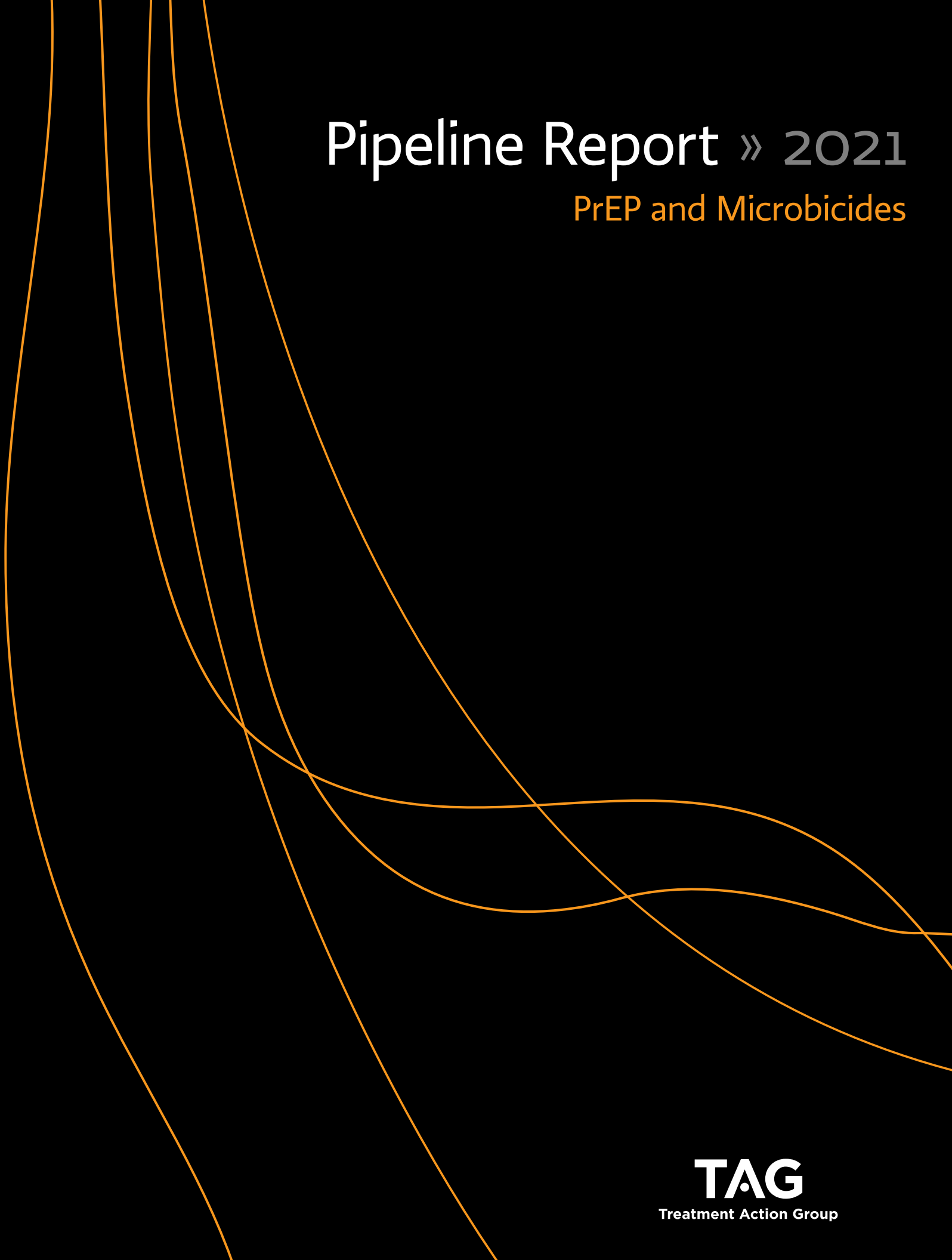
Pipeline Report » 2021

PrEP and Microbicides



TAG
Treatment Action Group

The PrEP and Microbicides Pipeline

By Richard Jefferys

The scientific development of medical interventions can sometimes become fixated on potential one-size-fits-all "home run" solutions. In the realm of biomedical HIV prevention research, community advocates have helped push back against this model, emphasizing the critical importance of creating an array of effective options that people can choose based on their individual situation. The PrEP and microbicide pipelines reflect the pursuit of diverse approaches, including oral, injectable, and topical candidates.

Despite the COVID-19 pandemic, 2020 was a year of exceptional progress in HIV prevention research. The most significant news in microbicide development is that, in July 2020, the dapivirine vaginal ring received a positive opinion from the European Medicines Agency (EMA) for use by cisgender women aged 18 and over in high-burden developing countries "when oral pre-exposure prophylaxis (PrEP) is not used, cannot be used or is not available." This was followed by the addition of the dapivirine vaginal ring to the World Health Organization (WHO) list of prequalified medicines, and in January 2021, the WHO issued a recommendation for the ring as "a new choice for HIV prevention for women at substantial risk of HIV infection."

The International Partnership for Microbicides (IPM) is now seeking regulatory approval for the ring in Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe. For Eswatini and Lesotho, IPM is taking steps to make the ring available under national import license processes. An application to the U.S. Food and Drug Administration (FDA) was submitted in December 2020.

A number of trials aimed at facilitating implementation of the dapivirine vaginal ring are ongoing (see Table 2). Results from the DREAM and HOPE open-label extension studies that followed the two efficacy trials were published in *Lancet HIV* in February 2021. Modeling studies indicate that the dapivirine vaginal ring could contribute to further lowering HIV incidence in populations at risk and importantly, it would represent the first woman-controlled, long-acting HIV prevention method (the ring is replaced once a month).

The future of microbicide research more broadly is clouded by the upcoming closure of the Microbicide Trials Network (MTN) at the end of November 2021. The primary sponsor of the MTN, the National Institute of Allergy and Infectious Diseases (NIAID), recently restructured HIV clinical trials networks and did not include an option for the MTN to reapply, a decision that activists protested. NIAID ultimately extended support for the MTN for an additional year, but going forward, prevention trials will primarily be conducted under the aegis of either the HIV Prevention Trials Network (HPTN) or the HIV Vaccine Trials Network (HVTN). NIAID has not ruled out future microbicide trials by the HPTN, but it has outlined several criteria that would need to be met, including comparable efficacy to oral PrEP.

The PrEP landscape is also changing. At the time of our last pipeline report, news had just emerged that the long-acting integrase inhibitor cabotegravir (CAB LA) demonstrated non-inferiority to Truvada PrEP in the HPTN 083 trial, which recruited 4,566 cisgender men and transgender women who have sex with men. Since that initial announcement, the picture has improved: In an extended analysis presented at the virtual AIDS 2020 conference in July 2020, injections of CAB LA every eight weeks showed superior efficacy to Truvada PrEP. Out of 52 participants who acquired HIV, 13 were in the CAB LA arm compared with 39 in the Truvada arm. The HIV incidence rates were 0.41% and 1.22%, respectively, which equated to a 66% lower incidence among CAB LA recipients. Adverse events among those receiving CAB LA primarily included fever and mild injection site pain and tenderness.

Additional analyses reported at AIDS 2020 found that the efficacy of CAB LA was consistent across different populations and regions. The trial took place in Argentina, Brazil, Peru, South Africa, Thailand, the U.S., and Vietnam. In the U.S., 50% of the participants were Black or African American. Two-thirds of participants were under 30 years of age, and 12% identified as transgender women.

On November 9, 2020, results were announced from a complementary CAB LA PrEP trial in cisgender women (HPTN 084). Again, CAB LA achieved superiority compared with Truvada. Out of 3,223 participants, 38 acquired HIV during the trial—four in the CAB LA arm versus 34 in the Truvada arm. Calculated as HIV incidence rates, the comparison was 0.21% for CAB LA and 1.79% for Truvada, indicating an 89% reduction in incidence among those receiving CAB LA. The trial originally planned to continue through 2022 but was truncated on the recommendation of the Data Safety Monitoring Board after an interim review revealed CAB LA's superiority. Details were subsequently reported at the 2021 HIVR4P conference, adding information on adverse events, which were mainly mild injection site reactions. There were a small number of pregnancies among participants, without evidence of congenital abnormalities.

ViiV Healthcare announced on May 4, 2021, that the company has initiated a rolling submission of a new drug application to the FDA for CAB LA PrEP. The adoption of a rolling submission approach allows ViiV to submit portions of the application for review as they're completed, continuing the process until all the required documentation is in the FDA's hands. The aim is to accelerate the timeline for approval, which appears likely to occur later this year.

An important priority for researchers is to understand the mechanism for the relatively small number of breakthrough infections among CAB LA recipients. At the 2021 Conference on Retroviruses and Opportunistic Infections (CROI), investigator Raphael Landovitz described the status of this work from HPTN 083. Importantly, he revealed that one of the people with HIV infection in the CAB LA arm was belatedly discovered to have already been infected at study entry. This slightly alters the final results, making the comparison 12 HIV infections in the CAB LA arm versus 39 in the Truvada arm, and a 68% (rather than 66%) reduction in HIV incidence among CAB LA recipients.

The person in question had initiated CAB before seroconversion to HIV-positive on a confirmatory antibody test, and receipt of the drug suppressed viral load and delayed diagnosis. However, resistance to CAB was not observed. In another case of baseline HIV infection that wasn't mistakenly included among the originally reported trial endpoints, resistance to CAB did develop as a result of the person's receiving a period of monotherapy before the diagnosis, but viral load was successfully suppressed after initiation of an ART regimen including a boosted protease inhibitor.

Landovitz also outlined three instances of HIV acquisition in HPTN 083 that occurred during the "tail phase" of declining CAB levels, due to delayed receipt of a scheduled injection. Encouragingly, no integrase inhibitor resistance mutations were observed in these three people even though there was a period of exposure to suboptimal CAB LA levels. Only four trial participants acquired HIV infection during receipt of CAB LA despite adequate drug levels. In two cases, evidence emerged of mutations associated with resistance to integrase inhibitors; in the remaining two, analyses of mutations in the virus integrase gene were not possible because of low levels of HIV. All four subsequently suppressed viral load on non-integrase ART regimens. Details on all the HIV infections that occurred among HPTN 083 participants will be forthcoming in a paper in the *Journal of Infectious Diseases*.

The potential for partial suppression of HIV replication and delayed antibody seroconversion suggests a need to use viral load testing to screen for HIV infection before and during CAB LA PrEP, and this approach will be evaluated in the open-label extension phase of the HPTN 083 trial. Experimental home viral load tests that are being evaluated for monitoring HIV rebound during cure-related analytical treatment interruption trials might also deserve consideration as a monitoring tool for recipients of CAB LA (or any long-acting PrEP intervention), if they can be enhanced to detect low enough levels of HIV.

An alternative method of delivering CAB via implant has been assessed in preclinical macaque and rat studies. The implant was reported to be well tolerated, with the potential for stable release of drug for at least six months and potentially up to a year. The study authors note that drug levels rapidly declined after implant removal, suggesting that if the approach can be developed for human use, it could avoid the issue of a prolonged CAB tail that is seen with the injectable LA formulation.

Toward the end of 2020, two phase III efficacy trials were launched evaluating monthly oral dosing of Merck's islatravir for PrEP. Islatravir is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) that potently inhibits HIV reverse transcriptase via multiple mechanisms. Interim results of a phase IIa trial in men and women at low risk for HIV infection were presented at HIVR4P 2021, indicating that monthly dosing of either 60 mg or 120 mg of islatravir was well tolerated and maintained levels likely to be associated with protection against HIV.

The 60 mg dose has been selected for the efficacy trials, both of which will compare islatravir to Truvada PrEP. The Impower-022 trial aims to enroll 4,500 cisgender women at high risk of HIV infection, while Impower-024 is recruiting 1,500 cisgender men and

transgender women who have sex with men and are at high risk of HIV infection. Both studies have estimated completion dates in 2024. Merck is also continuing preclinical evaluations of implant delivery methods for islatravir, with a view to creating a PrEP option that requires renewal only once a year.

The newest addition to the PrEP pipeline is lenacapavir, a long-acting drug developed by Gilead Sciences that inhibits the HIV capsid protein (an internal component of the virus that shields its genetic material). Lenacapavir injections every six months have been shown to be safe and active in HIV treatment studies. At the IDWeek 2020 conference, Gilead announced plans for two efficacy trials of lenacapavir for PrEP. The first will involve adding a lenacapavir arm to the Women's HIV Prevention Study, which the company was already designing to assess its drug Descovy as PrEP. The plan is to enroll adolescent girls and young women at risk of HIV infection in South Africa and Uganda. The second trial is the men who have sex with men (MSM) and persons of trans experience lenacapavir for PrEP study, with sites likely to include South Africa and the U.S. The launch date for both studies is anticipated to be mid- to late 2021.

Returning to the opening theme of one size not fitting all, results from one of the last MTN studies (035) were presented at CROI 2021 by José Bauermeister. The research didn't involve investigating a specific candidate in the pipeline, but rather examined the acceptability, tolerability, and adherence of three different non-gel rectal microbicide placebo delivery methods (an insert, suppository, and enema) among 217 young MSM and transgender people in five countries (Malawi, Peru, South Africa, Thailand, and the U.S.). All of these modalities have the potential to deliver PrEP locally before receptive anal sex, and the goal was to gain insight into which might be preferred among participants.

Participants were asked to use each modality 30 minutes to three hours before receptive anal sex (or once a week in the absence of receptive anal sex). Taking a market research approach, the researchers identified several key features of a preferred product profile: an enema that could be employed around 30 minutes before receptive anal sex with high (>95%) protective efficacy lasting three to five days, with no side effects, and available over the counter. Importantly, however, preferences were situational, with variations related to circumstances. For example, inserts had a high appeal when discretion might be needed (because of their small size and ease of carriage), while suppositories had a lubricant effect that would lead to their selection in circumstances when other lubricants might be unavailable.

Sadly, the de-prioritizing of microbicide research by NIAID leaves a great deal of uncertainty as to whether these insights can be applied to develop topical products that suit the needs expressed by communities who would stand to benefit from them. There is arguably an awkward contrast with the investment in broadly neutralizing antibodies for HIV prevention, the first of which (VRC01) recently failed to show significant protective efficacy in two large and expensive clinical trials (see TAG's HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline Report for additional details and commentary). Hopefully, despite the closing of MTN, other sources can support the continued development of a full spectrum of potential HIV prevention choices.

Table 1: Pre-Exposure Prophylaxis (PrEP)

Agent	Class/Type	Manufacturer/ Sponsor	Delivery	Status
Cabotegravir NCT03164564 (cisgender women) NCT02720094 (MSM and transgender women) NCT04692077 (adolescents assigned male at birth) NCT03422172 (Chinese men)	INSTI	ViiV Healthcare	IM	Phase III (HPTN 084) Phase IIb/III (HPTN 083) Phase II Phase I
■ New drug application initiated with FDA on May 4, 2021. ■ Results from HPTN 083 and 084 reported at AIDS 2020 and R4P 2021 respectively (see main report text). ■ A substudy of HPTN 83 was launched in December 2020 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. Enrollment target is 50 participants, and the estimated completion date is August 2022. ■ A phase I trial assessing pharmacokinetics (PK), safety, tolerability, and acceptability of CAB LA in adult Chinese men at low risk for HIV acquisition has been completed. Results were submitted to clinicaltrials.gov on April 13, 2021.				
Islatravir (MK-8591) NCT04644029 (Impower-022) NCT04652700 (Impower-024) NCT04003103	NRTTI	Merck	Monthly oral PrEP, implant	Phase III Phase IIa
■ Islatravir is an investigational antiretroviral drug classed as a nucleoside reverse transcriptase translocation inhibitor (NRTTI). The drug is reported to be highly potent with a long half-life, making it suitable for intermittent dosing. Safety has been demonstrated in treatment trials. ■ Studies of tissue drug concentrations and challenge experiments in macaques support the potential for use as PrEP. ■ Positive interim results reported at R4P 2021 from the ongoing phase IIa trial assessing safety, tolerability, and PK of once-monthly oral doses of either 60 mg or 120 mg compared with placebo in adults at low risk for HIV infection. ■ Two phase III efficacy trials underway recruiting cisgender women (Impower-022), cisgender men and transgender women who have sex with men (Impower-024). ■ An implant formulation is also in development. Phase I testing of a prototype implant showed potential for once-yearly administration.				
Genvoya (EVG + COBI + FTC + TAF) NCT02985996	INSTI/NtRTI/NRTI	Emory University	Oral PrEP	Phase I
■ Results from phase I trial included in a paper published in *EBioMedicine* in July 2020. Based on tissue drug levels, the study authors suggest that Genvoya may represent a potential "single-dose before or after sex HIV prevention regimen" but note that additional trials are needed.				
Aspirin NCT03629327	Nonsteroidal anti-inflammatory	University of Manitoba	Oral	N/A
■ Trial planning to recruit 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.				

Table 2: Topical/Local PrEP and Multipurpose Technologies

Agent	Class/Type	Manufacturer/ Sponsor	Delivery	Status
Microbicide Rings, Gels, Enemas, Films, and Other Insertables				
Dapivirine NCT03965923 (pregnant women) NCT04140266 (breastfeeding mother-infant pairs) NCT03593655 (adolescent and young adult females) NCT03234400 (three-month vaginal ring) NCT03239483 NCT03393468 (MTN-026 and MTN-033, rectal gel)	NNRTI	IPM (vaginal ring/ gel/film); DAIDS/ MTN (rectal gel)	Monthly vaginal ring	Phase IIIb Phase IIa
			Three-month vaginal ring	Phase I
			Rectal gel	Phase I
■ Phase IIIb safety evaluations of monthly dapivirine (DPV) ring are ongoing in pregnant women and breastfeeding mother-infant pairs. ■ Acceptability data from the ASPIRE efficacy trial 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. ■ 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. 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 were reported from MTN-033 at the same conference.				
TAF/EVG NCT04047420	NRTI/INSTI	CONRAD and MTN	Rectal insert	Phase I
■ A phase I trial (MTN-039) evaluating safety, acceptability, and concentrations of drug in the rectal tissue completed follow-up on April 7, 2021. Results are pending.				
Tenofovir NCT04195776 (DREAM-02) NCT04016233 (DREAM-03) NCT04686279 (ATN DREAM)	NtRTI	Johns Hopkins University	Enema	Phase I
■ Results of DREAM-01 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. ■ Another phase I trial, DREAM-03, is underway, evaluating a single dose of the TFV enema in different sequences of administration with a nonmedicated enema. ■ DREAM-02, a third phase I study assessing the TFV enema used in sequence with tap water enemas, is not yet enrolling. ■ A phase I study of the safety, PK, PD, and acceptability of a one-dose TFV douche in adolescents aged 15–24 (ATN DREAM) was registered in clinicaltrials.gov on December 28, 2020, but is yet to begin enrolling.				

Agent	Class/Type	Manufacturer/ Sponsor	Delivery	Status
IQP-0528 NCT03082690	NNRTI	ImQuest U19	Rectal gel	Phase I
▪ A phase I study looking at safety and PK for rectal use of IQP-0528 completed in June 2019. Results were published in *AIDS Research and Human Retroviruses* in January 2021, demonstrating safety and tissue concentrations above the target for HIV inhibition lasting ~3–24 hours after dosing. In three female participants, rectal administration did not lead to detectable levels in cervicovaginal tissue. The study authors suggest that the short half-life of the drug may make it better suited to episodic use.				
Griffithsin NCT04032717 (Q-Griffithsin enema)	Cell-viral fusion-blocking agent	Population Council (vaginal gel) U19 University of Louisville/ University of Pittsburgh (enema)	Enema	Phase I
▪ The Population Council has completed a phase I study evaluating the safety of griffithsin (GRFT) for vaginal use. Results were presented at the 2018 R4P conference, indicating that the product was well tolerated without any evidence of GRFT detectable in plasma (see Friedland et al., abstract P05.19LB, AIDS Research and Human Retroviruses 2018 34:S1). ▪ A freeze-dried vaginal insert formulation has shown protective efficacy in a preclinical study involving macaques and mice. The insert is being developed for human trials. ▪ In July 2019, the PREVENT rectal microbicide program operated by the University of Louisville and the University of Pittsburgh began a clinical trial using an enema containing a genetically modified version of griffithsin designed to be more stable and resistant to oxidation (Q-GRFT). Unfortunately, the trial had to be prematurely terminated because of the COVID-19 pandemic.				
DS003 NCT02877979	EI	IPM	Vaginal tablet	Phase I
▪ Phase I IPM 042 was a double-blind, randomized, placebo-controlled, dose-escalation trial to evaluate the safety and PK of DS003 vaginal tablets administered to healthy HIV-negative women. Results were presented at the 2018 R4P conference, showing safety and achievement of potentially protective drug levels in tissues (see Chantél et al., abstract P05.08 and Nuttall et al., abstract P21.02, *AIDS Research and Human Retroviruses 2018 34:S1*). ▪ Considered as a candidate for combining with dapivirine in a vaginal ring, but research currently paused because of funding limitations. ▪ An ethylene vinyl acetate ring demonstrated very limited release of DS003 in a preclinical study presented at R4P 2021.				
MK-2048/Vicriviroc (MK-4176)	CCR5 inhibitor/ INSTI	MTN	Vaginal ring	Phase I
▪ Results from two phase I trials published in Clinical Infectious Diseases in April 2019, see Liu et al. and Hoesley et al. The rings were safe and well tolerated during short-term use and achieved inhibitory concentrations in tissues. However, ex vivo inhibition of HIV could not be demonstrated using tissue samples, possibly because of technical issues.				
MK-2048 NCT04319718	INSTI	NIAID	Vaginal film	Phase I
▪ Ongoing phase I trial at the University of Pittsburgh assessing the safety and PK of two different doses of an extended-release vaginal film designed to deliver drug for seven days.				
OB-002H NCT04791007	CCR5 antagonist	Orion Biotechnology	Vaginal and rectal gel	Phase I
▪ 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 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.				

Agent	Class/Type	Manufacturer/ Sponsor	Delivery	Status
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. ▪ CDC and CONRAD are collaborating on an ongoing 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.				
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 registered with clinicaltrials.gov, one located in Zimbabwe and the other in South Africa. Both are estimated to start in early 2022.				
Dapivirine + levonorgestrel NCT03467347	NNRTI/HC	IPM	Three-month vaginal ring	Phase I
▪ Phase I study evaluating PK and safety of a vaginal ring containing DPV and LNG (MTN-030/IPM 041) 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 achieved the desired drug levels. ▪ 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).				
MB66 NCT02579083	Anti-HIV + anti-HSV antibodies	LeafBio, Inc.	Vaginal film	Phase I
▪ MB66 combines monoclonal antibodies specific for HIV (VRC01-N) and herpes simplex virus (HSV8-N) in a film for vaginal application as microbicide. ▪ Phase I study assessing safety, PK, and PD completed in July 2018, with results published in the journal *PLoS Medicine* in February 2021. MB66 was found to be well tolerated with antibody levels considered likely to be protective maintained for 24 hours after administration.				
PC-1005 NCT03408899 (rectal gel)	NNRTI, ZA, CGN	Population Council/MTN	Rectal gel	Phase I
▪ PC-1005 is a multipurpose prevention microbicide to prevent HIV, HPV, and HSV-2 acquisition. ▪ A phase I trial, MTN-037, evaluated the safety and PK of a rectal PC-1005 gel. Results reported at R4P 2021 showed that while the gel was well tolerated, the rectal tissue concentrations were transient and did not reach the target threshold for protective efficacy. The researchers concluded that "a longer-acting reformulation delivering more MIV-150 to rectal tissues is likely needed to support further development of PC-1005 as an on-demand HIV rectal microbicide."				

ABBREVIATIONS

CDC: the Centers for Disease Control and Prevention

CGN: carrageenan

CONRAD: Contraception Research and Development

CROI: Conference on Retroviruses and Opportunistic Infections

DAIDS: Division of AIDS

DPV: dapivirine

EI: entry inhibitor

EVG: elvitegravir

FTC: emtricitabine

GRFT: griffithsin

HC: hormonal contraception

HSV: herpes simplex virus

IM: intramuscular

INSTI: integrase strand transfer inhibitor

IPM: International Partnership for Microbicides

LNG: levonorgestrel

MTN: Microbicide Trials Network

NIAID: National Institute of Allergy and Infectious Diseases

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

TAF: tenofovir alafenamide

TDF/FTC: tenofovir disoproxil fumarate/emtricitabine

TFV: tenofovir

ZA: zinc acetate