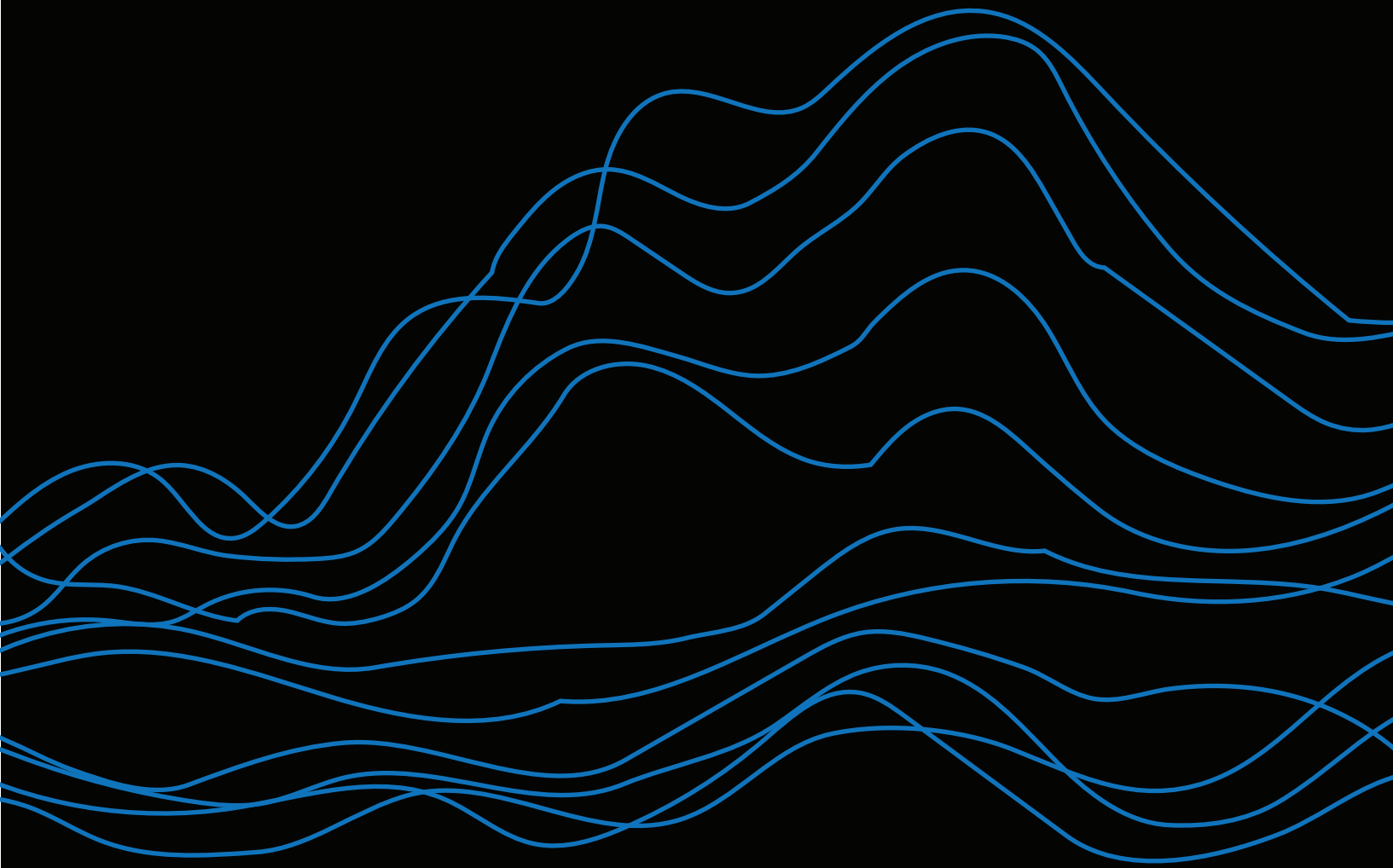
Pipeline Report » 2023

PrEP and Microbicides



TAG
Treatment Action Group

PrEP and Microbicides Pipeline 2023

By Richard Jefferys

The pipeline of potential interventions for HIV pre-exposure prophylaxis (PrEP) has seen a shift toward longer-acting candidates, which echoes current trends in the development of new antiretrovirals for treatment. Regulatory approval for several highly efficacious PrEP options — most recently long-acting cabotegravir (CAB LA) — has also shifted the research landscape, because ethically assessing the efficacy of novel candidates becomes more challenging when potentially effective alternatives are already on the market.

Currently there are two ongoing PrEP efficacy trials, both investigating the long-acting injectable form of the HIV capsid inhibitor lenacapavir (given every six months). Lenacapavir was recently approved in the United States for the treatment of people with multidrug-resistant HIV infection. PURPOSE 1 is assessing lenacapavir or Descovy compared with Truvada PrEP in young women aged 16–25 in South Africa and plans to enroll 5,010 participants.

PURPOSE 2 is comparing lenacapavir with Truvada PrEP in around 3,000 cisgender men, transgender women, transgender men, and gender nonbinary people who have condomless receptive anal sex with partners assigned male at birth. The study has sites in the United States, Puerto Rico, and South Africa. The researchers published a paper in June 2022 describing their strategies optimizing the engagement of Black, Hispanic/Latinx, transgender, and nonbinary individuals in PURPOSE 2.

Both PURPOSE trials are employing a new method for assessing efficacy known as a counterfactual study design. The statistical approach involves measuring the baseline incidence of HIV infection in the populations being enrolled, and then using that information to evaluate whether the candidate PrEP interventions significantly lowered HIV incidence during the trial.

The impetus for the approach is the difficulty of comparing experimental PrEP modalities to extant efficacious options. To statistically demonstrate that a new intervention is non-inferior to (works as well as) CAB LA, for example, would require extremely large numbers of trial participants. The PURPOSE trials represent an important test of these alternative efficacy trial designs, which longtime HIV prevention advocate Bill Snow has noted "are speculative and controversial, to say the least."

Over the past year, TAG has been able to identify only one new trial of a PrEP or microbicide candidate entered in the clinicaltrials.gov registry: a study in South African women comparing a longer-acting version of the dapivirine vaginal ring that requires replacement every three months to the current monthly formulation. The research aims to assess whether the two approaches deliver comparable drug levels.

The only other PrEP-related addition to the registry is a social science study sponsored by the University of Texas Southwestern Medical Center in collaboration with Merck, which plans to assess the perspectives of clinicians and men who have sex with men (MSM) regarding hypothetical long-acting PrEP products that are implanted under the skin.

Merck has already tested one such product, an implantable version of islatravir, the first of a novel class of antiretrovirals called nucleoside reverse transcriptase translocation inhibitors (NRTTIs). The drug was until recently considered a promising long-acting oral candidate, but an unexpected finding of decreased white blood cell and CD4+ T cell counts in clinical trials has prompted Merck to discontinue further development of the once-monthly oral compound for PrEP.

The adverse effect of islatravir on white blood cell counts is thought to result from high peak drug levels achieved with the doses used for weekly or monthly administration, and it may be possible for the implant to move forward because it's designed to deliver steady drug levels that would not rise to potentially toxic peaks. A planned study is currently pending. Merck continues to investigate a compound from the same class, MK-8527, which is metabolized differently and may become a candidate for future studies as oral PrEP.

Most currently active registered studies of HIV PrEP and microbicide products do not involve experimental candidates in the pipeline, but rather focus on how best to implement the recently approved CAB LA (trade name Apretude). These include:

- PILLAR: An evaluation of implementation strategies at low- and high-volume PrEP sites in the United States for MSM and transgender men.
- EBONI: An evaluation of implementation strategies for Black cis- and transgender women in U.S. Ending the Epidemic priority areas. Sites are located in the District of Columbia, Florida, Georgia, Nevada, New York, Pennsylvania, Tennessee, Texas, and Virginia.
- A study in Pennsylvania addressing the optimization of CAB LA PrEP for women who inject drugs.
- The SEARCH SAPPHIRE CAB-LA extension study assessing implementation in Kenya and Uganda.
- A planned implementation study at public health facilities in Brazil for cisgender men and transgender or gender nonbinary individuals who have sex with persons assigned male at birth.
- OPTIMIZE: A planned study of a pharmacist-run PrEP program for women at a community-based organization in Orlando called Let's Beehive. Sponsored by the Orlando Immunology Center.

Efforts to promote greater access to CAB LA have been buoyed by the announcement of an agreement between ViiV Healthcare and the Medicines Patent Pool designed to allow for its generic manufacture and the issuance of World Health Organization recommendations for offering the product as a prevention option.

The decision by the National Institute of Allergy and Infectious Diseases (NIAID) to discontinue funding for the Microbicide Trials Network (MTN) in 2021 may be at least partly responsible for the dearth of new studies opening over the past year. Potentially promising results continue to emerge from MTN-supported research, such as trials evaluating rectal or vaginal inserts containing tenofovir alafenamide plus elvitegravir and important evaluations of the safety of PrEP and microbicide interventions during pregnancy (see table 2).

The field has also been affected by the winding down of the International Partnership for Microbicides (IPM), a leader in research and development since its founding by Dr. Zeda Rosenberg in 2002. In October 2022, the Population Council announced the acquisition of key assets from IPM: the monthly dapivirine ring, the three-month dapivirine ring that is currently under evaluation in an ongoing trial, and a three-month dapivirine-contraceptive ring.

When NIAID discontinued the MTN, it was stated that potentially promising microbicides could still be studied within the HIV Prevention Trials Network (HPTN). Encouragingly, this appears to have been borne out with the HPTN planning further evaluation of the tenofovir douche investigated by Craig Hendrix and colleagues at Johns Hopkins University in their DREAM (development of rectal enema as microbicide) program (see table 2).

Advocates for biomedical HIV prevention research continue to stress the importance of developing a range of options to allow potential users to make informed choices regarding the optimal HIV prevention method for their current situation. As Raphael Landovitz, principal investigator for CAB LA trials, clearly articulated during a presentation at CROI 2023: “The best PrEP agent is the one the person will take and adhere to. Full stop.”

The challenge for the future is ensuring that new options continue to be pursued and that methods for robustly evaluating efficacy are developed and validated so that individual choices are fully informed. Optimizing implementation will also be critical.

A recent paper by Katie M. Williams and colleagues from the Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) consortium outlines a set of principles for a choice-based approach to HIV prevention, focused on core concepts of nondiscrimination, availability, accessibility, acceptability, quality, privacy and confidentiality, participation, and accountability. AVAC has also initiated an email discussion group, The Choice Agenda, which is led by consultant and respected advocate Jim Pickett to facilitate global dialogue on the topic. The listserv has rapidly grown to well over a thousand members and offers an important venue for communal discussion of the issues now faced by the biomedical HIV prevention field.

Table 1: Pre-exposure Prophylaxis (PrEP)

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Cabotegravir **NCT05418868** **(subcutaneous delivery with recombinant human hyaluronidase PH20)** **NCT03164564** **(cisgender women)** **NCT02720094** **(MSM and transgender women)** **NCT04692077** **(adolescents assigned male at birth)**	**INSTI**	**ViiV Healthcare**	**IM**	**Phase III (HPTN 084)** **Phase IIb/III (HPTN 083)** **Phase II**

- Approved by the FDA for adults and adolescents at risk of HIV acquisition on December 20, 2021.
- World Health Organization guidelines recommending CAB LA as an HIV prevention option issued July 28, 2022.
- Also on July 28, 2022, ViiV Healthcare and the Medicines Patent Pool announced a voluntary licensing agreement designed to allow for generic manufacture and "help enable access in 90 countries."
- A trial launched in June 2022 (NCT05418868) is investigating whether a substance called recombinant human hyaluronidase PH20 (rHuPH20) can improve delivery of CAB LA. The purpose of rHuPH20 is to ease passage of injectable drugs through the subcutaneous space.
- Results from HPTN 083 and 084 were published in the *New England Journal of Medicine* and *The Lancet*, respectively. Open-label extension phases of both trials are ongoing.
- A substudy of HPTN 83 is investigating the safety, tolerability, and acceptability of CAB LA among HIV-uninfected adolescents assigned male at birth, including men who have sex with men, transgender women, and gender nonconforming people. The enrollment target is 50 participants, and the estimated completion date is August 2023.
- A phase I trial assessing PK, safety, tolerability, and acceptability of CAB LA in adult Chinese men at low risk for HIV acquisition has been completed. Results were published in *Antimicrobial Agents and Chemotherapy* on March 15, 2022.

Lenacapavir **NCT04994509** **(PURPOSE 1)** **NCT04925752** **(PURPOSE 2)**	**Capsid inhibitor**	**Gilead**	**SC, oral**	**Phase III**

- An inhibitor of the HIV capsid protein. The long-acting formulation for subcutaneous injection is administered once every six months.
- Gilead is sponsoring two phase III efficacy trials:
  - PURPOSE 1 is evaluating lenacapavir and Descovy compared with Truvada PrEP in young women aged 16–25 in South Africa. The trial plans to enroll 5,010 participants.
  - PURPOSE 2 is evaluating lencapavir compared with Truvada PrEP in cisgender men, transgender women, transgender men, and gender nonbinary people who have condomless receptive anal sex with partners assigned male at birth. The study has sites in the United States, Puerto Rico, and South Africa and plans to enroll 3,000 participants.
- Trials were temporarily placed on hold by the FDA in December 2021 because of concerns related to the safety of the storage vials for injectable lenacapavir. On May 16, 2022, Gilead announced that the issue had been resolved and the hold lifted.

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Tenofovir alafenamide + emtricitabine (Descovy), tenofovir disoproxil fumarate + emtricitabine (Truvada) **NCT04937881**	**NtRTI/NRTI**	**University of California, Los Angeles**	**Oral PrEP**	**Phase III**
■ A study in pregnant and postpartum women in South Africa to establish benchmarks of TFV diphosphate concentrations as measures of adherence in this population. Either Descovy or Truvada will be administered once daily under direct observation for eight weeks during pregnancy and for eight weeks in the postpartum period.				
Islatravir **NCT05115838**	**NRTTI**	**Merck**	**Implant**	**Phase IIa**
■ Islatravir is an investigational antiretroviral drug classed as an NRTTI. The drug is reported to be highly potent with a long half-life, potentially allowing for intermittent dosing. ■ In September 2022, Merck announced that the once-monthly PrEP development program is being discontinued because of evidence of dose-dependent declines in white blood cell counts associated with islatravir administration. In the clinical trials, dosing has been stopped and participants are being offered approved PrEP options as an alternative. A revised treatment program is continuing, using low daily or weekly doses deemed to be safe for further study. ■ The fate of an implant formulation in development is currently unclear. Phase I testing of a prototype implant showed potential for once-yearly administration, with results published in *Nature Medicine* in October 2021. Results from a larger phase I trial of a radiopaque subdermal implant were published in *JAIDS* on April 1, 2023. The main side effects were implant-site reactions and irritation, with systemic drug levels achieving concentrations considered inhibitory of HIV. The 12-week duration of the study did not allow for evaluations of effects on lymphocyte counts. ■ A phase IIa study of a radiopaque matrix implant (NCT05115838) is planned but on hold; Merck is currently working through a strategy for the implant and hopes to eventually proceed with the study. ■ A presentation by Jay Grobler at the 2022 Long-Acting/Extended Release Antiretroviral Research Resource Program (LEAP) Investigator Meeting and Annual Workshop reported average declines in lymphocyte counts of -21% in the 60 mg dose group and -36% in the 120 mg dose group in a phase IIa PrEP trial. ■ Results from a phase I study evaluating interactions between islatravir and the oral contraceptive levonorgestrel/ethinyl estradiol were published in the *Journal of the International AIDS Society* in December 2021, indicating no requirement for dose adjustments.				
Tenofovir alafenamide subdermal implant **PACTR201809520959443**	**NtRTI**	**Centre for the AIDS Programme of Research in South Africa**	**Implant**	**Phase I/II**
■ A phase I/II trial to evaluate the safety, acceptability, tolerability, and PK in women (CAPRISA 018) is underway in South Africa. As described in a paper published in *BMJ Open*, an initial phase I portion of the study aims to determine the optimal dosing, implant location, and implant replacement interval before proceeding to a larger phase II trial. ■ Recruitment is currently listed as suspended for safety and PK assessments (the suspension is part of the study protocol).				
Aspirin **NCT03629327**	Nonsteroidal anti-inflammatory	University of Manitoba	Oral PrEP	Not applicable
■ An ongoing trial is recruiting 300 women in Nairobi to assess the potential for aspirin to induce immune quiescence in the female genital tract. The goal is to develop a method of HIV prevention that works by reducing the availability of target cells for the virus at the site of exposure. ■ Results from a pilot study (NCT02079077) were published in *Frontiers in Immunology* in November 2021, indicating that aspirin levels were detectable in the genital tract and were associated with significant declines in the proportion of activated, potentially HIV-susceptible CD4+ T cells.				

Table 2: Topical/Local PrEP and Multipurpose Technologies

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Microbicide Rings, Gels, Enemas, Films, and Other Insertables				
Dapivirine ring **NCT05416021 (relative bioavailability trial of DPV ring-004 and DPV ring-008)** **NCT03965923 (pregnant women)**	**NNRTI**	**Population Council (vaginal ring); DAIDS/MTN (rectal gel)**	**Monthly vaginal ring**	**Phase III** **Phase IIa**
■ Licensed by regulatory authorities in Kenya, South Africa, Uganda, Zambia, and Zimbabwe. ■ The Population Council acquired the rights to develop the DPV ring from IPM in October 2022. ■ Preliminary results from a demonstration project in Zimbabwe, as reported by AIDSMap, suggest the HIV incidence among users over the first six months was similar to that observed with oral PrEP in other studies. ■ Results from the ongoing study in pregnant women were presented at CROI 2023. The study abstract concludes: "adverse pregnancy outcomes and complications were uncommon when DVR [dapivirine ring] and TDF/FTC [Truvada] were used in the third trimester of pregnancy and were similar to rates observed in the communities where the study is being conducted. These data support plans for subsequent investigation of DVR safety earlier in pregnancy." ■ A phase IIIb safety evaluation of monthly DPV ring in pregnant women and breastfeeding mother-infant pairs has been completed. Results were presented at CROI 2023, reporting a favorable safety profile. ■ Results from the REACH study reporting high acceptability among adolescent girls and young women were presented at CROI 2022. ■ Acceptability data from the ASPIRE efficacy trial were published in the journal *AIDS and Behavior* in March 2021. ■ Phase I MTN-036/IPM 047 assessed the potential of a three-month vaginal ring. Results were presented at CROI 2021, demonstrating that the extended-duration rings were well tolerated and achieved higher DPV levels compared with monthly rings, supporting further evaluation. Acceptability data were published in *PLoS One* on February 22, 2022. A larger trial comparing the standard ring with a three-month version containing a DPV dose of 100 mg is now recruiting 110 women in South Africa. ■ The phase I trials MTN-026 and MTN-033 investigated a rectal DPV gel in men and women. Results from MTN-026 were presented at R4P 2021 and published in the journal *AIDS Research and Human Retroviruses* in April 2022. Rectal tissue concentrations were found to be inadequate, and the study authors concluded that "a long-acting reformulation or higher dose is likely needed to provide protection from anal sex." Similar findings from MTN-033 were published in the journal *Antimicrobial Agents and Chemotherapy* in October 2022.				
TAF/EVG **NCT04047420**	**NRTI/INSTI**	**CONRAD and MTN**	**Vaginal or rectal insert**	**Phase I**
■ A phase I trial of the rectal insert (MTN-039) evaluating safety, acceptability, and concentrations of drug in the rectal tissue has recently been completed. Results were presented at CROI 2023 (see abstract and related press release), indicating safety and the potential to suppress HIV infection of rectal tissue for up to three days. ■ Results from a previous phase I study of the vaginal insert were published in April 2023, reporting that the intervention was found safe and acceptable and achieved drug concentrations that support further development. ■ According to an interview with Dr. Sharon Riddler by Juan Michael Porter II for TheBodyPro.com, the study sponsor CONRAD is planning additional studies of multiple doses administered over time.				

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Tenofovir **HPTN 106 (in development)**	**NtRTI**	**Johns Hopkins University/HPTN**	**Enema**	**Phase I**

- A phase II study is being planned by the HIV Prevention Trials Network (HPTN 106). The projected date for starting enrollment is September 2023.
- Results of DREAM-01 were presented at the 2018 R4P conference. The study was a phase I, open-label, dose-escalation, and variable osmolarity study to compare the safety, PK, PD, and acceptability of three formulations of a TFV enema. All three produced tissue concentrations above target levels and were well tolerated with no grade 2 or greater adverse events reported.
- Results from another phase I trial, DREAM-03, were presented as a poster at CROI 2022. The investigators reported that a TFV douche prior to receptive anal sex produced good drug coverage of the colorectal tract. Based on their results, the authors recommend administration prior to receptive anal sex in future studies.
- DREAM-02, a third phase I study assessing the TFV enema used in sequence with tap water enemas, has been completed with results pending.
- A phase I study of the safety, PK, PD, and acceptability of a one-dose TFV douche in adolescents aged 15–24 (ATN DREAM) has been completed, results are pending.

Griffithsin **NCT04032717** **(Q-Griffithsin rectal douche)**	**Cell-viral fusion-blocking agent**	**U19 University of Louisville/ University of Pittsburgh**	**Rectal douche**	**Phase I**

- A phase I study was stopped early because of the COVID-19 pandemic. An analysis of effects on rectal tissue integrity and local CD4+ T cells was published in the journal *Scientific Reports* in May 2023, reporting no evidence of adverse effects.

OB-002H	**CCR5 antagonist**	**Orion Biotechnology**	**Vaginal and rectal gel**	**Phase I**

- A study published in 2009 reported prevention of vaginal transmission of SHIV SF162P3 in a macaque model.
- At the 2021 R4P conference, results were presented from a phase I trial assessing the safety, acceptability, and PK profile of single and multiple doses administered either vaginally or rectally. Local adverse events were reported to be mild and transient, and there was no systemic absorption. A majority of the 30 participants found the gel acceptable and would consider use for HIV prevention if licensed. Study results were published in *AIDS Research and Human Retroviruses* on April 30, 2021.
- In December 2021, Orion Biotechnology announced a partnership with Evofem Biosciences that will assess the combination of OB-002H with Phexxi vaginal gel, with the aim of developing an MPT.

Multipurpose Technologies

Tenofovir + levonorgestrel **NCT03762382**	**NtRTI/HC**	**CONRAD**	**Vaginal ring**	**Phase IIa**

- CONRAD has completed two phase I, safety, PK, and PD studies of the TFV/LNG IVR. Favorable results from a one-month evaluation were published in *PLoS One* in June 2018, and similarly positive findings from a 90-day study were presented at R4P 2021. Full results from the 90-day assessment were published in *Frontiers in Cellular and Infection Microbiology* in March 2022.
- The CDC and CONRAD are collaborating on a phase IIa, 90-day safety, adherence, and acceptability study of IVRs releasing TFV with and without LNG among women in western Kenya (NCT03762382). A presentation of interim results at R4P 2021 indicated that the IVRs were safe and delivered drug levels likely to be associated with prevention of HIV and pregnancy. Results published in the journal *Scientific Reports* in July 2022 indicate that the IVRs were safe and didn't adversely affect genital microbiota. Results from an acceptability substudy were published in September 2022.

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
DPP capsule (dual prevention pill containing Truvada PrEP and combined oral contraceptive) **NCT04778514** **NCT04778527**	**NtRTI/HC**	**Population Council**	**Oral**	**Phase II**
■ Being developed by a coalition of partners for prevention of pregnancy and HIV infection in high-need countries. ■ Two phase II crossover trials comparing acceptability of DPP capsule versus individual PrEP and contraceptive pills among adolescent girls and young women are now recruiting, one located in Zimbabwe and the other in South Africa.				
Dapivirine + levonorgestrel **NCT05041699**	**NNRTI/HC**	**Population Council**	**Three-month vaginal ring**	**Phase Ia**
■ A phase I study evaluating PK and safety of a vaginal ring containing DPV and LNG (MTN-030/IPM 041) was completed in 2017, with results presented at the 2018 R4P conference (abstract OA12.02LB). A 14-day period of evaluation showed the ring to be well tolerated and that it achieved the desired drug levels. ■ A phase I study of 90-day administration either continuously or on a cyclic schedule (28 days in/two days out) was completed in October 2019 (MTN-044/IPM 053/CCN019, NCT03467347). Results demonstrating achievement of drug levels predicted to be efficacious in preventing HIV and pregnancy were presented at R4P 2021. The products were safe, with only one grade 4 adverse event reported (anemia related to cyclic use). ■ A 90-day phase Ib study of the safety and PK of two different vaginal ring formulations (NCT05041699) is now recruiting at sites in Oregon and Pennsylvania.				
PC-6500 (0.1% griffithsin in a carrageenan gel)	**Cell-viral fusion-blocking agent**	**Population Council**	**Vaginal gel**	**Phase I**
■ The Population Council has completed a phase I study evaluating the safety of griffithsin for vaginal use. Results were published in *PLoS One* in January 2022, with the product reported to be safe. Cervicovaginal lavage samples from study participants were capable of inhibiting both HIV and HPV. The authors conclude that the intervention is "a safe and promising on-demand multipurpose prevention technology product that warrants further investigation."				

ABBREVIATIONS

CAB LA: long-acting cabotegravir

CDC: Centers for Disease Control and Prevention

CONRAD: Contraception Research and Development

CROI: Conference on Retroviruses and Opportunistic Infections

DAIDS: Division of AIDS

DPP: dual prevention pill

DPV: dapivirine

EVG: elvitegravir

FDA: U.S. Food and Drug Administration

FTC: emtricitabine

HC: hormonal contraception

HPTN: HIV Prevention Trials Network

HPV: human papillomavirus

IM: intramuscular injection

INSTI: integrase strand transfer inhibitor

IPM: International Partnership for Microbicides

IVR: intravaginal ring

LNG: levonorgestrel

MPT: multipurpose prevention technology

MSM: men who have sex with men

MTN: Microbicide Trials Network

NNRTI: non-nucleoside analogue reverse transcriptase inhibitor

NRTI: nucleoside analogue reverse transcriptase inhibitor

NRTTI: nucleoside reverse transcriptase translocation inhibitor

NtRTI: nucleotide analogue reverse transcriptase inhibitor

PD: pharmacodynamics

PK: pharmacokinetics

PrEP: pre-exposure prophylaxis

R4P: HIV Research for Prevention Conference

SC: subcutaneous injection

TAF: tenofovir alafenamide

TDF: tenofovir disoproxil fumarate

TFV: tenofovir