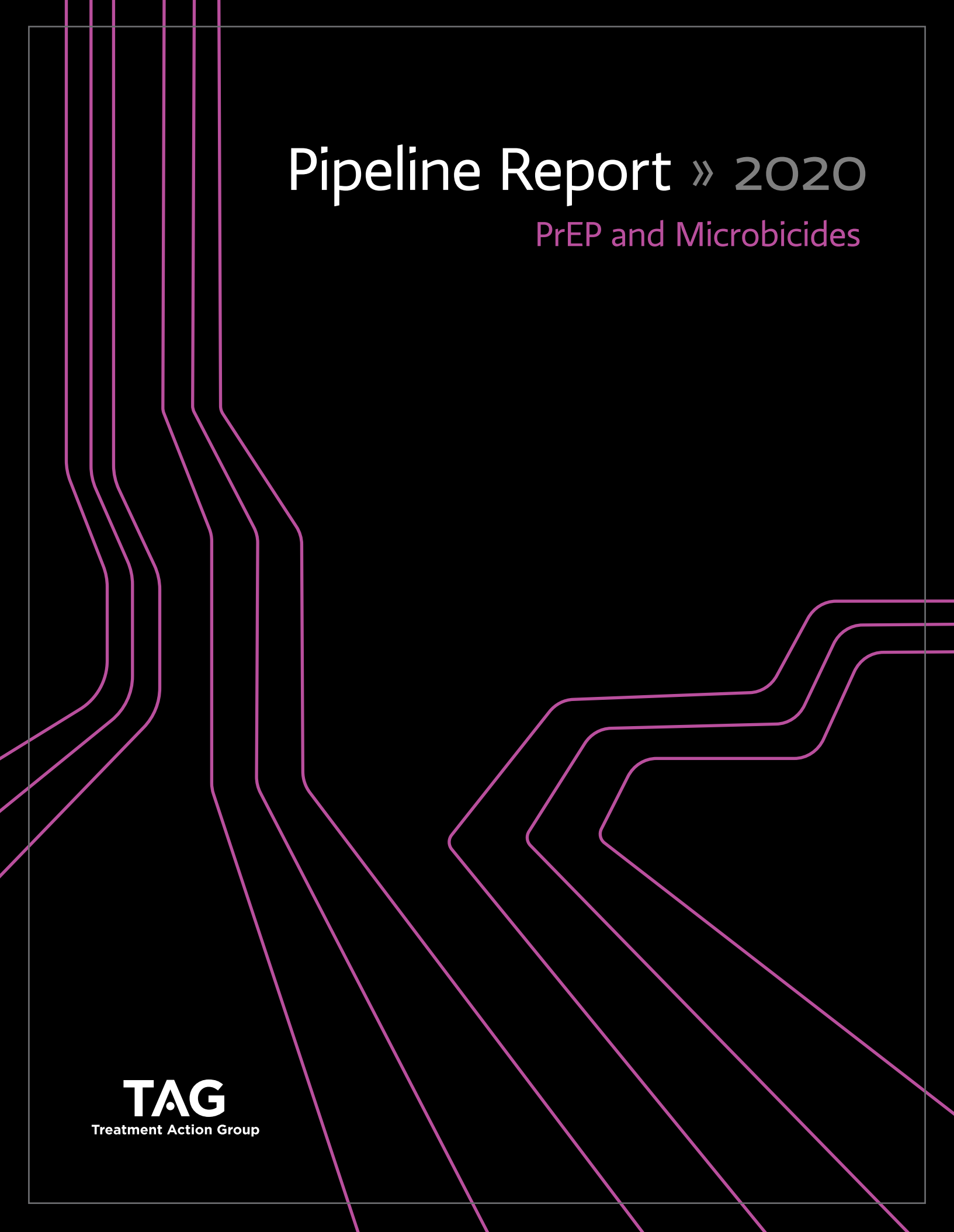
Pipeline Report » 2020

PrEP and Microbicides



TAG
Treatment Action Group

PrEP and Microbicides Pipeline 2020

By Richard Jefferys

The major news for pre-exposure prophylaxis (PrEP) over the past year was the May 18, 2020 announcement of highly anticipated results from the HIV Prevention Trials Network (HPTN) 083 study, which compared bimonthly administration of the long-acting injectable integrase inhibitor cabotegravir (CAB LA) with daily Truvada in 4,570 cisgender men and transgender women who have sex with men.

Over two years of follow up, 12 HIV infections occurred in the CAB LA arm and 38 in the Truvada arm. Expressed as HIV incidence rates, the difference was 0.38% (95% confidence interval [CI] 0.20% - 0.66%) versus 1.21% (95% CI 0.86% - 1.66%). The results met the trial's pre-specified statistical criteria for non-inferiority of CAB LA relative to Truvada and came close to reaching the threshold for superiority.

Trial investigator and protocol chair Raphael Landovitz has noted that it will be important to analyze the circumstances surrounding the 12 HIV infections that occurred in CAB LA recipients. The HPTN 083 announcements do not state whether any participants missed CAB LA injections or provide information on adherence to the initial 5-week lead-in period of oral CAB dosing. Lower body mass index has been associated with more rapid clearance of CAB LA and could be a factor. There is also the possibility of acquisition of HIV variants resistant to CAB LA.

A press release from ViiV Healthcare provided limited information on safety outcomes: The majority of CAB LA recipients (80%) reported pain or tenderness associated with injections, which are delivered into the gluteus (buttock) muscles, compared to 31% of participants in the Truvada arm (who received placebo injections). Injection site reactions or intolerance led to discontinuation for 2% of participants in the CAB LA arm. As yet there is no information available regarding any other CAB LA side effects during the trial.

HPTN 083 successfully enrolled an impressively diverse cohort from seven countries (Argentina, Brazil, Peru, Thailand, the U.S., Vietnam, and South Africa). Two-thirds of participants were under 30 years of age and 12% identified as transgender women. In the U.S., half of the participants identified as Black or African American.

The results represent a potentially important advance because CAB LA would be the first longer-acting option for individuals for whom daily or even "on demand" oral PrEP use is challenging. As outlined in a TAG statement released in response to the HPTN 083 announcement, a number of issues remain to be addressed. Chief among them is efficacy in cisgender women, which is being evaluated in the ongoing HPTN 084 study (results are expected in 2023). Optimal approaches to implementation will need to be determined as there are complex logistics associated with starting and stopping CAB LA, with transient oral dosing periods required to cover suboptimal drug levels.

U.S. FDA approval of CAB LA for treatment (in combination with long-acting rilpivirine) has been delayed by manufacturing issues related to efforts to scale up production.

ViiV Healthcare is working with the FDA to resolve the problem. The combination has received approval for the treatment of HIV in Canada which suggests that any issues are surmountable. Information is not yet publicly available on the timeline for ViiV Healthcare seeking approval of CAB LA for PrEP, or the price they intend to charge.

Another significant recent PrEP development was the October 3, 2019 U.S. approval of Descovy (emtricitabine and tenofovir alafenamide) in men and transgender women. The Food and Drug Administration (FDA) declined to approve Descovy for "those who have receptive vaginal sex" because the phase III non-inferiority trial that compared Descovy to Truvada PrEP (named Discover) did not enroll cisgender women, transgender men, or non-binary people with vaginas. In seeking approval for cisgender women the manufacturer, Gilead, could only offer pharmacokinetic data from a phase I study conducted by CONRAD. The FDA did not consider these results sufficient evidence that protective drug levels are achieved in the female genital tract (see FDA background documents).

The failure of Gilead to conduct a non-inferiority Descovy trial in cisgender women has caused justifiable outrage (see the excellent articles by Anna Forbes in *ReWire News* and Dr. Oni Blackstock in *STAT News*). In response, Gilead have issued a statement in which they commit to conducting a trial including cisgender women and adolescent females, claiming "the company has agreed with the FDA on the framework of an innovative trial design," but no such study has yet begun.

Extended follow-up from the Discover trial was presented at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI). Descovy's non-inferiority was maintained through 96 weeks with some evidence of lesser effects on bone mineral density and kidney biomarkers compared to Truvada. Greater weight gain (average ~1kg) was observed in the Descovy arm. An important cost-effectiveness analysis by Rochelle P. Walensky and colleagues has shown that the very limited advantages of Descovy over Truvada do not justify its high cost. Generic Truvada is expected to become available later in 2020 when the drug goes off-patent, and TAG has cautioned Gilead against claiming Descovy is safer or more effective in order to try to preserve the company's PrEP market share.

The newest addition to the PrEP pipeline is Merck's islatravir (formerly MK-8591), a nucleoside reverse transcriptase translocation inhibitor (NRTTI). The drug inhibits HIV reverse transcriptase via multiple mechanisms and has been reported to be extremely potent with a long half-life suitable for intermittent dosing. Safety and activity have been reported in phase I and phase II treatment trials. Merck have now launched the first clinical trial of monthly oral dosing in HIV-negative volunteers at low risk for HIV infection as a prelude to potentially evaluating efficacy as PrEP. The company is also developing an implant formulation; results from a phase I trial of a prototype version suggest once-yearly administration might be a possibility.

A research group led by Keith Fowke at the University of Manitoba is pursuing a novel approach to PrEP using a drug that does not specifically target HIV. The researchers found that administration of the ancient non-steroidal anti-inflammatory drug aspirin

can significantly diminish the proportion of CD4+ T cells expressing CCR5, the primary HIV co-receptor, in the female genital tract. Based on this finding, they have designed a larger trial, due to start enrolling this year, that will recruit 300 women in Nairobi. The hope is that reducing the number of potential target cells for HIV in the genital tract can offer an alternate route to preventing infection.

On the microbicide front, the dapivirine vaginal ring remains the most advanced candidate. In June 2017, the International Partnership for Microbicides (IPM) applied to the European Medicines Agency (EMA) for a review under Article 58, a mechanism that allows EMA to collaborate with the World Health Organization (WHO) to provide a scientific opinion on the use of the dapivirine vaginal ring in low- and middle-income countries. The EMA is expected to announce the outcome of the review in 2020. IPM is also planning to submit applications to the FDA and the South African Health Products Regulatory Authority (SAHPRA).

The final results from two open label follow-up studies—HOPE and DREAM—sugges t enhanced adherence and possibly a greater effect on incidence than was seen in the phase III study. Modeling indicates an HIV incidence reduction of 39% in HOPE and 63% in DREAM, compared to the 27% efficacy reported in the randomized, controlled trial.

Further research is ongoing, including an important assessment of the safety of the dapivirine ring compared to Truvada PrEP in pregnancy that has completed enrollment and is now in follow up. In addition to testing the dapivirine ring, the trial represents the most comprehensive evaluation of Truvada PrEP in pregnancy (two other trials are planned but have yet to start, see NCT03834909 and NCT03902418). A follow-up study comparing the safety of the dapivirine ring and Truvada PrEP in breastfeeding mother-infant pairs is due to start in 2020. Another ongoing trial is assessing safety and adherence outcomes with the dapivirine ring compared to Truvada PrEP in 300 adolescent and young adult females.

A broad range of other topically applied candidates are under evaluation, including gels, films, enemas, and inserts (see table 2).

An overarching concern for these pipelines is that the current COVID-19 crisis is likely to affect all ongoing clinical research. Statements issued by the HIV Prevention Trials Network (HPTN) and the Microbicide Trials Network (MTN) explain that, in general, new studies are on hold while screening and enrollment in ongoing trials is paused. Protocol teams are working on safe and feasible means to ensure continued follow up of currently enrolled participants. The MTN has also provided information on the status of individual trials. The Division of AIDS at the National Institute of Allergy and Infectious Diseases and the FDA have both issued guidance on responding to the current challenging situation The full extent of the impact of COVID-19 on research will not be clear until the pandemic abates.

Table 1: Pre-Exposure Prophylaxis (PrEP)

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Raltegravir Raltegravir + lamivudine NCT03205566	INSTI INSTI/NRTI	Guy's and St Thomas' NHS Foundation Trust	Oral PrEP	Phase IV
■ Phase IV trial determining ex vivo protection in genital tissue with a seven-day course of raltegravir or raltegravir + lamivudine. ■ Results presented at the April 2019 British HIV Association (BHIVA) conference and CROI 2020. High levels of ex vivo protection were observed and the addition of lamivudine appeared to enhance activity.				
Cabotegravir NCT03164564 (cisgender women) NCT02720094 (MSM and transgender women) NCT03422172 (Chinese men)	INSTI	ViiV Healthcare	IM	Phase III (HPTN 084) Phase IIb/III (HPTN 083) Phase I
■ Results announced May 18, 2020 from the Phase IIb/III HPTN 083 study evaluating the safety and efficacy of CAB LA in HIV-uninfected men who have sex with men (MSM) and transgender women compared with oral TDF/FTC (see main report text). ■ Phase III HPTN 084 study evaluating the safety and efficacy of long-acting injectable cabotegravir (CAB LA) in HIV-uninfected cisgender women compared with oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Estimated study completion date: May 2022. ■ A phase I trial is assessing pharmacokinetics (PK), safety, tolerability, and acceptability of CAB LA in adult Chinese men at low risk for HIV acquisition (NCT03422172). ■ Results from HPTN 077 evaluating safety, tolerability, and PK of CAB LA at 800 mg and 600 mg doses published in *PLoS Medicine* in November 2018. CAB LA was generally well tolerated and achieved PK targets at both doses. Injection site reactions were common but did not cause many discontinuations of study drug.				
Islatravir (MK-8591) NCT04003103	NRTTI	Merck Sharp & Dohme Corp.	Monthly oral PrEP, implant	Phase II
■ 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. Phase II trial now underway 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. ■ 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
■ Phase I trial to determine the potential for Genvoya as a future PrEP regimen in MSM and transgender women completed September 2017. Results are pending.				
Aspirin NCT03629327	Non-steroidal 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 NCT03593655 (adolescent and young adult females) NCT03965923 (pregnant women) NCT04140266 (breastfeeding mother-infant pairs) 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
			Three-month vaginal ring	Phase I
			Rectal gel	Phase I
■ Phase IIIb safety evaluations of monthly dapivirine (DPV) ring in pregnant women (ongoing) and breastfeeding mother-infant pairs (due to start in 2020). ■ Phase I MTN-036/IPM 047 launched to assess the potential of a three-month vaginal ring. Study completed in January 2019. Results are pending. ■ Phase I MTN-026 and MTN-033 are the first studies to assess a rectal DPV gel in HIV-1-uninfected men and women. Results from MTN-026 are posted to ClinicalTrials.gov, suggesting the gel was well tolerated compared to placebo. Presentation of the results from both trials is pending.				
Tenofovir NCT03762382	NtRTI	CONRAD	Vaginal ring	Phase II
■ 2015 Phase I study evaluated the safety of the tenofovir/levonorgestrel IVR (TFV/LNG IVR), TFV-only IVR, and placebo IVR, evaluated PK of TFV and LNG, evaluated pharmacodynamic (PD) surrogates of contraceptive efficacy of LNG, and acceptability of the IVRs. Favorable results published in *PLoS One* in June 2018. ■ Phase II trial ongoing (NCT03762382). Estimated completion date: April 2020.				
TAF/Elvitegravir NCT04047420	NRTI/INSTI	CONRAD and MTN	Rectal insert	Phase I
■ A Phase I trial (MTN-039) is ongoing, evaluating safety, acceptability, and concentrations of drug in the rectal tissue. The drugs are formulated in a fast-dissolving insert. Estimated completion date is August 2020 but delays due to the COVID crisis should be anticipated.				
Tenofovir NCT04195776 (DREAM-02) NCT04016233 (DREAM-03)	NtRTI	Johns Hopkins University	Enema	Phase I
■ Results of DREAM-01 presented at the 2018 R4P conference. The trial 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 non-medicated enema. ■ DREAM-02, a third phase I study assessing the TFV enema used in sequence with tap water enemas, is not yet 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 was completed in June 2019. Results were presented at CROI 2020, demonstrating safety and tissue concentrations above the target for HIV inhibition lasting 3-6 hours after dosing. The study authors suggest that the short half-life of the drug is better suited to episodic use. In three female participants, rectal administration did not lead to detectable levels in cervicovaginal tissue.				
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 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. ■ The PREVENT rectal microbicide program, operated by University of Louisville and University of Pittsburgh, began a clinical trial involving a griffithsin-based enema in July 2019. The trial is ongoing and is using a genetically modified version of griffithsin designed to be more stable and resistant to oxidation (Q-GRFT).				
PC-1005 NCT03408899 (rectal gel)	NNRTI, ZA, CGN	Population Council/MTN	Rectal gel	Phase I
■ A Phase I trial, MTN-037, evaluated the safety and PK of a rectal PC-1005 gel. PC-1005 is a multipurpose prevention microbicide to prevent HIV, HPV, and HSV-2 acquisition. The trial was completed in April 2019. Results are pending.				
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).				
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 due to technical issues.				
OB-002H	CCR5 antagonist	Orion Biotechnology	Vaginal and rectal gel	Phase I
■ Phase I trial underway in Poland assessing safety, acceptability, and PK profile of single and multiple doses administered either vaginally or rectally.				

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
Multipurpose Technologies				
Tenofovir + levonorgestrel NCT03762382	NtRTI/HC	CONRAD	Vaginal ring	Phase IIa
■ CONRAD completed a multi-center, Phase I, 90-day safety, PK, and PD study of the TFV/LNG IVR. Favorable results published in *PLoS One* in June 2018. ■ 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). Estimated completion: April 2020.				
Dapivirine + levonorgestrel	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 at the end of 2017, with results presented at the 2018 R4P conference. A 14-day period of evaluation showed the ring to be well tolerated and achieved the desired drug levels. ■ A PK study of 90-day administration (MTN-044/IPM 053/CCN019, NCT03467347) was completed in October 2019. Results are pending.				
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 presented at CROI 2020. MB66 was found to be well tolerated with antibody levels considered likely to be protective maintained for 24 hours after administration.				

TABLE ABBREVIATIONS

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