Retroviruses and Opportunistic Infections (CROI) 2017 meeting and were published in *Clinical Infectious Disease* in October 2018. Of 168 participants with incident HIV-1 infection in ASPIRE, 158 had at least one post-seroconversion assessment and were included in the analysis. Among the 158 participants (dapivirine ring, n= 65, placebo ring, n= 93), no significant differences between participants in the dapivirine and placebo arms were observed in CD4+ cell counts or plasma HIV-1 RNA over the first year after infection (prior to ART). During follow-up, 100/158 (63%) participants initiated NNRTI-containing ART (dapivirine: 39/65; placebo: 61/93); the median time to HIV-1 RNA <200 copies/ml was approximately 90 days for both dapivirine and placebo ring recipients (log-rank p=0.40). Among 81 participants with at least 6 months of post-ART follow-up, 19 (24%) experienced virologic failure (dapivirine: 6/32, 19%; placebo: 13/39, 27%, p=0.42). A total of 121 women enrolled into MTN-015 study. In conclusion, acquisition of HIV-1 infection during dapivirine or placebo treatment in ASPIRE did not lead to differences in HIV-1 disease progression. After initiation of NNRTI-containing ART, a similar time to virologic suppression and risk of virologic failure was observed in dapivirine and placebo participants. These results provide reassurance that NNRTI-based ART regimens are effective among women who acquired HIV-1 while receiving the dapivirine vaginal ring.

Clinical Research Sites:		
	Malawi	Blantyre CRS, Malawi (Lilongwe) CRS
	South Africa	CAPRISA Aurum CRS, eThekwini 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
	Uganda	MU-JHU Research Collaboration CRS
	Zambia	Kamwala Clinic CRS
	Zimbabwe	Seke South CRS, Spilhaus CRS, Zengeza CRS

Citations:

1. 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. PMCID: PMC4286368
2. Riddler SA, Husnik M, Gorbach PM, Levy L, Parikh U, Livant E, Pather A, Makanani B, Muhlanga 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. PMCID: PMC5002236
3. Riddler SA, Husnik M, Ramjee G, Premrajh A, Tutshana BO, Pather A, Siva S, Jeenarain N, Nair G, Selepe P, Kabwigu S, Palanee-Phillips T, Panchia R, Mhlanga F, Levy L, Livant E, Patterson K,
4. Elharrar V, Balkus J. HIV disease progression among women following seroconversion during a tenofovir-based HIV prevention trial. PLoS One 2017 Jun 28;12(6): e0178594. PMCID: PMC5489164
5. Riddler SA, Balkus JE, Parikh UM, Mellors JW, Akello C, Dadabhai S, Mhlanga F, Ramjee G, Mayo AJ, Livant E, Heaps AL, O'Rourke C, Baeten JM; MTN-015; MTN-020/ASPIRE Study Teams. clinical and virologic outcomes following initiation of antiretroviral therapy among seroconverters in the MTN-020/ASPIRE phase III trial of the dapivirine vaginal ring. Clin Infect Dis 2018 Oct 22 [Epub ahead of print]

MTN-016

Prevention Agent Pregnancy Exposure Registry

Protocol Chairs:	Richard Beigi, MD, MSc Samuel Kabwigu, MBChB, MMedr
Study Product:	Not Applicable
Date of First Enrollment:	1 October 2009
Total Enrolled/Expected:	459/550 Women as of 12/24/18 403/400 infants as of 12/24/18
Current Status:	MTN-002 and MTN-008 Cohorts – Primary Analysis Complete VOICE Cohort – Primary Analysis Complete ASPIRE Cohort – Primary Analysis Complete; Published HOPE Cohort – 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.

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 in 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 in MTN-016 participants who had been participants in MTN-003 (VOICE) were presented at International AIDS Society (IAS), July 19-22, 2015, Vancouver, Canada. 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. 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 Research for Prevention (HIV R4P) conference, October 17-20, 2016, Chicago, IL, USA. 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. Most 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 at the Conference on Retroviruses and Opportunistic Infections (CROI), February 13-17, 2017, Seattle, Washington and published in December 2018. Of 2629 women enrolled in ASPIRE, 2551 were available for analysis (78 reported prior history of tubal ligation). Overall, a total of 179 pregnancies were detected in 169 women (dapivirine arm, n=86; placebo arm, n=93), resulting in 181 pregnancy outcomes. Pregnancy incidence was similar in the dapivirine and placebo arms (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; HR=0.93, 95% CI 0.68-1.26). The distribution of pregnancy outcomes did not differ by study arm. Among 114 pregnancies that resulted in live births, data on potential congenital anomalies were available for 107 live births, with any anomaly seen in 4 infants (8%) in the dapivirine arm versus 4 (7%) in the placebo arm and no pattern of anomalies for those assigned to dapivirine. In summary, no differences were observed in the incidence of pregnancy between the dapivirine ring and placebo arms, and no adverse effects on pregnancy outcomes, infant congenital anomalies, or infant growth through the first year of life.

Clinical Research Sites:		
	Malawi	Blantyre CRS, Malawi CRS
	South Africa	CAPRISA Aurum CRS**,** eThekwini 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

Citations:

1. Mhlanga FG, Noguchi L, Balkus JE, Kabwigu S, Scheckter R, Piper J, Watts H, O'Rourke C, Torjesen K, Brown ER, Hillier SL, Beigi R. Implementation of a prospective pregnancy registry for antiretroviral based HIV prevention trials. HIV Clin Trials 2018; 19 (1): 8-14.

2. Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y, Moodley J, Kintu K, Reddy K, Kabwigu S, Jeenariain N, Harkoo I, Mgodi N, Piper J, Rees H, Scheckter R, Beigi R, Baeten JM. Pregnancy and infant outcomes among women using the dapivirine vaginal ring in early pregnancy**.** J Acquir Immune Defic Syndr 2018 Dec 15;79(5):566-572**.**

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

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

MTN-017

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

Protocol Chair:	Ross D. Cranston, MD, FRCP
Protocol Co-Chair:	Javier Lama, MD, MPH
Study Product:	• Reduced Glycerin (RG) Tenofovir 1% Gel • Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)
Date of First Enrollment:	25 September 2013
Closed to Accrual:	18 November 2014
Total Enrolled/Expected:	187 Evaluable/186 Evaluable (195 Total; includes replacement participants)
Current Status:	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 three 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. Primary results were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI), February 22-25, 2016 in Boston, MA.

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.

Clinical Research Sites:

USA:	The Fenway Institute CRS
	University of Pittsburgh CRS
	Puerto Rico CEMI CRS
	Bridge HIV CRS
Thailand:	Chiang Mai University HIV Prevention CRS
	Silom Community Clinic CRS
South Africa:	Groote Schuur HIV CRS
Peru:	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 2017 Mar 1;64(5):614-620. PMCID: PMC5850518

2. Carballo-Diéguez A, Balan IC, Brown III W, Giguere R, Dolezal C, Leu C, Marzinke MA, Hendrix CW, Piper JM, Richardson BA, Grossman C, Johnson S, Gomez K, Horn S, Kunjara Na Ayudhya RP, Patterson K, Jacobson C, Bekker L, Chariyalertsak S, Gonzales P, Holtz TH, Liu A, Mayer KH, Zorrilla C, Lama J, McGowan I, Cranston RD, on behalf of the MTN-017 Protocol Team. High Levels of Adherence to a Rectal Microbicide Gel and to Oral Pre-Exposure Prophylaxis (PrEP) Achieved in MTN-017. PLoS One 2017 Jul 27;12(7): e0181607. PMCID: PMC5531503

3. Giguere R, Brown Iii W, Balán IC, Dolezal C, Ho T, Sheinfil A, Ibitoye M, Lama JR, McGowan I, Cranston RD, Carballo-Diéguez A. Are participants concerned about privacy and security when using short message service to report product adherence in a rectal microbicide trial? J Am Med Inform Assoc 2018 April 1; 25(4): 393-400. PMCID: PMC5885798

4. Carballo-Diéguez A, Giguere R, Dolezal C, Leu CS, Balán IC, Brown W 3rd, Rael C, Richardson BA, Piper JM, Bekker LG, Chariyalertsak S, Chitwarakorn A, Gonzales P, Holtz TH, Liu A, Mayer KH, Zorrilla CD, Lama JR, McGowan I, Cranston RD; MTN-017 Protocol Team. Preference of oral tenofovir disoproxil fumarate/emtricitabine versus rectal tenofovir reduced-glycerin 1% Gel regimens for HIV Prevention among cisgender men and transgender women who engage in receptive anal intercourse with men. AIDS Behav 2017 Dec;21(12):3336-3345. PMCID:PMC5856109

5. Giguere R, Rael CT, Sheinfil A, Balán IC, Brown W 3rd, Ho T, Dolezal C, Leu CS, Liu A, Mayer KH, Lama JR, McGowan I, Carballo-Diéguez A, Cranston RD, MTN-017 Protocol Team. Factors supporting and hindering adherence to rectal microbicide gel use with receptive anal intercourse in a phase 2 trial. AIDS Behav 2018 Feb;22(2):388-401. PMCID: PMC5818328

6. Balán IC, Giguere R, Brown W 3rd, Carballo-Diéguez A, Horn S, Hendrix CW, Marzinke MA, Ayudhya RPKN, Patterson K, Piper JM, McGowan I, Lama JR, Cranston RD; MTN-017 Protocol Team. Brief participant-centered convergence interviews integrate self-reports, product returns, and pharmacokinetic results to improve adherence measurement in MTN-017. AIDS Behav 2018 Mar;22(3):986-995. PMCID: PMC5983888

7. Brown W 3rd, Giguere R, Sheinfil A, Ibitoye M, Balan I, Ho T, Brown B, Quispe L, Sukwicha W, Lama JR, Carballo-Dieguez A, Cranston RD. Challenges and solutions implementing an SMS text message-based survey CASI and adherence reminders in an international biomedical HIV PrEP study (MTN 017). J Biomed Inform 2018 April; 80: 78-86. PMCID: PMC5920551

8. Cranston RD, Carballo-Diéguez A, Gundacker H, Richardson BA, Giguere R, Dolezal C, Siegel A, KunjaraNaAyudhya RP, Gomez K, Piper JM, Lama JR, McGowan I; MTN-017 Protocol Team. Prevalence and determinants of anal human papillomavirus infection in men who have sex with men and transgender women. Int J STD AIDS 2018; Oct 18 [Epub ahead of print]
9. Leu CS, Giguere R, Bauermeister JA, Dolezal C, Brown W 3rd, Balán IC, Richardson BA, Piper JM, Lama JR, Cranston RD, Carballo-Diéguez A. Trajectory of use over time of an oral tablet and a rectal gel for HIV prevention among transgender women and men who have sex with men. AIDS Care 2018 Oct 14:1-9 [Epub ahead of print]
10. Liu AY, Norwood A, Gundacker H, Carballo-Diéguez A, Johnson S, Patterson K, Gail Bekker L, Chariyalertsak S, Chitwarakorn A, Gonzales P, Holtz TH, Mayer KH, Zorrilla C, Buchbinder S, Piper JM, Lama JR, Cranston RD, On Behalf of the Microbicide Trials Network-017 Team. Routine use of oral PREP in the first phase 2 rectal microbicide study of tenofovir reduced-glycerin 1% gel (MTN-017). Acquir Immune Defic Syndr 2019: *In Press*

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

Protocol Chair:	Jared Baeten, MD, PhD
Protocol Co-Chair:	Thesla Palanee, PhD
Study Product:	• Dapivirine (25 mg) Vaginal Ring (VR) • Placebo VR
Date of First Enrollment:	21 August 2012
Closed to Accrual:	12 June 2014
Total Enrolled/Expected:	2629/2629
Current Status:	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 at CROI 2016.

Results: Follow-up was completed on 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 ≥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 ≤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.

Clinical Research Sites:		
	Malawi	Blantyre CRS, Malawi CRS
	South Africa	eThekwini 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, Mgodi 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. PMCID: PMC4489588

2. Baeten J, Palanee-Phillips T, Brown E, Schwartz K, Soto-Torres L, Govender V, Mgodi 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. PMCID: PMC4993693

3. Montgomery ET, van der Straten A, Chitukuta M, Reddy K, Woeber K, Atujuna M, Bekker LG, Etima J, Nakyanzi T, Mayo AJ, Katz A, Laborde N, Grossman CI, Soto-Torres L, Palanee-Phillips T, Baeten JM; MTN-020/ASPIRE Study. Acceptability and use of a dapivirine vaginal ring in a phase III trial. AIDS 2017 May 15;31(8):1159-1167. PMCID: PMC5557083

4. Balkus JE, Palanee-Phillips T, Reddy K, Siva S, Harkoo I, Nakabiito C, Kintu K, Nair G, Chappell C, Kiweewa FM, Kabwigu S, Naidoo L, Jeenarain N, Marzinke M, Soto-Torres L, Brown ER, Baeten JM. Brief Report: Dapivirine vaginal ring use does not diminish the effectiveness of hormonal contraception. J Acquir Immune Defic Syndr 2017 Oct 1;76(2): e47-e51. PMCID: PMC5597463

5. van der Straten A, Shapley-Quinn M, Reddy K, Cheng H, Etima J, Woeber K, Musara P, Palanee-Phillips T, Baeten JM, Montgomery ET, on behalf of the MTN-020/ASPIRE Study Team. Favoring "peace of mind": a qualitative study of African women's product formulation preferences from the MTN-020/ASPIRE trial. AIDS Patient Care and STDs 2017;31(7):305-314. PMCID: PMC5512310

6. Husnik MJ, Brown ER, Marzinke M, Livant E, Palanee-Phillips T, Hendrix C, Kiweewa FM, Nair G, Soto-Torres LE, Schwartz K, Hillier SL, Baeten JM; MTN-020 ASPIRE Study Team. Implementation of a novel adherence monitoring strategy in a phase III, blinded, placebo-controlled, HIV-1 prevention clinical trial. J Acquir Immune Defic Syndr 2017 Nov 1;76(3):330-337. PMCID: PMC5634926

7. Balkus JE, Brown ER, Palanee-Phillips T, Kiweewa FM, Mgodi N, Naidoo L, Mbilizi Y, Jeenarain N, Gaffoor Z, Siva S, Nair G, Pather A, Baeten JM. Performance of a validated risk score to predict HIV-1 acquisition among African women participating in a trial of the dapivirine vaginal ring. J Acquir Immune Defic Syndr 2018 Jan 1;77(1): e8-e10. PMCID: PMC5720924

8. Laborde ND, Pleasants E, Reddy K, Atujuna M, Nakyanzi T, Chitukuta M, Naidoo S, Palanee-Phillips T, Baeten JM, Montgomery ET; MTN-020/ASPIRE Study Team. Impact of the dapivirine vaginal ring on sexual experiences and intimate partnerships of women in an HIV prevention clinical trial: managing ring detection and hot sex. AIDS Behav 2018 Feb;22(2):437-446. PMCID: PMC5866044

9. Mensch BS, Richardson BA, Husnik M, Brown ER, Kiweewa FM, Mayo AJ, Baeten JM, Palanee-Phillips T, van der Straten A; MTN-020/ASPIRE study team. Vaginal Ring Use in a Phase 3 Microbicide Trial: A Comparison of Objective Measures and Self-reports of Non-adherence in ASPIRE. AIDS Behav 2018; Sep 14 [Epub ahead of print]

10. Palanee-Phillips T, Roberts ST, Reddy K, Govender V, Naidoo L, Siva S, Gafoor Z, Pather A, Matovu F, Hlahla K, Makanani B, Nair G, Schwartz K, Torjesen K, Brown E, Soto-Torres L, Baeten J, Montgomery ET. Impact of partner-related social harms on women's adherence to the dapivirine vaginal ring during a Phase III trial. J Acquir Immune Defic Syndr 2018 Dec 15;79(5):580-589. PMCID: PMC6231955

11. Chitukuta M, Duby Z, Katz A, Nakyanzi T, Reddy K, Palanee-Phillips T, Tembo T, Etima J, Musara P, Mgodi NM; van der Straten A, for the MTN-020/ASPIRE Study Team. Negative rumours about a vaginal ring for HIV-1 prevention in Sub-Saharan Africa. Cult Health Sex 2019; *In Press*

MTN-023/IPM 030

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

Protocol Chair:	Kathleen E. Squires, MD
Protocol Co-Chair:	Katherine Bunge, MD
Study Product:	• Dapivirine (25 mg) Vaginal Ring (VR) • Placebo VR
Date First Enrollment:	9 July 2014
Closed to Accrual:	11 January 2016
Total Enrolled/Expected:	96/96 participants
Status:	Primary analysis complete

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 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 on July 5, 2016. Results were presented at the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment & Prevention, July 23-26, 2017 in Paris, France.

Results: Dapivirine VRs were safe and found to be acceptable in adolescent females in the U.S. The mean age of the 96 enrolled participants was 16.3 years; 59% were black and 34% white. Adherence to study visits was 97%. There were no differences in safety outcomes between treatment arms. By self-report, 42% (95% CI 32, 52) of participants reported that they never removed the ring except to replace it monthly. In the dapivirine group, drug levels indicated adherence in 87% of plasma samples and 95% of used rings. Participants noted no discomfort due to the ring at 87% of visits and "liking" the ring at 93% of visits. The most frequently cited concern (28%) involved their primary sex partner feeling the ring during sex.

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

Abstracts:

Bunge K, Levy L, Szydlo D, Zhang J, Meyer K, Futterman D, Gaur A, Hoesley C, Reirdan D, Hillier S, Marzinke M, Dezzutti C, Wilson C, Soto-Torres L, Kapogiannis B, Nel A, Squires K, MTN-023/IPM 030 Protocol Team. Safety and acceptability trial of the dapivirine vaginal ring in U.S. adolescents. International AIDS Society - Conference on HIV Pathogenesis, Treatment & Prevention, July 23-26, 2017, Paris, France. Abstract #TUAC0206LB

Gorbach PM, Moore J, Brosnan H, Squires K, Bunge K, Zimet G, Mensch B, Soto-Torres L, Levy L, and the MTN 023 Protocol Team. Acceptability of a Dapivirine Vaginal Ring among US Adolescent Females in Phase 2a Safety Trial (MTN 023). International AIDS Society - Conference on HIV Pathogenesis, Treatment & Prevention, July 23-26, 2017, Paris, France. Abstract #WEPEC0933

Farr Zuend C, Noël-Romas L, Marrazzo J, Hillier SL, Dezzutti C, Squires K, Bunge KE, Burgener A. Microbiome and proteome alterations with dapivirine ring use in adolescent girls. Conference on Retroviruses and Opportunistic Infections (CROI), March 4–7, 2018, Boston, MA. Abstract #2073

MTN-024/IPM 031

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

Protocol Chair:	Beatrice Chen, MD, MPH
Study Product:	• Dapivirine (25 mg) Vaginal Ring (VR) • Placebo VR
Date of First Enrollment:	23 December 2013
Closed to Accrual:	28 January 2015
Total Enrolled/Expected:	96/96 Participants
Current Status:	Primary Analysis Complete; Published

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 45 years of age. MTN-024/IPM 031 filled 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), February 22-25, 2016, in Boston, MA.

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

Citation:

Chen BA, Zhang J, Gundacker HM, Hendrix CW, Hoesley CJ, Salata RA, Dezzutti CS, van der Straten A, Hall WB, Jacobson CE, Johnson S, McGowan I, Nel AM, Soto-Torres L, Marzinke MA; MTN-024/IPM 031 Protocol Team for the Microbicide Trials Network. Phase 2a safety, pharmacokinetics, and acceptability of dapivirine vaginal rings in US postmenopausal women. Clin Infect Dis 2018 Oct 4 [Epub ahead of print]

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

Protocol Chair:	Jared Baeten, MD, PhD
Protocol Co-Chairs:	Nyaradzo M. Mgodi, MBChB, MMed Thesla Palanee-Phillips, PhD
Study Product:	Dapivirine (25 mg) Vaginal Ring (VR)
Target Sample Size:	All Eligible Participants from the ASPIRE Trial
Date of First Enrollment:	15 August 2016
Closed to Accrual:	24 May 2018
Total Enrolled:	1456 (+120 in Decliner Population)
Current Status:	Closed to follow-up

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, was a multi-site, open-label, Phase 3B trial. Eligible HIV-uninfected former ASPIRE participants were offered a silicone elastomer VR containing 25 mg of dapivirine. Participants could choose not to accept study product at any time and still take part in the study. Study follow-up visits occurred 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 had the option of completing behavioral questionnaires and a subset were selected for qualitative evaluation assessing reasons for non-interest in enrolling (decliner population).

A total of 1,456 participants enrolled in the main HOPE cohort (and 120 in the decliner cohort) between August 15, 2016 and 24 May 2018. Participants enrolled between September 15, 2017 and 24 May 2018 were assigned a truncated follow-up schedule of less than 13 months. The final allowable date for all HOPE study exit visits was 10 October 2018.

Results: Interim results of the ongoing study were presented at the Conference on Retroviruses and Opportunistic Infections (CROI), March 4–7, 2018, in Boston, MA. Between August 2016 and October 2017, 1407 women enrolled into HOPE, 57% of those HIV-1 uninfected at completion of ASPIRE. The median age was 31 years (IQR 27-37), with 13% aged 20-24 and 28% 25-29 years; 16% had a curable sexually transmitted infection. Of 1407 enrollees, 1299 (92%) accepted the dapivirine vaginal ring. 89% of returned rings had residual dapivirine levels consistent with some use during the prior month. A total of 12 HIV-1 infections in 616 person-years of follow-up have been observed (incidence 1.9 per 100 person-years, 95% CI 1.0-3.4). Given the site, age, and sexually transmitted infection distribution of the population enrolled, HIV-1 incidence was expected to be 4.1 per 100 person-years (95% CI 3.2-5.1) in the absence of access to the dapivirine vaginal ring, and an incidence of 1.9 would be expected to occur with a frequency of less than 1 in 10,000 samplings. Interim results from this open-label extension trial of the dapivirine ring demonstrate high uptake and adherence, and HIV-1 incidence has been half of the expected rate. These findings are limited by the lack of a contemporaneous placebo group and prior participation of

the study population in ASPIRE, but they suggest important HIV-1 prevention effectiveness of the dapivirine vaginal ring when used by African women in an open-label setting.

Clinical Research Sites:

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

Abstracts:

Balan IC. Implementation of an MI-based adherence intervention in a multi-site biomedical HIV prevention study in Sub-Saharan Africa. International Conference on Motivational Interviewing, June 19-21, 2017, Philadelphia, PA

Baeten J, Palanee-Phillips T, Mgodi N, Mayo A, Nel A, Rosenberg Z, Hillier S, Brown E, MTN-025/HOPE Study Team. High uptake and reduced HIV-1 incidence in an open-label trial of the dapivirine ring. Conference on Retroviruses and Opportunistic Infections (CROI), March 4–7, 2018, Boston, MA. Abstract #143LB

van der Straten A, Katz A, Balan IC, Reddy K, Etima J, Weber K, Tauya T, Atujuna M, Scheckter R, Ngure K, Soto-Torres L, Mgodi N, Palanee-Phillips T, Baeten J, on behalf of the MTN-025/HOPE Study Team .A qualitative evaluation of women's experience receiving drug feedback in MTN-025/HOPE - an HIV prevention open-label trial of the dapivirine vaginal ring. AIDS 2018, July 23-27, 2018, Amsterdam, The Netherlands. Abstract # THPEC334

Mgodi NM, Szydlo DW, Palanee-Phillips T, Mayo A, Mansoor L, Nair G, Mirembe-Gati B, Mugwagwa N, Siziba B, Hunidzarira P, Jeenarain N, Siva S, Naidoo J, Soto-Torres L, Baeten J, Brown E, for the MTN-025/HOPE Study Team. Characteristics of women who enrolled into an open label extension trial of the dapivirine intravaginal ring for HIV-1 Prevention. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P05.03

Balán IC, Lentz C, Giguere R, Mayo A, Tagliaferri Rael C, Zanele Forde E, Kajura-Manyindo C, Kadyamusuma M, Tuswa-Haynes N, Kachenjera L, Soto-Torres L, Pan J, Baeten J, on behalf of the HOPE Study Team.Fidelity Monitoring to ensure accurate implementation of an evidence-based adherence counseling intervention in MTN-025 (The HOPE Study). HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P14.13

Kemigisha D, T Nakyanzi, S Nanyonga, SC Nanziri, J Etima, CA Akello, C Nakabiito, BG Mirembe. Benefits of prescreening workshops on participants' understanding of CHOICE, ADHERENCE and OPEN REPORTING concepts in MTN-025/HOPE study: Kampala site experience. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P06.07

Nabisere J, Gandhi M, Nagawa CV, Kemigisha D, Kamya J, Etima J, Nasoma Z, Kamira B, Akello CA, Nakabiito C, Mirembe BG. Site approaches to working with participant concerns regarding hair collection: Kampala site experience with women in MTN 025/HOPE, the dapivirine ring trial. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P03.11

Nakyeyune J, Nansamba W, Nakabiito C, Mirembe BG, Valerie C Nagawa, Kawuma C, Kiiza B, Akello CA, Peda M. Embracing medidata rave in the 21ST century: tips to successful implementation. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P09.09

Zalwango A, Etima J, Akello C, Nampiira S, Biira Asiimwe F, Byogero R, Mwebaza D, Lentz C, Kajura Manyindo C, Balan I. From theory to practice: Implementation of client centered adherence counselling at the Kampala site for the HOPE study. HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P25.03

Nanziri SC, Teopista Nakyanzi, Kemigisha D, Nanyonga S, Muwawu R, Etima J, Nakabiito C, Mirembe BG, Akello CA. Innovative approaches for the effective recruitment of former trial participants for an open label trial: MTN 025/HOPE study; How the Kampala team did it! HIV Research for Prevention (HIVR4P), October 21-25, 2018, Madrid, Spain. Abstract # P06.06

Kamira B, Harkoo I, Palanee-Phillips T, Mhlanga F, Bunge K, Chappell C, Singh D, Szydlo D, Baeten JM, Hillier SL, and Balkus JE, on behalf of the MTN-020/ASPIRE and MTN-025/HOPE Study Teams. Long-term use of long acting reversible contraceptive methods among women participating in HIV prevention trials. International Conference on Family Planning, November 12-15, 2018, Kigali, Rwanda.

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

Protocol Chair:	Ross D. Cranston, MD, FRCP
Study Product:	• Dapivirine Gel (0.05%) • Universal Hydroxyethylcellulose (HEC) Placebo Gel
Date of First Enrollment:	05 December 2017
Closed to Accrual:	19 July 2018
Total Enrolled/Expected:	27 Evaluable (28 overall; includes replacement participant)
Current Status:	Closed to follow-up

Primary Objectives:

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

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

MTN-026 was 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. All MTN-026 follow-up visits were completed in September 2018, and data analysis is ongoing at this time.

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

Protocol Chair:	Craig Hoesley, MD
Study Product:	• Vicriviroc (MK-4176) Intravaginal Ring (IVR) containing 182 mg of vicriviroc (MK-4176) • MK-2048 IVR containing 30 mg MK-2048 • MK-2048A IVR containing the combination of vicriviroc (MK-4176) (182 mg) and MK-2048 (30 mg) • Placebo IVR
Date of First Enrollment:	8 June 2015
Closed to Accrual:	1 February 2016
Total Enrolled/Expected:	48/48
Current Status:	Primary Analysis Complete; Published

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- to 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 allowed for safety comparisons of each study product to a placebo and provided 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. The primary results manuscript was published in *Clinical Infectious Diseases*, along with the primary results manuscript for Protocol MTN-028.

Results: VCV and/or MK-2048 containing VRs were safe, well-tolerated and acceptable: there were no statistically significant differences in the number of participants with related genitourinary adverse events or any AE between VCV and/or MK-2048 containing IVR study arms compared to placebo IVR arm. VCV and MK-2048 released from single or combination IVRs both achieved peak concentrations in vaginal fluids which were substantially higher compared to plasma (200x for VCV, 30x for MK-2048) and rectal fluid. In an *ex vivo* challenge assay, the antiviral activity of VCV and/or MK-2048 was not correlated with

issue-associated drug concentrations. These data highlight the need to assess the adequacy of drug dosing in the IVR and to measure genital tissue drug concentrations to develop more precise concentration-response relationships.

Clinical Research Sites: USA Alabama CRS
University of Pittsburgh CRS

Citation:

Hoesley CJ, Chen BA, Anderson PL, Dezzutti CS, Strizki J, Sprinkle C, Heard F, Bauermeister J, Hall W, Jacobson C, Berthiaume J, Mayo A, Gundacker H, Richardson-Harman N, Piper J; Microbicide Trials Network 027 Study Team. Phase 1 safety and pharmacokinetics study of MK-2048/Vicriviroc (MK-4176)/MK-2048A intravaginal rings. Clin Infect Dis 2018; Oct 4 [Epub ahead of print]

MTN-028

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

Protocol Chair:	Albert Liu, MD, MPH
Study Product:	• Formulation A (Low dose): MK-2048A intravaginal ring (IVR) containing the combination of vicriviroc (MK-4176) (91 mg) + MK-2048 (10 mg) • Formulation B (Original dose): MK-2048A intravaginal ring (IVR) containing the combination of vicriviroc (MK-4176) (182 mg) + MK-2048 (30 mg)
Date of First Enrollment:	13 July 2015
Closed to Accrual:	16 February 2016
Total Enrolled/Expected:	18/18 Evaluable
Current Status:	Primary Analysis Complete; Published

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 were 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 evaluated in MTN-028 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. The primary results manuscript was published in *Clinical Infectious Diseases*, along with the primary results manuscript for Protocol MTN-027.

Results: The two doses/formulations of a combination VCV/MK-2048 IVR were safe and well-tolerated: all AEs were of Grade 1 or 2 severity, with no statistically significant differences in related genitourinary AEs or AEs of Grade 2 or higher severity observed between the two study arms (p=1.00). VCV and MK-2048 were detectable in plasma, CVF, and cervical tissue, and higher drug release and plasma drug exposure was observed in the original versus low-dose IVR. Future studies are needed to determine the optimal

drug release and concentration profiles of VCV and MK-2048 needed to achieve protection from HIV acquisition.

Clinical Research Sites: USA Bridge HIV CRS

Citation:

Liu AY, Zhang J, Anderson PL, Wagner T, Pan Z, Peda M, Gomez K, Beamer M, Jacobson C, Strizki J, Dezzutti CS, Piper JM; MTN-028 Protocol Team for the Microbicide Trials Network. Phase 1 pharmacokinetic trial of 2 intravaginal rings containing different dose strengths of vicriviroc (MK-4176) and MK-2048. Clin Infect Dis 2018; Oct 4 [Epub ahead of print]

MTN-029/IPM 039

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

Protocol Chair:	Lisa Noguchi, PhD, CNM
Protocol Co-Chair:	Richard Beigi, MD, MSc
Study Product:	• Dapivirine (25 mg) Vaginal Ring (VR-004)
Date of First Enrollment:	16 March 2016
Closed to Accrual	15 February 2017
Total Enrolled/Expected	16/16
Current Status:	Primary Analysis Complete; Published

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 as well as adherence to the dapivirine vaginal ring 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/IPM 039 was completed on 15 February 2017 and follow-up was completed in early March 2017. Primary results were presented at the International AIDS Society (IAS) HIV Pathogenesis, Treatment & Prevention meeting, July 23- 26, 2017, in Paris, France and at the Infectious Diseases Society for Obstetrics and Gynecology (IDSOG) meeting, Aug 10- 12, 2017, Park City, Utah.

Results: Dapivirine concentrations were detectable in milk and plasma in all participants at all tested time points (except for one participant with undetectable plasma levels at the 3-hour post insertion time point). Median dapivirine peak concentration were 676 pg/mL in breast milk, 327 pg/mL in plasma (milk:plasma ratio ~2.0), and 36.25 ng/mg in CVF. The estimated mean daily infant intake was low, at 74.3 ng/kg/day or for an 8 kg infant (median weight for male infant at ~6 months old), at approximately 594.4 ng/day (<1 µg/day). Six of 16 (38%) participants experienced a total of ten AEs, most of which were mild and unrelated to study product. In summary, dapivirine vaginal ring use was associated with low concentrations of detectable dapivirine in milk and plasma and a favorable safety profile in lactating women.

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

Citations:

Noguchi LM, Hoesley C, Kelly C, Scheckter R, Bunge K, Nel A, Marzinke MA, Hendrix CW, Dezzutti CS, Hillier SL, Bogen DL, Piper JM, Beigi RH. Pharmacokinetics of dapivirine transfer into blood plasma, breast milk, and cervicovaginal fluid of lactating women using the dapivirine vaginal ring. Antimicrob Agents Chemother 2019 Jan 2. pii: AAC.01930-18 [Epub ahead of print]

MTN-030/IPM 041

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

Protocol Chair:	Sharon L. Achilles, MD, PhD
Protocol Co-Chair:	Beatrice A. Chen, MD, MPH
Study Product:	• Vaginal ring (VR) containing 200 mg of DPV (Ring-104) • VR containing 200 mg of DPV + 320 mg LNG (Ring-102)
Date of First Enrollment:	3 May 2017
Closed to Accrual	2 August 2017
Total Enrolled/Expected:	24/24 participants
Current Status:	Closed to Follow-up

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 was a multi-site, randomized (1:1), double blind Phase 1 trial. The study assessed 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 consisted of healthy, HIV-uninfected, non-pregnant women between 18-45 years of age. The participants used one of the two vaginal rings for a period of approximately 14 days and were followed up for a total duration of approximately 16 days. The primary objectives of MTN-030/IPM 041 was to collect 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. The effects, if any, the study product had on vaginal bleeding patterns was also examined. MTN-030/IPM 041 assessed the acceptability of and adherence to this biomedical HIV prevention-plus-contraception method and evaluated the vaginal microenvironment (microflora and biomarkers) during 14 days of continuous study product use. MTN-030/IPM 041 was the first in human study of a vaginal ring containing a combination of dapivirine and levonorgestrel.

The study enrolled 24 participants from May 3, 2017 to August 2, 2017, and follow-up was completed on August 18, 2017. Results were presented at the HIV Research for Prevention (HIVR4P), October 22-25, 2018, in Madrid, Spain.

Results: Of the 24 enrolled participants, 23 were evaluable. Both formulations were well-tolerated and no safety concerns were identified. A total of 43 AEs were reported (36 Grade 1 and 7 Grade 2). The number of women with related Grade 2 genitourinary AEs in the dapivirine vs dapivirine/ levonorgestrel arms was not significantly different (2/11 (18%) vs 0/12 (0%), p=0.2). No Grade 3 or higher AEs were reported in the study. All participants reported full adherence to within 15-min over 14-days. Median plasma dapivirine C_{max} trended higher in dapivirine/ levonorgestrel arm compared to the dapivirine arm (661 vs 499 pg/mL, respectively, p=0.05). Median vaginal fluid dapivirine C_{max} was not significantly different between dapivirine/levonorgestrel and dapivirine users (183 vs 107 ng/mL, respectively, p=0.09). The median plasma dapivirine $t_{1/2}$ was 50h (IQR 37-52h) for the dapivirine/ levonorgestrel ring. Median plasma levonorgestrel C_{max} was 1.6 ng/mL (IQR 1.1-2.6). These reported local and systemic dapivirine and levonorgestrel concentrations support further evaluation of this vaginal ring.

Clinical Research Sites: USA Alabama CRS
University of Pittsburgh CRS

Citation:

Achilles S, Hendrix C, Poloyac S, Hoesley C, Peda M, Gundacker H, Mensch B, Marzinke M, Nel A, Piper J, Johnson S, Chen B, on behalf of the MTN-030/IPM 041 Protocol Team. Safety and pharmacokinetics of dapivirine and levonorgestrel vaginal rings for multipurpose prevention of HIV and pregnancy. HIV Research for Prevention (HIVR4P), October 22-25, 2018, Madrid, Spain. Abstract # OA12.02LB

MTN-032

Assessment of ASPIRE and HOPE Adherence

Protocol Chair:	Elizabeth Montgomery, PhD, MHS
Protocol Co-Chairs:	Sarita Naidoo, PhD; Jonathan Stadler, PhD, MA (Phase 1 of the study)
Study Product:	Not Applicable
Date of First Enrollment:	13 June 2016
Target Sample Size:	Phase 1 – Up to 192 former ASPIRE participants Phase 2 – Up to 156 HOPE participants; up to 120 male partners of HOPE participants
Total Enrolled:	Phase 1 – 187 participants Phase 2 – 115 participants as of 12/21/18
Current Status:	Phase 1 – Primary analysis complete; Published Phase 2 – Enrolling (pending management decision regarding additional FGDs)

Primary Objectives:

- To explore socio-contextual and trial specific issues which affected participants' adherence to the dapivirine vaginal ring (VR)
- To explore male partner attitudes towards and experiences with the dapivirine VR, and their perspective of their female partner's attitudes and experiences

Summary: In the first phase of MTN-032, 187 ASPIRE participants with varying levels of adherence to the dapivirine VR were enrolled. Based upon participants' ASPIRE plasma dapivirine levels and residual drug levels from returned VRs, participants were pre-selected and approached for study participation. Enrolled participants were categorized into groups of low or high adherence.

After being presented their ASPIRE ring adherence results (plasma dapivirine levels and residual drug level results), participants were asked to complete a single in-depth interview (IDI) or a focus group discussion (FGD) (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. The protocol was revised to: allow sampling for Phase 2 from all HOPE participants, not just those who completed Phase 1 of MTN-032; expand the Phase 2 sample to include male partners of HOPE participants; and add female FGDs to possible Phase 2 visit procedures. A single IDI or FGD 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 who were inconsistently or not adherent
- VR uptake, marketing and other product roll-out issues
- Key unexpected and/or important findings of HOPE trial results
- Role male partners may have had on study product adherence for HOPE participants

- Male partner attitudes will also be explored to examine the following:
  - o HIV risk and perceptions of HIV risk, and how this impacted their support of HOPE participants' use of the dapivirine VR.
  - o ASPIRE results and ring efficacy, and how their understanding of these impacted their support of HOPE participants' trial participation and use of the dapivirine VR.
  - o Preferred drug delivery modalities and attributes that might encourage end-user uptake.
  - o How other men in their social networks and communities would view the VR.
  - o How they should and could be engaged in scale up of VR demonstration projects and licensure in the future.
  - o Physical sensation of women's VR use during sex

.

Phase 1 results were presented at the International AIDS Society (IAS), HIV Pathogenesis, Treatment & Prevention July 23- 26, 2017, in Paris, France.

Results: A total of 187 former ASPIRE participants aged 19-48 years were enrolled in the first phase of MTN-032 study; 37% of these participates were aged 18-21 years at ASPIRE enrollment. Although 24% of the 187 participants had concordant plasma and residual ring results suggesting consistent ring use at every visit measured, most women (73%) had results suggesting inconsistent use throughout ASPIRE. Visual tools elicited participant descriptions of many instances of non-adherence, including removals ranging from short-term (for sex or bathing), to multiday (menses) to multi-week (often with reinsertion one-three days before the next visit). Reasons for non-use included influence from peers and communities mistrusting researchers (particularly foreign); worries about the ring causing cancer or infertility; non-disclosure to partners and partner objections; and experience of discomfort or side effects.

Sites are currently at an accrual pause for Phase 2 of the study, which seeks to enroll both former HOPE participants as well as the partners of former HOPE participants. Sixty female participants and 55 male participants have so far been enrolled into Phase 2. Resumption or termination of Phase 2 enrollment activities will be determined in Q1/Q2 2019 after HOPE study results are disseminated.

A second abstract representing findings from female interviews conducted during Phase 2 of the study is currently under review for submission to IAS 2019.

Clinical Research Sites:		
	Malawi	Malawi CRS
	South Africa	eThekwini CRS, Botha's Hill CRS, Wits RHI CRS
	Uganda	MU-JHU Research Collaboration CRS
	Zimbabwe	Spilhaus CRS (Phase 1 only), Zengeza CRS

Citation:

Montgomery ET, Stadler J, Naidoo S, Katz AW, Laborde N, Garcia M, Reddy K, Mansoor LE, Etima J, Zimba C, Chitukuta M, Soto-Torres L. Reasons for non-adherence to the dapivirine vaginal ring: Narrative explanations of objective drug-level results**.** AIDS 2018 July 17; 32(11):1517-1525. PMCID: 29957723

.

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

Protocol Chair:	Ken Ho, MD
Study Product:	• Dapivirine Gel (0.05%)
Date of First Enrollment:	31 May 2018
Close to Accrual	2 November 2018
Total Enrolled/Expected:	16/16 Evaluable
Current Status:	Closed to follow-up

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 administered a single dose of dapivirine gel (DPV 0.05%) in each study sequence. Participants were randomized to one of two product application sequences. Product sequences included 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 was randomly selected. A washout period occurred between each product application visit. This design allowed 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.

The study enrolled 16 participants from between May-November 2018; follow-up was completed on December 5, 2018.

Clinical Research Site: USA University of Pittsburgh CRS

MTN-034 (REACH)

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

Protocol Chair:	Gonasagrie Nair, MBChB, MPH
Protocol Co-Chairs:	Connie Celum, MD, MPH and Kenneth Ngure, PhD
Study Product:	• Dapivirine (25 mg) Vaginal Ring • Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)
Target Sample Size:	300 Evaluable
Current Status:	Open to accrual

Primary Objectives:

- To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine (25 mg) vaginal matrix ring inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population
- To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine (25 mg) vaginal matrix ring inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

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 disproportionally 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 objectives of MTN-034 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) daily FTC/TDF oral tablets for 24 weeks, followed by use of the dapivirine VR inserted monthly for 24 weeks; or (b) monthly dapivirine VR for 24 weeks, followed by daily FTC/TDF oral tablets 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. In total, participants will be followed up for approximately one and a half years. Participants will be able to choose either or neither study product at any time during the third product use period. The study is currently open to accrual at some sites and it is anticipated that remaining sites will be activated to enroll participants in Q1 2019 and that participants will be followed up for approximately one and a half years.

Clinical Research Sites:

Kenya	Kisumu CRS
South Africa	Emavundleni CRS; Wits RHI CRS
Uganda	MU-JHU Research Collaboration CRS
Zimbabwe	Spilhaus CRS

MTN-035 (DESIRE)

Acceptability, Tolerability, and Adherence of Three Rectal Microbicide Placebo Formulations among HIV Seronegative Cisgender Men, Transgender Men and Transgender Women Who Engage in Receptive Anal Intercourse

Protocol Chair:	José Bauermeister, PhD, MPH
Study Product:	• Placebo rectal insert • Placebo rectal douche • Placebo rectal suppository
Target Sample Size:	Approximately 210 participants
Current Status:	Pending

Primary Objectives:

- To evaluate the acceptability and tolerability of each dosage form (insert, douche, suppository) when applied rectally and used prior to receptive anal intercourse (RAI)
- To evaluate adherence to each dosage form (insert, douche, suppository) prior to RAI over a 4-week-long period
- To evaluate the safety of each study product (insert, douche, suppository) when applied rectally and used prior to RAI

Summary: MTN-035 is a multi-site, randomized-sequence, 1:1:1:1:1:1, three-period, open-label crossover study. The study will evaluate the safety, acceptability and tolerability of and adherence to three placebo dosage forms (insert, douche, suppository) when each is applied rectally and used prior to RAI over a 4-week-long period. The study population will consist of healthy, HIV-uninfected men (cisgender and transgender) and transgender women (TGW) who are 18-35 years of age and who report engaging in RAI. Participants will be randomized equally across six application sequences which determine the order each dosage form will be used. Each dosage form will be used for approximately four weeks, and there will be a 1-week washout period between each dosage form application period.

It is hypothesized that the placebo rectal insert, the placebo rectal douche, and the placebo rectal suppository will be safe acceptable and tolerable to participants, and that adherence will be high. It is anticipated that this study will take approximately 9-12 months to enroll the target sample size, and each participant will be followed up for approximately 3.5 months. It is also anticipated that sites in the US will be activated to enroll participants in Q1 2019, while international sites will be activated in Q2 2019.

Clinical Research Sites:

Malawi:	Blantyre CRS
Peru:	San Miguel CRS
South Africa:	Wits RHI CRS
Thailand:	Chiang Mai University HIV Prevention CRS
USA:	University of Pittsburgh CRS, Alabama CRS, Bridge HIV CRS

MTN-036/IPM 047

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

Protocol Chair:	Albert Liu, MD, MPH
Study Products:	• Dapivirine (25 mg) Vaginal Ring • Dapivirine (100 mg) Vaginal Ring • Dapivirine (200 mg) Vaginal Ring
Date of First Enrollment:	04 December 2017
Closed to Accrual	23 October 2018
Total Enrolled/Expected:	49/48
Current Status:	Closed to accrual

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 current 25 mg DPV VR when replaced every 4 weeks for 8 weeks and then worn for an additional five weeks for a total of 13 weeks)
- To compare the safety of the two-extended duration DPV VRs (100 mg and 200 mg) to the current 25 mg DPV VR when used 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, 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 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 fluid samples following insertion of the VR to allow for detection of burst release from the ring. PK parameters of DPV will be calculated for blood plasma, cervicovaginal 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 due to sustained release from the 100 mg and 200 mg VRs for 13 weeks will be safe, and that dose-proportionality will be demonstrated in tissue and systemic PK.

The first participant was enrolled December 4, 2017 and the last participant was enrolled October 23, 2018. It is anticipated that participant follow-up for this study will be completed in January 2019.

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

Protocol Chair:	Craig Hendrix, MD
Study Product:	• PC-1005 Rectal Gel (0.002%MIV-150/0.3% Zinc Acetate [ZA] in 3.0% Carrageenan [CG] gel)
Date of First Enrollment:	20 August 2018
Total Enrolled/Expected:	12/12 Evaluable as of 1/8/19
Current Status:	Closed to accrual

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 gel 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. Each participant will receive a total of three doses of PC-1005 (1st dose = 4mL, 2nd dose = 16mL, and 3rd 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 among healthy men and women (cis or transgender). MTN-037 is the first study to assess the safety and PK of PC-1005 gel applied rectally.

The final participant enrolled on January 8, 2019 and participant follow-up will be completed in Q2 2019.

Clinical Research Sites: USA Alabama CRS
University of Pittsburgh CRS

MTN-038

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

Protocol Chair:	Albert Liu, MD, MPH
Study Product:	• Tenofovir Intravaginal Ring • Placebo Intravaginal Ring
Date of First Enrollment:	02 January 2019
Total Enrolled/Expected:	2/48 as of 1/22/19
Current Status:	Enrolling

Primary Objectives:

- To characterize the local and systemic pharmacokinetics (PK) of one tenofovir (TFV) intravaginal ring (IVR) used continuously for 91 days
- To evaluate the safety of one TFV IVR used continuously for 91 days

Summary: Multiple clinical trials have evaluated the safety and effectiveness of TFV for the prevention of HIV acquisition in vaginal gel and in oral tablet formulations. These clinical trials support the favorable safety profile and tolerability of TFV in general and specifically in vaginal and oral delivery formulations. The development of an extended duration intravaginal ring (IVR) may allow less frequent IVR replacements (e.g., quarterly basis instead of monthly basis) that may further reduce patient and provider burden, streamline follow-up, and improve adherence. Such a delivery mechanism could overcome the adherence and efficacy issues observed with the vaginal gel formulation of TFV and challenges with daily dosing of oral TDF/FTC, thus providing a viable vaginal delivery complement to the oral tablet.

MTN-038 is a Phase 1, two-arm, 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. MTN-038 will evaluate TFV and TFV-DP levels in plasma, cervicovaginal fluid (CVF), rectal fluid, and cervical tissue during approximately 91 days of continuous use of a single ring containing 1.4 g TFV. PK data will help determine the concentration-time profile using pooled data across all participants. The study design includes frequent collection of corresponding blood, rectal and CVF samples following the insertion of a TFV IVR to allow for the detection of drug release from the ring. PK parameters of TFV will be calculated for blood plasma, CVF, rectal fluid, and cervical tissue. It is hypothesized that plasma, CVF, and rectal fluid TFV levels and cervical tissue TFV and TFV-DP levels will be measurable in all participants, and that continuous exposure to TFV due to sustained release from the 1.4 g TFV IVR for 91 days will be safe.

It is anticipated that accrual will be completed in Q2/Q3 2019, and that participant follow-up will be completed in Q3/Q4 2019.

Clinical Research Sites: USA
Bridge HIV CRS
University of Pittsburgh CRS
Alabama CRS

MTN-039

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

Protocol Chair:	Sharon Riddler, MD, MPH
Study Product:	• Insert containing 20mg tenofovir alafenamide (TAF) and 16mg elvitegravir (EVG)
Target Sample Size:	Approximately 20 participants
Current Status:	In development

Primary Objectives:

- To evaluate the safety of an insert containing TAF/EVG administered rectally
- To characterize the systemic and rectal pharmacokinetics of the insert containing TAF/EVG administered rectally

Summary: MTN-039 is an open-label, multi-site single arm, study designed to evaluate the safety and pharmacokinetics (PK) of an insert containing TAF and EVG. TAF is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir and EVG is an integrase inhibitor. Approximately 20 healthy, HIV-uninfected individuals who are 18 years of age and older who have a history of consensual receptive anal intercourse (RAI) will be enrolled in MTN-039. Enrolled participants will use a TAF/EVG insert at two dose levels (1 TAF/EVG insert and 2 TAF/EVG inserts) in the clinic, separated by a washout period of at least seven days. They will undergo sample collection (blood, rectal fluid and rectal tissue) for PK and PD at specified timepoints over a three-day period following dosing.

It is anticipated that sites will be activated to enroll participants in Q2 2019, and that participants will be followed up for approximately 6-13 weeks.

Clinical Research Sites: USA Alabama CRS
University of Pittsburgh CRS

MTN-041

Qualitative Assessment of Acceptability of a Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use during Pregnancy and Breastfeeding

Protocol Chair:	Ariane van der Straten, PhD, MPH
Protocol Co-Chair:	Petina Musara, BSW
Study Product:	Not Applicable
Date of First Enrollment:	31 May 2018
Closed to Accrual	2 November 2018
Total Enrolled:	196 focus group discussion (FGD) participants 36 key informant (KI) in-depth interview (IDI) participants
Current Status:	Closed to follow-up

Primary Objectives:

- To explore attitudes about use of a vaginal ring (VR) during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of a VR during pregnancy and breastfeeding
- To explore attitudes about use of oral PrEP during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of oral PrEP during pregnancy and breastfeeding

Summary: MTN-041 was a multi-site qualitative acceptability study that utilized focus group discussions (FGDs) and in-depth interviews (IDIs) to explore the attitudes of community members and key informants (KI) from the community about the use of a VR or oral PrEP during pregnancy and breastfeeding.

196 participants were enrolled in FGDs within the following three groups:

- HIV-uninfected women aged 18-40 who were pregnant or breastfeeding, or who had been pregnant or breastfeeding within the previous two years;
- Men aged 18 or older whose partners were pregnant or breastfeeding, or whose partners had been pregnant or breastfeeding within the previous two years; and
- Maternal and paternal grandmothers whose daughters or daughters-in-law were pregnant or breastfeeding, or had been pregnant or breastfeeding within the previous two years

Additionally, MTN-041 enrolled 36 KIs (e.g., health providers, midwives, social service providers, local leaders, etc.) to participate in IDIs. A single FGD was conducted with men and women, and a single IDI was conducted with KIs, to explore topics such as:

- Use of oral medications and/or vaginal microbicides by pregnant and breastfeeding women
- VR and oral PrEP uptake, marketing and other product roll-out issues among pregnant and breastfeeding women
- HIV risk during pregnancy and breastfeeding
- Sexual activity among pregnant and breastfeeding women
- Vaginal practices during pregnancy and lactation

The first FGD was conducted in May 2018 and the last IDI was conducted in November 2018. It is anticipated that preliminary results for this study will be disseminated to the MTN-042 and MTN-043 protocol teams in Q1 2019.

Clinical Research Sites:

Malawi:	Blantyre CRS
South Africa:	Wits RHI CRS
Uganda:	MU-JHU Research Collaboration CRS
Zimbabwe:	Zengeza CRS

MTN-042 (Deliver)

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

Protocol Chairs:	Katherine Bunge, MD & Bonus Makanani, MBBS, FCOG
Protocol Co-Chair:	Lee Fairlie, MBChB, FCPaeds
Study Product:	• Dapivirine (25 mg) Vaginal Ring • Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)
Target Sample Size:	Approximately 750 women and their newborns
Current Status:	In development

Primary Objectives:

- To describe the maternal and infant safety profile associated with study product exposure during pregnancy
- To describe the pregnancy outcomes associated with study product exposure during pregnancy

Summary: MTN-042 is a Phase 3b, open-label, multi-site, randomized (2:1 to VR: tablet) trial designed to assess the safety, adherence and acceptability profiles of the dapivirine VR and FTC/TDF oral tablet when used during pregnancy. Approximately 750 healthy, HIV-uninfected women who are 18-45 years of age, pregnant with a single child, and willing to use study product during pregnancy will be enrolled in MTN-042 along with their newborn infants. Participants will be enrolled into one of four cohorts, with onset of dosing period for each cohort to occur within the following gestational age (GA) ranges:

- Cohort 1: 36 0/7 weeks – 37 6/7 weeks 150 women
- Cohort 2: 30 0/7 weeks – 35 6/7 weeks 150 women
- Cohort 3: 20 0/7 weeks – 29 6/7 weeks 150 women
- Cohort 4: 12 0/7 weeks – 19 6/7 weeks 300 women

The cohorts will be enrolled sequentially, with pauses between cohorts to review interim safety data. Enrolled maternal participants will be on study product for up to 30 weeks and followed up for up to 36 weeks, depending on GA at enrollment and timing of pregnancy outcome. Enrolled newborn participants will be followed up for approximately 1 year. It is anticipated that sites will be activated to enroll participants in Q3/Q4 2019.

Clinical Research Sites:

Malawi:	Blantyre CRS
South Africa:	Shandukani CRS
Uganda:	MU-JHU Research Collaboration CRS
Zimbabwe:	Zengeza CRS

MTN-042B

Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa

Protocol Chairs:	Katherine Bunge, MD; Bonus Makanani, MBBS, FCOG; Lee Fairlie, MBChB, FCPaeds
Study Product:	N/A
Target Sample Size:	Approximately 11,000 deliveries
Current Status:	Pending

Primary Objectives:

- To determine the frequency of pregnancy outcomes (full term and premature live births, as well as stillbirth/intrauterine fetal demise) in sub-Saharan Africa

Summary: MTN-042B is a cross-sectional chart review study designed to provide an estimate of pregnancy outcome frequency data (term delivery, preterm delivery, still birth) for MTN-042 and other clinical trials involving pregnant women in sub-Saharan Africa. The medical charts of all women delivering or receiving immediate post-partum care (within one week of delivery) at one or two facilities affiliated with each of the 4 sites within an 8-week period will be abstracted; once the participant is discharged home and/or seven days from delivery has passed if the participant remains in the facility, the data entry will be considered complete

Clinical Research Sites:

Malawi:	Blantyre CRS
South Africa:	Shandukani CRS
Uganda:	MU-JHU Research Collaboration CRS
Zimbabwe:	Zengeza CRS

Open-Label, Pharmacokinetic, Mother-infant Pair Study of Dapivirine Vaginal Ring and Oral Truvada ® Use in Breastfeeding

Protocol Chair:	Maxensia Owor, MBChB, MMed
Protocol Co-Chairs:	Lisa Noguchi, PhD, CNM Jennifer Balkus, PhD, MPH
Study Product:	• Dapivirine (25 mg) Vaginal Ring • Emtricitabine (FTC)/Tenofovir (TDF) 200 mg/300 mg Tablet (Truvada®)
Target Sample Size:	Up to 200 mother-infant pairs
Current Status:	In development

Primary Objectives:

- To describe the maternal safety profile associated with study product exposure during breastfeeding in both study arms.
- To describe the infant safety profile associated with study product exposure during breastfeeding in both study arms.
- To summarize the frequency of study drug detection and concentration of study drug(s) in mothers and their breastfeeding infants.

Summary: MTN-043 is an open-label, multi-site, mother-infant pair PK study designed to assess the safety, PK, adherence, and acceptability of the dapivirine VR (25 mg), inserted every 4-weeks, and once-daily, Truvada (200 mg FTC/300 mg TDF) tablet used by women from sub-Saharan countries during breastfeeding. Approximately 200 healthy, HIV-uninfected breastfeeding women and their healthy infants between 6-12 weeks old (inclusive) will be enrolled in MTN-043. Enrolled maternal participants will be on study product for approximately 12 weeks, and enrolled mother-infant pairs will be followed up for up to three and a half months. It is anticipated that sites will be activated to enroll participants in Q4 2019/Q1 2020.

Clinical Research Sites:

Malawi:	Blantyre CRS
South Africa:	Shandukani CRS
Uganda:	MU-JHU Research Collaboration CRS
Zimbabwe:	Zengeza CRS

MTN-044/IPM 053/CCN019

A Randomized, Phase 1, Open-Label Study in Healthy HIV-Negative Women to Evaluate the Pharmacokinetics, Safety and Bleeding Patterns Associated with 90-Day Use of Matrix Vaginal Rings Containing 200 mg Dapivirine and 320 mg Levonorgestrel

Protocol Chair:	Sharon L. Achilles, MD, PhD
Protocol Co-Chair:	Beatrice A. Chen, MD, MPH
Study Product:	• Vaginal Ring containing 200 mg DPV + 320 mg LNG (Ring-102)
Date of First Enrollment:	17 July 2018
Total Enrolled/Expected:	13/24 participants as of 01/22/19
Current Status:	Enrolling

Primary Objective:

- To characterize the local and systemic pharmacokinetics of one DPV-LNG vaginal ring formulation used either continuously or cyclically (~28/2) for approximately 90 days

Summary: MTN-044/IPM 053/CCN019 is a single-site, randomized (1:1), open-label Phase 1 trial. The study will assess the pharmacokinetics and safety of one silicone elastomer vaginal matrix rings containing 200 mg of dapivirine and 320 mg of levonorgestrel. The MTN-044/IPM 053/CCN019 study population consists of healthy, HIV-uninfected, non-pregnant women between 18-45 years of age. The participants will use the vaginal ring either continuously or cyclically (worn for 28 days and taken out for two days) for approximately 90 days and will be followed up for a total duration of approximately 26 weeks. The primary focus of MTN-044/IPM 053/CCN019 is the collection of pharmacokinetic and safety data on the vaginal ring containing a combination of dapivirine and levonorgestrel, formulated with higher dapivirine dose strengths than previously evaluated in Phase 3 trials. Furthermore, MTN-044/IPM 053/CCN019 will assess the vaginal bleeding patterns associated with using the DPV-LNG VR either continuously or cyclically for approximately 90 days. This study 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) and the HIV inhibitory activity in cervical tissue during approximately 90 days of continuous or cyclic study product use. MTN-044/IPM 053/CCN019 is the first study to assess local and systemic PK, safety and tolerability of the DPV-LNG VR when used by women continuously versus cyclically (worn for approximately 28 days and taken out for two days) for approximately 90 days.

Clinical Research Sites: USA University of Pittsburgh CRS

MTN-045

Couple User Preferences in Dual Purpose Prevention Products (CUPID)

Protocol Chair:	Alexandra Minnis, PhD
Protocol Co-Chair	Juliane Etima, MA Psy
Study Product:	Not Applicable
Target Sample Size:	Approximately 400 couples
Current Status:	In development

Primary Objectives:

- To determine heterosexual couples' preferences for a DPP product to inform product delivery and future product design to maximize uptake and willingness to use among sub-Saharan African heterosexual couples.
- To assess the level of influence of the male partner on a woman's preferences for a DPP product and on her decision-making process regarding product preferences and use.

Summary: MTN-045 is a cross-sectional study that will utilize questionnaires, including a Discrete-Choice Experiment (DCE) and joint decision task, to assess couples' preferences related to DPP products that could be used to prevent unintended pregnancies and HIV infection. Couple members' preferences will be evaluated with each partner separately and also with both partners together. Post-survey explanatory IDIs will be conducted with a subset of couples (N= up to 80 participants from up to 40 couples). The following DPP product forms will be evaluated: vaginal ring, vaginal insert, vaginal film, and oral tablets.

It is anticipated that sites will be activated to enroll participants in Q2/Q3 2019, and that accrual will be completed by Q3/Q4 2020.

Clinical Research Sites:

Uganda	MU-JHU Research Collaboration CRS
Zimbabwe:	Zengeza CRS