

**TAG**

Treatment Action Group

**HIV PrEP AND MICROBICIDICALS**

**PIPELINE**

**REPORT**

**2018**



## 2018 PrEP and Microbicides Pipeline

HIV prevention has been undergoing a true revolution over the past decade. With three major studies (HPTN 052,<sup>1</sup> PARTNER,<sup>2</sup> and Opposites Attract<sup>3</sup>) now showing zero new infections linked to an HIV-positive person who has achieved viral suppression through antiretroviral treatment, it is now apparent that a person with an ‘undetectable’ HIV viral load (as measured by the most sensitive currently available commercial tests, for example, <10–20 copies/milliliter (mL) of blood) will not transmit the virus sexually.

**TDF/FTC PrEP** continues to be a game changer, with an expanding body of literature demonstrating its essential role in driving down new infections. Most notably, a rapid scale-up of PrEP in Australia that began in 2016 has corresponded with a 35 percent decline in the number of new diagnoses in gay, bisexual, and other men who have sex with men (MSM) in New South Wales, and a 44 percent decline in the number of early infections in that same population.<sup>4</sup> Even more recently, Public Health England’s preliminary data from 2015–2017 indicates a 28 percent drop in new infections over those three years, with a 31 percent drop among MSM.<sup>5,6</sup> Although youth continue to be left behind in the fight against HIV, the Food and Drug Administration’s (FDA) recent approval of PrEP for adolescents is a long overdue and essential step toward protecting this vulnerable population from HIV infection.<sup>7</sup>

Although we have made tremendous strides, the revolution is far from over. Sustainably ending HIV as an epidemic for all affected communities will require even more options for prevention, even as we continue to advocate for a vaccine and a cure. Alternative oral PrEP regimens continue to be researched, most notably **TAF/FTC** (Gilead’s ‘Descovy’); however, advocates will need to ensure that future PrEPs and other preventive technologies are priced in a way that ensures access for marginalized populations around the world. Also of note, MK-8591, a long-acting oral nucleoside reverse transcriptase translocation inhibitor (NRTTI) that may only require weekly dosing for treatment, has been shown to protect rhesus macaques against **SHIV** infection at weekly doses of 1.3 and 0.43 mg/kg, which would translate into weekly doses of less than 250 µg in humans. Clinical trials have not yet been announced for MK-8591 as PrEP, but are anticipated. With several barriers to adherence for oral PrEP limiting its efficacy for many individuals, long-acting injectable cabotegravir (CAB LA)—currently the focus of two phase III studies with results being expected in late 2021 (MSM and transgender women) and early 2022 (cisgender women)—may eventually provide the option of injections every two months as opposed to taking pills daily.<sup>8,9</sup>

In addition, for cisgender women, the promising open-label extension HOPE and DREAM studies for the dapivirine vaginal ring indicate that an important new option is on the way with an estimated 50 percent decline in the number of new infections.<sup>10,11</sup> A regulatory application for the ring was submitted to the European Medicines Agency in 2017.<sup>12</sup>

Although changes to the clinical trials network architecture and potential funding cuts threaten to significantly reduce future possibilities for microbicide research, innovative

**TDF:** The nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate, one of two medications contained in *Truvada*

**FTC:** The nucleoside reverse transcriptase inhibitor emtricitabine, one of two medications contained in *Truvada*

**PrEP:** Pre-exposure prophylaxis; any treatment(s) that may be administered **prior to exposure** that prevents the acquisition of HIV. TDF/FTC is the only FDA-approved PrEP at this time.

**TAF:** Tenofovir alafenamide, a newer form of tenofovir that Gilead Sciences hopes will replace the now off-patent TDF.

**SHIV:** Simian/human immunodeficiency virus

## ORAL FORMULATIONS

products such as enemas containing tenofovir, rectal and vaginal gels, and multipurpose technologies that may one day protect individuals from other sexually transmitted infections (STIs) and pregnancy in addition to HIV, remain in the pipeline.<sup>13</sup> Other innovations, such as long-acting implants and microneedle array patches, remain in preclinical development.

The following provides a summary of the PrEP and microbicides pipeline as of September 2018. This information is updated annually; for previous chapters on preventive technologies, visit [www.pipelinereport.org](http://www.pipelinereport.org).

### Oral Formulations

With scale-up initiatives being under way to bolster TDF/FTC awareness and use where it is approved as PrEP—along with ongoing efforts to see that the coformulation is registered and covered by national health programs in other countries—additional oral products are making their way through the biomedical prevention pipeline.

The advantages of these compounds—which include Gilead’s TAF plus FTC (Descovy); possibly its other TAF-based single-tablet regimen product, which includes elvitegravir, cobicistat, and FTC (E/C/F/TAF; Genvoya); and raltegravir with or without lamivudine—as PrEP remain unclear at the time of publication, but both a phase I study involving Genvoya and a phase IV study with raltegravir and lamivudine are expected to wrap up this year.<sup>14,15</sup> Possibilities include improved renal and bone safety relative to TDF-inclusive regimens, although a recent meta-analysis has shown that TAF may only be an improvement in the case of boosted regimens containing cobicistat or ritonavir, and not for TDF/FTC as PrEP.<sup>16</sup> Although kidney and bone problems remain uncommon and mild and are almost always reversible following drug cessation among long-term TDF/FTC PrEP users in clinical trial and demonstration project cohorts, new oral compounds may prove to be useful for those with other risk factors (for example, underlying renal insufficiency, baseline bone mineral deficiency, simultaneous use of medications that may have some toxicity for kidneys or deplete bone mineral, and greater age).<sup>17,18,19,20,21,22</sup>

A new ‘mini-pillbox’ device that is presently in development with funding from the Bill and Melinda Gates Foundation has the potential to deliver two or three antiretroviral drugs through a once weekly dose.<sup>23</sup> The star shape prevents the device from passing through the stomach into the small intestine until the drugs have been released and the polymer matrices breakdown. One drawback is that the device is only suitable for medications that are stable in stomach acid. TAF has had to be abandoned for research for this reason; however, dolutegravir, cabotegravir, and rilpivirine have all shown early promise in preclinical trials in pigs.

### TAF and FTC

Similar to TDF, TAF is a prodrug formulation of tenofovir. Unlike TDF, which is converted in the blood to the active drug tenofovir diphosphate (TFV-DP) and then taken up into cells, TAF is primarily metabolized and converted to TFV-DP inside of cells. Using a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90

percent lower but intracellular concentrations that are approximately four- to sevenfold higher.<sup>24,25</sup> The reduced systemic exposure, although achieving high levels in the cells in which antiretroviral drug activity occurs, has the potential for fewer renal- and bone-related toxicities compared with TDF. However, a recent systematic review and meta-analysis showed that “In randomized clinical trials where TAF and TDF were used without pharmacokinetic enhancers—ritonavir and cobicistat—there was no benefit of TAF versus TDF for HIV RNA suppression, clinical adverse events, discontinuation for renal adverse events, bone fractures, or discontinuation for bone-related adverse events... By contrast, in randomized clinical trials where TAF and TDF were boosted by ritonavir or cobicistat, TAF showed significantly higher rates of HIV RNA suppression than TDF, and there were lower risks of renal and bone-related adverse events.”<sup>26</sup>

TAF’s low-milligram dosing has the potential for reduced generic production costs and, ultimately, greater affordability versus TDF/FTC in low-income countries. Thus, TAF/FTC is also being eyed as an alternative to Truvada, Gilead Sciences’ brand-name coformulation of TDF/FTC that remains the only FDA-approved PrEP in the U.S.

The DISCOVER trial is looking at this very question. A phase III safety and efficacy trial comparing TAF/FTC to TDF/FTC for the prevention of HIV infections in HIV-negative men and transgender women who have sex with men is being run by Gilead Sciences, the manufacturer of both Descovy and Truvada. The trial began recruitment in September of 2016 and has now fully enrolled with 5,400 participants from across the U.S., Canada, and Western Europe. It is estimated to be completed in September 2020.<sup>27</sup> Participants have been randomized to two arms, one receiving active TAF/FTC and placebo TDF/FTC and the other receiving active TDF/FTC and placebo TAF/FTC. Following community pushback, Gilead modified the initial study protocol, which called for a 30-day washout period for individuals already on Truvada for PrEP; participants on Truvada can now switch without a washout period.<sup>28,29</sup> After at least 96 weeks of blinded treatment, and provided that TAF/FTC shows sufficient efficacy, the study will be unblinded and participants will be offered the option to continue as part of an open-label extension of DISCOVER.

With TDF already off patent in the U.S., thereby enabling FDA approval and US market entry for Mylan’s Cimduo (lamivudine (3TC) plus TDF at 300/300mg) and for Merck’s Delstrigo (the novel NNRTI doravirine plus TDF plus 3TC in a complete daily fixed-dose combination) for HIV treatment, and FTC going off patent in 2021, there is little mystery as to why Gilead has taken TAF off the shelf after development was inexplicably delayed for the past decade.<sup>30</sup> The pharmaceutical giant is now following up on the FDA approval of Descovy or HIV treatment by aggressively pursuing a phase III trial of TAF/FTC as PrEP before generics can come to market. If TAF/FTC is shown to be non-inferior, its improved safety profile may give a competitive edge to Descovy over generic TDF/3TC or, eventually, TDF/FTC. Given the already excellent safety profile of TDF/FTC, healthcare professionals and potential PrEP users should be wary of this scheme. Although TAF/FTC as PrEP will be the better option for some, particularly individuals with decreases in renal function, for the vast majority of PrEP users the additional financial costs of Descovy will greatly outweigh any benefits compared with generics.

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Researchers are optimistic that Descovy will be non-inferior to Truvada as PrEP, given positive outcomes in nonhuman primate trials. Results from the Centers for Disease Control and Prevention (CDC) evaluations of TAF plus FTC in rhesus macaques that were rectally challenged with SHIV were published in 2016 and more thoroughly covered in our 2016 *Pipeline Report* (<http://treatmentactiongroup.org/pipeline-report/2016>).<sup>31</sup> None of the TAF-treated macaques were infected after 19 exposures—100 percent protection—whereas the previous macaque studies of TDF/FTC observed 94 percent protection after 14 SHIV exposures. Still, mixed findings in a 2017 study looking at the pharmacokinetics (PK) of TAF in cisgender women emphasize the importance of running the DISCOVER trial before making any assumptions about the efficacy of TAF/FTC as PrEP in humans. Although tenofovir alafenamide results in approximately sevenfold higher concentrations of TFV-DP in **PBMCs**, the study found limited TFV-DV in mucosal tissues.<sup>32</sup>

**PBMC** Peripheral blood mononuclear cell; drug levels in PBMCs tend to correlate strongly with PrEP efficacy\*

Although DISCOVER will seek to answer lingering questions and to determine efficacy for men and transgender women who have sex with men, CONRAD has finalized clinical investigation of the pharmacology of TAF in cervicovaginal tissues as a next step for understanding the potential value of TAF as PrEP for cisgender women.<sup>33</sup> Final results from the phase I trial are estimated to be released by the end of 2018. In the meantime, CONRAD has already launched a phase 2 study of TAF/FTC as PrEP in African women that is set to complete in 2021.<sup>34</sup>

### MK-8591

A novel NRTTI being developed by Merck has shown promise as a possible weekly oral PrEP, as well as a weekly option for treatment.<sup>35,36</sup> The drug blocks two different stages of the HIV lifecycle: it stops HIV from making a DNA copy of its genes and stops integrated HIV DNA inside of cells from being used to replicate new viral particles. The medication also has a long half-life of 50–60 hours in the blood and 120 hours inside cells, making it suitable for weekly dosing. A study presented at **CROI** 2017 found that an extremely low weekly dose of 4.3 mg/kg fully protected eight rhesus macaque monkeys from infection. The drug levels seen in the monkeys indicated that even a lower dose might work; to follow up, researchers reduced weekly doses to 1.3 mg/kg and challenged the monkeys with SHIV four times, with none becoming infected. The experiment was then repeated at 0.43 mg/kg, with no resulting infections. At 0.1 mg/kg, two of the eight monkeys became infected with SHIV—one after three challenges and one after four—resulting in an 86 percent reduction compared with the placebo group. Presenting these additional results from the study at CROI 2018, lead researcher Martin Markowitz predicted that MK-8591 could achieve protective levels in humans at 250 µg weekly or 10 µg daily. Ongoing research for MK-8591 as PrEP is planned, and Merck continues to investigate the medication for weekly treatment in combination with another new drug, the NNRTI doravirine. As discussed further on in this report, MK-8591 has also shown promise for annual dosing via a slow-release removable implant.

**CROI:** The Conference on Retroviruses and Opportunistic Infections

\* Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. 2012 Sep 12;4(151):151ra125.

## Important Updates on TDF/FTC as PrEP

*The body of evidence demonstrating the real-world efficacy of TDF/FTC as PrEP continues to expand, with many important new findings coming out in the past year.*

In May of this year, the FDA finally approved Truvada as PrEP for adolescents weighing more than 35 kg, dramatically improving access for youth who continue to be failed by traditional HIV prevention efforts in the U.S.<sup>37</sup> However, the six-year lag behind the 2012 approval of PrEP for adults demonstrates current failures to address the prevention needs of youth in a timely way. One study in particular, ATN 113, provided key additional evidence of PrEP efficacy for youth and paved the way for approval. ATN 113 enrolled gay and bisexual men age 15 to 17 in six U.S. cities; 79 participants were recruited with a mean age of 16.5 years. Nearly one-third of participants were black, a third were of mixed or other race/ethnicity, 21 percent were Latino, 14 percent were white, and 3 percent were Asian. Three participants became HIV positive during the study, leading to an extremely high incidence rate of 6.41 per 100 person-years and strongly indicating the importance of PrEP access for this population. None of the three infections occurred among participants with sufficiently high levels of tenofovir in their blood, indicating that the drug combination could be used safely by adolescents and would likely prevent HIV infection. Although the study showed no clinically significant effects on bone or kidneys, study participants did have evidence of minor losses in bone mass, and studies are in progress to determine the safety of the drug for this group over long periods of time. Of note, this essential trial was only able to commence thanks to a conference convened in 2009 regarding inclusion of adolescents in biomedical HIV prevention research.<sup>38</sup> Conference attendees concluded that it might be possible to waive parental consent for participation in HIV prevention studies if the youth already had access to confidential sexual and reproductive health services in the local jurisdictions in which the research was being conducted. An external ethics advisory panel for ATN agreed, as did officials from the FDA and the Office of Human Research Protections, which oversees issues related to participants in research conducted or supported by agencies of the U.S. Department of Health and Human Services. Subsequently, FDA approved testing of the drug in the ATN without parental consent, and Project PrEPare began, enrolling 72 participants by the fall of 2014.

Key updates to intermittent PrEP also emerged over the past year. Initial results from the French study Ipergay on the efficacy of intermittent (also known as event driven or on demand) PrEP in gay men, which found an 86 percent reduction in new infections compared with placebo, were unclear as to what kinds of intermittent use were most protective.<sup>39</sup> Intermittent PrEP involves taking a double dose in the 24 hours before possible sexual exposure, and one dose per day for the two following days. Because iPrEX data found that just four doses a week conferred total protection for gay and bisexual men, for highly sexually active Ipergay participants it

**IAS 2017** The 9th  
International AIDS Society  
Conference on HIV  
Pathogenesis, Treatment,  
and Prevention

was difficult to determine if the protection was from intermittent usage, or because they were averaging over four doses a week. A subanalysis presented at **IAS 2017** appeared to demonstrate that on-demand PrEP was also effective in less sexually active participants. The subanalysis looked only at men who indicated that they were using PrEP systematically during risky sex and were also found to use fewer pills than the average, as this was the closest approximation to finding individuals who were experiencing less frequent possible sexual exposure but were likely using PrEP on demand. Two-thirds of trial participants fell into this category during at least one two-month period during the study, which generated 134 of a total 431 person-years in the study. In this group, six infections occurred over the study; however, all of those infections occurred among members of the placebo group. The 95 percent confidence interval (CI) was similar to the whole study, ranging from 39 to 100 percent effective.

**IAC 2018** The 2018  
International AIDS  
Conference

Updated results from the open-label extension of Ipergay presented at **IAC 2018** have further solidified both daily and on-demand TDF/FTC PrEP as important options for gay and bisexual men.<sup>40, 41</sup> From May 3rd, 2017 to May 1st, 2018, 1,435 subjects were enrolled across 22 sites, 59 percent being PrEP experienced for a median of 10 months. Median age was 37 years, 98.7 percent were MSM. At enrollment, PrEP was used daily in 44 percent and on-demand in 53 percent of participants. The median numbers of partners in the three months before enrollment were 15 in the daily group and 10 in the on-demand group. The median numbers of condomless sex in the prior four weeks were 3 and 2, respectively. The follow-up period lasted 302 and 361 person-years in the daily and on-demand groups, respectively. The incidence of HIV-1 infection was 0 (95 percent CI: 0–1.2) per 100 person-years and 0 (95% CI: 0–1.0) in the daily and on-demand groups, respectively, and the incidence of study discontinuation was 3.0 and 3.6 per 100 person-years, respectively, including 1.3 and 1.1 per 100 person-years drop out of PrEP because participants no longer felt at risk. No participant discontinued PrEP for drug-related adverse events.

Findings from the iFACT study will be of great importance for transgender women and other gender-nonconforming individuals taking feminizing hormones.<sup>42, 43</sup> A 2017 study found that some transwomen living with HIV may be reluctant to take antiretroviral therapy due to concerns that it may affect levels of their hormone therapy,<sup>44</sup> a concern that may extend to PrEP for HIV-negative transwomen. iFACT enrolled 20 HIV-negative transwomen who had not had bottom surgery nor received injectable hormones in the past six months. All participants were in their early to mid-twenties and had normal body weight and kidney function. Participants started a feminizing hormone therapy regimen of estradiol valerate (2 mg/day) plus the androgen blocker cyproterone acetate (25 mg/day). The women started taking Truvada at week three, and the hormone regimen was stopped at week five to compare TDF/FTC levels on and off hormones. At week eight, participants resumed hormones and continued taking PrEP through week 15. The study found that TDF/

FTC did not lower levels of feminizing hormones; however, it was important to note that tenofovir levels in the blood were reduced by 13 percent in transwomen on estradiol, although tenofovir remained above protective levels even with this dip. It is difficult to say whether this was an interaction with estradiol or related to adherence.

In a follow-up analysis from iPrEX, researchers found that TDF/FTC PrEP did not raise lipids or alter body fat.<sup>45</sup> Researchers followed 500 PrEP users and a placebo group for a year and a half and found that PrEP users did not suffer long-term fat loss. The findings came from the same substudy that previously reported modest declines in bone mineral density for PrEP users that were reversed within 6 months of stopping PrEP.

A study out of Kings County, which contains Seattle, in Washington state shed light on just how rare it is to encounter TDF/FTC-resistant forms of HIV.<sup>46,47</sup> Using drug-resistance test records from 2003 to the end of 2017, University of Washington researchers found that no more than 0.3 percent of the local HIV-positive population had both a viral load over 10,000 copies/ml and high-level resistance to tenofovir and emtricitabine. In cases of newly diagnosed individuals, only three cases total, or 1 of every 606 individuals diagnosed, demonstrated primary resistance to TDF and FTC. Most of those with PrEP drug-resistant HIV had been living long term with HIV. Only a small proportion of their virus still carried the resistance-conferring mutations, meaning that transmission is theoretically unlikely.

A case out of New York involving a man with indeterminate and contradictory HIV test results following PrEP initiation has highlighted challenges with ‘blunted’ HIV infections.<sup>48,49</sup> The patient likely contracted HIV just before starting PrEP. An initial third-generation HIV ELISA test and a pooled HIV RNA test both indicated an HIV-negative status one week before the man received one more negative test, this time fourth generation, and began taking Truvada. Four weeks later, the patient returned, reporting perfect PrEP adherence. A fourth-generation test came back weakly positive at this point, leading the clinic to once again perform an HIV RNA test. That test, along with another fourth-generation test four days later, came back negative. Out of precaution, the clinic started the patient on dolutegravir in addition to Truvada. Ten days later, another fourth-generation test came back positive, with an additional RNA test also coming back positive. A quantitative HIV RNA test, however, came back negative, indicating a very low viral load, and a test for integrated HIV DNA also yielded a negative result. The confusing case raises the possibility that PrEP guidelines may need to be modified to provide better guidance on how to handle these sorts of confusing ‘blunted’ test results among PrEP users, particularly as intermittent PrEP usage scales up. There may also be a need for tests that are more sensitive to detect new infections among patients who have been using PrEP.

## IMPLANTS AND INJECTABLE LONG-ACTING FORMULATIONS

### Implants and Injectable Long-Acting Formulations

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. Investment in subcutaneous implants to deliver antiretrovirals for PrEP has increased, including significant investment by the U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation.<sup>50</sup> Particular focus is also being placed on the development of long-acting nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for doses that are separated by weeks or months. The drug furthest along the development path is Cabotegravir (CAB) LA, ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog). However, the unexpectedly long persistence of CAB LA in a significant minority of ECLAIR trial participants, possibly tied to higher body mass index (BMI), has led to some uncertainty about how to manage this long 'PK tail' in some individuals. A long-acting injectable version of rilpivirine (RPV LA), Janssen's non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), was previously being researched as another viable option for PrEP, but it will not move forward after disappointing phase II results. Positive 48-week results reported from the ATLAS study indicate that using CAB LA and RPV LA together will be viable as a new monthly injectable option for treatment of HIV; however, this novel treatment delivery option carries many questions related to real-world administration.<sup>51</sup>

As long-acting formulations become more likely candidates for real-world use, it is imperative that researchers and key stakeholders begin actively looking at implementation challenges early. An NIH-funded review article published in 2015 looked at the importance of addressing long-acting formulation implementation issues at three levels: patient, provider, and system.<sup>52</sup> Patient-level factors include targeted education and messaging, tailored supports to enhance acceptability and uptake, and effective strategies for promoting adherence, persistence, and retention in care. Provider-level factors include engaging a broad mix of providers while ensuring adequate training and support for patient assessment, counseling, and follow-up. Systems-level factors include optimal delivery modalities, resource allocation, and ensuring access to populations most in need of new prevention options. A follow-up implementation blueprint for long-acting injectable PrEP, anticipated by the end of 2019 and led by primary investigator Sarit Golub, promises to shed further light on recommendations for real-world application of injectables.<sup>53</sup>

### CAB LA

Encouraging preliminary results presented at CROI 2016 from the ECLAIR trial, which looked at the safety and tolerability of CAB LA as a PrEP, have led the HIV Prevention Trials Network (HPTN) to launch the first of two planned phase III studies looking at efficacy. However, significant questions remain about optimal dosing and feasibility of implementation given the unexpectedly long persistence of CAB LA in the plasma of a minority of ECLAIR participants.

TAG has previously given a detailed review of the outcomes of the ECLAIR trial.<sup>54</sup> The study randomized 127 HIV-negative men between 18 and 65 years of age and at low risk of acquiring HIV at screening to either CAB (N = 106) or placebo (N = 21). For the first four weeks of the trial, oral CAB (30 mg) or placebo were administered,

followed by a seven-day washout period. The injection phase began at week 5 and ended at week 41, with CAB LA 800 mg or saline being administered via intramuscular (IM) injections during visits at weeks 5, 17, and 29. CAB LA was found to be well tolerated in comparison with placebo, although a minority of participants withdrew as a result of injection tolerability (4 percent) and a small proportion experienced grade 2 events such as fever, injection site itching, and injection site swelling. Two seroconversions were reported: one in the placebo group at week 23 and one in the CAB LA group at week 53, 24 weeks after the participant's final injection; however, the participant in the CAB LA group who ultimately seroconverted had no detectable CAB in blood plasma at week 53. CAB PK data throughout each 12-week dosing interval were reported. The results showed trough concentrations to be lower than the prespecified ideal at the end of the dosing intervals in approximately two-thirds of participants. On the basis of these findings, a new dosing strategy of 600-mg IM injections every eight weeks has been selected for CAB LA's continued development.

The study included a follow-up phase with preliminary results presented at the **HIVR4P** conference in October 2016. There, researchers reported that, in 14 of 86 participants (17 percent), drug levels of CAB LA remained above the lower limit of quantification and below the protein-adjusted 90 percent inhibitory concentration (PA-IC90) a year after their last injection.<sup>55</sup> Persistence of CAB LA was associated with a higher range of BMIs, with higher BMIs leading to a longer PK tail. These findings raise questions about CAB LA discontinuation and the possibility of drug resistance should individuals become infected with HIV while they maintain subtherapeutic, yet quantifiable, levels of CAB LA, which would promote resistance, a year or more beyond their last injection.

**HIVR4P:** The HIV Research for Prevention conference

To better understand the effect of CAB LA's prolonged PK, a companion phase IIa study to ECLAIR, HPTN 077, was extended by 24 weeks.<sup>56</sup> The study aims to find out how long measurable drug levels persist, and whether smaller and more frequent injections of 600 mg every 8 weeks might shorten the tail. HPTN 077 has enrolled approximately 200 HIV-negative participants in the U.S., South America, and sub-Saharan Africa. The estimated primary completion date was set for August 2018 according to clinicaltrials.gov; updated findings on the PK tail were not available at the time of publication for this Pipeline update. However, updated results from HPTN 077 were presented at IAS 2017 regarding safety and tolerability, as well as viability, of the 600-mg IM injection dosage every 8 weeks currently being evaluated in HPTN 083 and 084.<sup>57</sup> The median age of participants was 31 years, BMI was 27, 66 percent were female, 41 percent were black, 27 percent white, 24 percent latino, and 8 percent mixed/other. Overall, 94 percent completed the oral phase, 89 percent received at least one injection, and 75 percent completed all of the injections, which did not differ by arm, cohort, or sex. Over 41 weeks, injection site pain and injection site reactions (ISR) were more common in CAB LA versus placebo. No other differences were found in safety or tolerability. ISR led to injection discontinuation in 2 of 134 individuals (1.5 percent), indicating that CAB LA was well tolerated among low-risk HIV-negative men and women. PK from the study support the development of CAB LA for HIV prevention using 600-mg IM every 8 weeks with a 4-week loading dose for all sexes.

Despite ongoing questions related to CAB LA persistence, HPTN 083, a phase IIb/III head-to-head safety and efficacy trial of CAB LA versus oral TDF/FTC, was launched in December 2016.<sup>58</sup> In step 1 of the trial, lasting five weeks, participants will receive oral TDF/FTC or oral CAB (30 mg daily), depending on the randomization. In step 2,

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participants will receive a daily oral placebo plus active CAB LA 600-mg injections at two time points four weeks apart and every eight weeks thereafter, or active daily oral TDF/FTC plus placebo injections, for up to 180 weeks. In step 3, to cover the prolonged PK tail associated with CAB LA dosing, all participants will be required to take daily oral TDF/FTC for at least one year, starting no later than eight weeks after the last injection. The HPTN 083 trial is still in recruitment and has a planned enrollment of 4,500 transgender and MSM individuals 18 years of age and older who are at high risk for sexually acquiring HIV infection. The estimated study completion date has been extended to fall of 2021.

A companion study to HPTN 083, HPTN 084, was launched at the end of 2017 and is currently in recruitment.<sup>59</sup> Approximately 3,200 HIV-negative cisgender women from sub-Saharan Africa will be enrolled and randomized 1:1 to active CAB LA and placebo TDF/FTC versus active TDF/FTC and placebo CAB LA to measure the safety and efficacy of CAB LA in women. The study duration is expected to be 4.6 years. After the study reaches the required number of incident HIV endpoints, participants will begin an open-label daily oral TDF/FTC extension for approximately 48 weeks. As part of HPTN 084, an injectable contraceptive substudy will run simultaneously for 100 evaluable participants to study the effect of CAB LA on depot medroxyprogesterone acetate and norethisterone enanthate.

### *Implantable Devices*

Various implant technologies have been developed for sustained release of drugs used in the treatment and prevention of several conditions including hormonal contraception, prostate cancer, and coronary artery disease.<sup>60</sup> A small number of implants are currently being developed for the delivery of antiretrovirals for treatment or prevention; among the most advanced is a subcutaneous implant containing MK-8591. Implants were studied in rodents and non-human primates to establish MK-8591 pharmacokinetics and intracellular levels of the active triphosphate of MK-8591.<sup>61</sup> The apparent half-life was nearly 100 days, suggesting the possibility for developing human implants with a dosing interval of 1 year or longer.

Intarcia Therapeutics is a Boston-based company developing an implantable minipump about the size of a matchstick to deliver a drug for control of blood sugar in people with type 2 diabetes. The company has received a \$50 million grant from the Bill & Melinda Gates Foundation to develop minipump technology to deliver antiretroviral drugs for PrEP, with an additional \$90 million if they are successful.<sup>62</sup>

Other researchers have looked at extended-release implants containing TAF. The Oak Crest Institute for Science (Monrovia, California) published encouraging animal PK data from a study of a subdermal delivery system similar to that used for removable contraceptive rods (for example, Norplant).<sup>63</sup> Auritec, a Pasadena drug delivery company, received NIH funding to test an implant containing TAF in dogs.<sup>64</sup> The 40-day study found that the implant maintained drug levels 30 times higher than those needed to protect against HIV infection throughout the study period. The Sustained Long-Acting Protection from HIV (SLAP-HIV) partnership, based at Chicago's Northwestern University and supported by a \$17 million NIH grant, is working to develop an implant that can deliver either cabotegravir, rilpivirine, TAF, or the tenofovir analogue tenofovir exalidex.<sup>65</sup>

Table 1

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
<b>Oral Formulations</b>				
TAF + FTC <a href="#">NCT02842086</a>	<b>NtRTI/NRTI</b>	Gilead Sciences	Oral PrEP	Phase III
<ul style="list-style-type: none"> <li>Gilead's Phase III DISCOVER trial, evaluating the safety and efficacy of TAF/FTC compared with TDF/FTC in MSM and TGW, is projected to complete toward the end of 2020.</li> </ul>				
TAF + FTC <a href="#">NCT02904369</a>	NtRTI/NRTI	CONRAD	Oral PrEP	Phase I (in cis-gender women)
<ul style="list-style-type: none"> <li>CONRAD's Phase I exploratory pharmacokinetic and pharmacodynamic study of Oral TAF/FTC for the prevention of HIV acquisition. Clinical phases are complete and results are expected by the end of 2018</li> </ul>				
F/TDF, Truvada F/TAF, Descovy	NtRTI/NRTI	CONRAD	Oral PrEP	Phase II
<ul style="list-style-type: none"> <li>CONRAD's Phase II evaluation of daily Truvada versus daily Descovy oral PrEP in African women. Estimated completion: 2021</li> </ul>				
Raltegravir Raltegravir + Lamivudine <a href="#">NCT03205566</a>	<b>INSTI</b> INSTI/NRTI	Guy's and St Thomas' NHS Foundation Trust	Oral PrEP	Phase IV
<ul style="list-style-type: none"> <li>Phase IV determining <i>ex vivo</i> protection for genital tissue with a seven-day course of Raltegravir or Raltegravir+Lamivudine. Estimated study completion date: June 2018</li> </ul>				
Genvoya (EVG + COBI + FTC + TAF) <a href="#">NCT02985996</a>	INSTI/NtRTI/NRTI	Emory University	Oral PrEP	Phase I
<ul style="list-style-type: none"> <li>Phase I trial to determine the potential for Genvoya as a future PrEP regimen in MSM and TGW. Estimated study completion of September 2018.</li> </ul>				
<b>Long-Acting Formulations</b>				
Cabotegravir <a href="#">NCT03164564</a> (Cisgender Women) <a href="#">NCT02720094</a> (MSM and Transgender Women)	INSTI	ViiV Healthcare	IM	Phase IIb/III (HPTN 083) Phase III (HPTN 084)
<ul style="list-style-type: none"> <li>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 TDF/FTC. Estimated study completion date: May 2022</li> <li>Phase IIb/III HPTN 083 study evaluating the safety and efficacy of long-acting injectable cabotegravir (CAB LA) in HIV-uninfected MSM and transgender women compared with oral TDF/FTC. Estimated study completion date: September 2021</li> <li>Results from HPTN 077 pending on <a href="#">ClinicalTrials.gov</a>, evaluating safety, tolerability, and PK of CAB LA at both 800-mg and 600-mg doses. Study follow up was extended following findings in the ECLAIR study that CAB LA persisted beyond 52 weeks in a minority of participants.</li> </ul>				

**NtRTI/NRTI** Nucleotide/  
Nucleoside Reverse  
Transcriptase Inhibitors

**INSTI** Integrase Strand  
Transfer Inhibitor

### U still equals U

The Prevention Access Campaign (PAC) has in recent years championed the message that U=U: undetectable = untransmittable. The debate around using such absolute, unequivocal messaging will probably continue indefinitely, and it will remain important for us to understand the systems-level and individual factors that cause people living with HIV to experience viral rebound. Establishing wider availability of viral load testing will also be paramount for all people living with HIV to truly benefit from the U=U message. However, with zero linked HIV infections found between a virally suppressed HIV-positive partner and their serodiscordant partners in three large-scale studies involving both heterosexual and gay male participants (HPTN 052, PARTNER, and Opposites Attract) and mounting consensus regarding PAC's campaign, the U=U message has been increasingly validated in the past three to four years.

Results from the PARTNER 2 study at IAC 2018 are the most recent to add to the already substantial evidence base for U=U.<sup>66, 67</sup> PARTNER 1 results, originally announced in 2014 from the first phase of the study, firmly established that U=U for heterosexual partners; however, the statistical certainty of the findings for gay men were not as robust. PARTNER 2 looked only at gay men to bolster the stage 1 findings for this population. Stage 2 recruited 635 additional gay couples from 75 sites in 14 European countries, adding to the 337 couples from phase 1. Couples only contributed 'couple-years of follow up' if they had had condomless sex since the last data collection, if the positive partner had maintained a viral load under 200 copies/mL, and if the HIV-negative partner had not used PrEP or PEP. Ultimately, 783 couples from both stages contributed 1,596 years of data, reporting a median 42 acts of condomless sex per couple year. Ten percent of negative partners and 14 percent of positive partners were diagnosed with an STI during PARTNER. In the end, the study found no linked transmissions in gay couples in which the HIV-positive partner had a viral load under 200 copies/ml, even though there were nearly 77,000 acts of condomless sex between partners.

For all people living with HIV to fully benefit from the preventive benefits and peace of mind that come from viral suppression, greater attention must be paid to ensure that people living with HIV are diagnosed early, have unfettered access to treatment, and receive comprehensive and scientifically accurate U=U messaging from their healthcare providers and social workers. To this end, in the past year, a number of additional examples of highly successful quick start ARV programs have emerged. At CROI 2018, San Francisco Department of Public Health representatives reported that their median time from diagnosis to viral suppression in the city was a mere 61 days, a finding that is considered to be a major success of the city's RAPID program.<sup>68</sup> Similar results are being seen in New York City's sexual health and wellness clinics, where the JumpstART program provides newly diagnosed HIV-positive individuals with thirty days of treatment right on the spot.<sup>69</sup> Although many clinicians may still have reservations providing treatment prior to receiving results from resistance testing, recent modeling has indicated a vanishingly small benefit of delaying treatment in the era of integrase inhibitors.<sup>70</sup> A paper published in *Clinical Infectious Diseases* at the end of 2017 revealed that resistance testing for integrase inhibitors (IRs) resulted in worse clinical outcomes than no IR testing and increased costs by 200 USD/person/year. In addition, the prevalence of transmitted INSTI-R virus did not affect the favored strategy.

## Microbicides

### Intravaginal Rings

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women vulnerable to HIV infection, provided that adherence is consistent, there has been considerable interest in more user-friendly and longer-acting technologies. Polymeric intravaginal rings (IVRs), similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology, and are in various stages of development.

IPM's dapivirine ring, which has shown highly encouraging results in sub-Saharan African women as part of the open-label extensions of the ASPIRE and Ring studies, has generated the most excitement. CONRAD has also completed a phase I trial for a tenofovir-containing ring, and IPM has launched the development of a ring containing the protease inhibitor darunavir.<sup>71</sup> A three-month version of the dapivirine ring is currently being evaluated by IPM and MTN in a phase I trial, whereas IPM and CONRAD are both looking at versions of their rings that also contain the contraceptive levonorgestrel as a multipurpose prevention tool that may better meet the needs of women seeking to avoid both HIV and unwanted pregnancies. CONRAD has a planned multi-center phase I 90-day safety, pharmacokinetic, and pharmacodynamics study of the tenofovir/levonorgestrel IVR (TFV/LNG IVR) with an estimated completion date in the third quarter of 2019. The CDC and CONRAD are also collaborating on a phase IIa, 90-day safety, adherence, and acceptability study of IVRs releasing tenofovir with and without levonorgestrel among women in western Kenya, with an estimated completion date in the fourth quarter of 2019.

### Dapivirine

The most clinically advanced candidate ring is a silicone elastomer IVR containing 25 mg of dapivirine, an NNRTI licensed to IPM by Janssen Sciences Ireland UC. Data from two registrational trials, the Microbicide Trials Network's ASPIRE study (MTN-020) and the International Partnership for Microbicides' Ring Study (IPM 027), were reported at CROI 2016, with the final ASPIRE results being simultaneously published in the *New England Journal of Medicine*.<sup>72,73,74</sup>

Preliminary results from both studies, presented more comprehensively in previous Pipeline Reports, suggested that the dapivirine IVR is safe and moderately effective at reducing incident HIV in African women. HIV infection rates were reduced by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older: 56 percent in ASPIRE and 37 percent in the Ring Study, with little to no protection among women 21 years of age and younger—most likely as a result of lower levels of adherence. However, an updated adherence analysis from ASPIRE, presented at the 21st International AIDS Conference in Durban, South Africa, found that consistent users of the ring experienced 65 percent fewer infections compared with those given placebo.<sup>75</sup> Qualitative interviews with 214 participants were also published in 2016, providing insight into important issues related to adherence.<sup>76</sup>

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The rings were largely acceptable to women; however, concerns about side effects, the appearance of the rings, and the experimental nature of the rings were highlighted as barriers. In addition, possible detection by male partners during sex and partner opinions were of importance to the women interviewed. Fewer than five percent of all ASPIRE study participants reported incidents of intimate-partner-related violence or other social harms, but women who did report violence or social harm within a month of the interview were nearly 2.5 times more likely to have low adherence to the ring. Younger age at enrollment, having a new primary partner, and not disclosing study participation or ring use to the primary partner were significantly associated with reporting social harms.

Preliminary results from HOPE and DREAM, the two open-label extensions of ASPIRE and The Ring Study, first presented at CROI 2018 in Boston, have generated even more excitement for real-world implementation of the dapivirine ring.<sup>77,78</sup> In a planned interim analysis of data conducted in October 2017, both studies saw a 54 percent reduction in the number of new infections compared with expected estimates of new infections. HIV-1 incidence in both open-label extensions was compared with that expected by weighted bootstrap sampling of the placebo arm of the original randomized control trials (RCTs): ASPIRE and The Ring Study. Both studies are set to end in December 2018. In the meantime, IPM submitted a dossier of dapivirine IVR evidence required for licensure to the European Medicines Agency (EMA), where it remains under review at this time.<sup>79</sup> The application was submitted under a procedure called Article 58. This procedure allows the EMA, in cooperation with the World Health Organization (WHO), to provide a scientific opinion on the safety, efficacy, and quality of medicines that would be marketed exclusively outside of the European Union, specifically in low- and middle-income countries, for diseases of major public health interest. Should the EMA grant a positive scientific opinion on the dapivirine ring, IPM will then seek WHO prequalification for the product, which many African national regulatory authorities consider when conducting their own product reviews. This may help facilitate approvals in regions in which women face the highest HIV risk. IPM also plans to submit applications to the South African Health Products Regulatory Authority (formerly the Medicines Control Council) in 2018. Additional applications to national regulatory authorities in sub-Saharan Africa would follow.<sup>80</sup>

Several follow-up safety studies have been planned and are in different stages of implementation. A trial looking at compatibility between the dapivirine ring and an antifungal clotrimazole cream commonly used to treat vaginal yeast infections completed last year, and a trial looking at tampon use and menses in women using the ring was previously finalized.<sup>81</sup> MTN-029 and IPM-039 assessed the presence of dapivirine in the breast milk of lactating women, finding that DPV VR use was associated with low levels of detectable DPV in milk and plasma, very low estimated levels of infant exposure, and a favorable safety profile.<sup>82</sup> In MTN-042, researchers are proposing to evaluate the safety of the ring as well as oral PrEP in approximately 750 pregnant women, whereas MTN-043 would involve approximately 100 women who are breastfeeding as well as their infants.<sup>83,84</sup>

Researchers also investigated the potential effect of bacterial vaginosis on ring efficacy after a substudy of 41 women from the FAME-04 vaginal microbicide study, presented at CROI 2017, found a significant correlation between higher levels of non-*Lactobacillus* bacteria and lower tenofovir levels in vaginal fluid and cervical tissue.<sup>85</sup> In contrast with tenofovir, genital and plasma concentrations of dapivirine were not affected in the study by increasing concentrations of vaginal bacteria associated with bacterial vaginosis.<sup>86</sup>

An extended duration dapivirine vaginal ring is also in development by IPM and MTN.<sup>87</sup> If successful, the new version would have the potential to be inserted for up to three months. A phase I study is currently recruiting 48 participants to be randomized to one of three study vaginal rings in a 1:1:1 ratio. Participants will receive either 25-, 100-, or 200-mg dapivirine rings, and those randomized to the 100- and 200-mg rings will not be told their group assignment. They will then insert one IVR to be used continuously for 13 weeks (in the case of the 100- and 200-mg rings) or one ring to be replaced every 4 weeks for 8 weeks (25 mg), then worn an additional five weeks for a total of 13 weeks. Primary outcome measures include DPV concentration in plasma, cervicovaginal fluid, and cervical tissue, as well as a safety comparison of the two extended duration formulations to the 25-mg ring. At present, the study is estimated to be completed in October 2018.

Finally, a phase 1 study evaluating PK and safety of a vaginal ring containing DPV and LNG completed at the end of 2017, with results expected later in 2018.<sup>88</sup> In addition, MTN-044/IPM 053/CCN019 is a single-site, randomized, open-label Phase 1 trial that will assess the PK and safety of one silicone elastomer vaginal matrix rings containing 200 mg of dapivirine and 320 mg of levonorgestrel for three-month usage. The MTN-044/IPM 053/CCN019 study population consists of healthy, HIV-negative, non-pregnant women between 18 and 45 years of age. The participants will use the vaginal ring either continuously or cyclically (worn for 28 days and taken out for 2 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, and CCN019 is the collection of PK 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.<sup>89</sup>

### **Rectal Microbicide Gel and Enemas**

Although researchers have largely moved away from tenofovir-based gels, several phase I studies are set to look at other compounds for possible gel, insert, and suppository formulations. MTN-026 is a phase I, randomized, double-blind, multi-site, placebo-controlled trial designed to evaluate the safety and acceptability of dapivirine gel (0.05 percent) when administered rectally to healthy, HIV-1-negative men and women.<sup>90</sup> Another study, MTN-033, is a recently launched phase I study looking at the PK of the dapivirine gel when administered rectally via a vaginal applicator and a coital simulation device to healthy, HIV-1-negative men and transgender women.<sup>91</sup> Participants will be randomized to administer a single dose of study product using an applicator or up to 10 mL of gel applied as a rectal lubricant using a phallic device to simulate anal sex. Specimens will be collected at multiple time points to assess drug concentrations, ex vivo efficacy, and biomarkers of safety.

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MTN-037 is a phase I trial currently enrolling that is looking at a rectal gel formulation for MIV150, a new NNRTI;<sup>92</sup> MTN-039 in collaboration with CONRAD is a phase I trial set to look at the integrase inhibitor elvitegravir as a rectal insert;<sup>93</sup> and ImQuest is currently enrolling for a phase I study looking at another NNRTI, IQP-0528.<sup>94</sup> The cell-viral fusion-blocking agent Griffithsin, which has been shown to inhibit both HIV and herpes simplex virus (HSV) infection, is also being assessed as a possible rectal enema at the University of Louisville.<sup>95</sup> The PREVENT rectal microbicide program, operated by University of Louisville and University of Pittsburgh, will begin a clinical trial involving a griffithsin-based enema starting in mid-2019. Researchers have moved away from a gel formulation.

For at least five years, scientists have been looking at a rectal douche or enema as a possible microbicide delivery system for protection during anal sex. Enemas, already frequently used in preparation for receptive anal sex, have the added benefit of achieving more comprehensive coverage than rectal gels.

A challenge with developing enemas is finding the right formulation with an osmolarity, or concentration in solution, that is likely to lead to cellular uptake of the ARV. At HIVR4P in October, researchers presented promising results from a nonhuman primate study involving a tenofovir-containing gel that is hypo-osmolar.<sup>96</sup> Four formulations were tested: two were iso-osmolar and two were hypo-osmolar. Two concentrations of tenofovir were tested: 1.76 and 5.28 mg/mL. Nonhuman primates were given a single dose via rectal insertion and evacuation of the TFV liquid medium; researchers then measured concentrations of tenofovir in their blood and in rectal tissue biopsies an hour, a day, and three days after the dose. Challenges to extracted tissue with simian immunodeficiency virus (SIV) were conducted in each case. Hypo-osmolar formulations led to faster uptake of tenofovir, with the higher dose leading to drug concentrations both in blood and inside cells that were 5–11-fold higher than any of the other formulations, with no indication of damage to rectal tissues with any formulation. Biopsies taken one hour after dosing with the high-dose hypo-osmolar formulation were completely protected from infection; 24 hours after dosing, two of six samples became infected, as compared with infections in biopsies from all other microbicide doses.

A study from Johns Hopkins University is moving forward with this concept in humans. DREAM-01 is an early phase I open-label dose-escalation and variable-osmolarity study to compare the safety, PK, pharmacodynamics, and acceptability of three formulations of a TFV enema.<sup>97</sup> Eighteen men will be enrolled, with results expected in October 2018. The goal of the study will be to identify the dose and osmolarity of a TFV enema for HIV PrEP that achieves the desired tenofovir diphosphate target concentrations in colonic mucosal mononuclear cells that have previously been shown to confer protection from HIV acquisition in MSM.

## PC-1005

The Population Council has been developing PC-1005, a combination gel containing the NNRTI MIV-150, zinc acetate, and carrageenan. PC-1005 potentially offers protection not just against HIV, but also against HSV-2 and human papillomavirus (HPV). Phase

I safety, PK, acceptability, and adherence data were presented at CROI 2016 and published in JAIDS in December of last year.<sup>98,99,100</sup> The trial enrolled 25 HIV-negative women between 19 and 44 years of age. Following a three-day open-label evaluation of PC-1005 in five participants, 20 women were randomized to apply PC-1005 4 mL or placebo once daily for 14 days. Seventeen women completed the randomized phase of the trial (two were lost to follow up and one withdrew before dosing). There were no severe adverse events or early discontinuations because of adverse events. MIV-150 was absorbed systemically at low levels, and there was no measurable HIV and HPV activity in cervicovaginal lavages. Acceptability was also high: 94 percent of participants reported a willingness to use the gel in the future. Additional data also indicate that PC-1005 inhibits HIV and HSV-2 infection in cervical explants in a dose-dependent manner.

At present, Population Council has discontinued development of a PC-1005 vaginal gel. Rectal gel formulations are progressing, however. As previously mentioned, phase I MTN-037 will evaluate the safety and PK of a rectal PC-1005 gel. The study is set to begin in summer 2018 with an estimated completion of May 2019.

### ***Vaginal Microbicide Gels and Inserts***

The future of vaginal microbicides remains uncertain following the disappointing data from both the FACTS 001 and VOICE studies evaluating 1 percent tenofovir gel.<sup>101,102</sup> Given these results, CONRAD has moved away from tenofovir gels, although IVRs containing tenofovir remain in the pipeline. Although adherence, rather than potency, was believed to be the primary factor associated with poor efficacy in the FACTS 001 and VOICE studies, a few other gel-based microbicides containing alternative compounds—dapivirine, maraviroc, griffithsin, and DS003 (an entry inhibitor)—are at various stages of early development. The Population Council is set to begin a phase 1 study evaluating the safety of GRFT for vaginal use in the summer of 2018, with an estimated completion in August of this year.<sup>103</sup> Favorable preclinical findings in mice and rhesus macaques were presented at CROI 2018. The GRFT fast-dissolving inserts significantly protected macaques against SHIV infection: eight of ten macaques remained uninfected in the GRFT group, whereas all of the macaques acquired SHIV in the placebo group, signifying 80 percent protection.<sup>104</sup> Similarly, the GRFT inserts protected mice against HSV-2 (60-73 percent uninfected in the GRFT group versus placebo) and HPV (100 percent uninfected in the GRFT/CG FDI group versus placebo).

Other microbicide studies continue in early development. Phase 1 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. The study completed in 2016, and the product still in development. LeafBio has launched a phase 1 study evaluating the PK and safety of a monoclonal antibody (MB66) vaginal insert to reduce transmission of HSV and HIV, with an estimated study completion date of October 2018.<sup>105</sup> And, as mentioned previously, a broad-spectrum coformulation of MIV-150, zinc acetate, and carrageenan called PC-1005 that was previously in development as a vaginal gel by the Population Council is not presently in development.

## MICROBICIDES

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
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### Microbicide Rings, Gels, Enemas, Films, And Other Insertables

Dapivirine NCT03234400 (three-month vaginal ring)	NNRTI	IPM (vaginal ring/gel/ film); DAIDS/MTN (rectal gel)	Monthly vaginal ring	Phase IIIb
MTN-026 and MTN-033 (rectal gel)			Three-month vaginal ring	Phase I
NCT02858037 (HOPE)			Rectal gel	Phase I
NCT02862171 (DREAM)				

- Open label extensions of MTN-025 (HOPE) and IPM-032 (DREAM) continue to gather data on safety and adherence data on monthly vaginal rings. Hopeful early efficacy/adherence estimates presented at CROI 2018.
- Phase I MTN 036/IPM 047 launched to assess the potential of a three-month vaginal ring. Study estimated to complete in October 2018.
- 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 to be presented at CROI 2019.

Tenofovir NCT02235662	NtRTI	CONRAD	Vaginal ring	Phase I
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- 2015 Phase 1 study evaluated the safety of the TFV/LNG IVR, TFV-only IVR, and placebo IVR, evaluated PK of TFV and LNG, evaluated pharmacodynamic surrogates of contraceptive efficacy of LNG, and acceptability of the IVRs. Product still in development.

TAF/Elvitegravir	NRTI/INSTI	CONRAD and MTN	Vaginal or rectal insert	Advanced preclinical; Phase 1
Tenofovir NCT02750540	NtRTI	Johns Hopkins University	Enema	Phase I

- DREAM-01 is an early phase 1, open-label, dose-escalation, and variable osmolarity study to compare the safety, PK, pharmacodynamics, and acceptability of three formulations of a TFV enema. Estimated study completion date of October 2018.

IQP-0528 NCT03082690	NNRTI	ImQuest U19	Rectal gel	Phase I
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- Phase I study looking at safety and PK for rectal use of IQP-0528, a DuoGel formulated for both rectal and vaginal use. Estimated study completion date: May 2018

Griffithsin NCT02875119 (vaginal gel)	Cell-viral fusion-block- ing agent	U19 University of Louisville/University of Pittsburgh (enema) Population Council (vaginal gel)	Enema	Phase I
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- The Population Council is set to begin a phase 1 study evaluating the safety of GRFT for vaginal use in the summer of 2018. Estimated study completion: August 2018. Favorable preclinical findings in mice and rhesus macaques were presented at CROI 2018.
- The PREVENT rectal microbicide program, operated by University of Louisville and University of Pittsburgh, will begin a clinical trial involving a griffithsin-based enema starting in mid-2019. Researchers have moved away from a gel formulation.

## THE PIPELINE REPORT

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
PC-1005 NCT03408899 (rectal gel)	NNRTI, ZA, CGN	Population Council/MTN	Rectal gel	Phase I

- Phase I MTN-037 will evaluate 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. Study set to begin in summer 2018 with an estimated completion of May 2019. A vaginal formulation previously being investigated by the Population Council is not presently in development.

DS003 NCT02877979	EI	IPM	Vaginal tablet	
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- Phase 1 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. Study completed in 2016, product still in development.

Dapivirine + DS003 In Development	NNRTI/EI	IPM	Vaginal ring	Preclinical
Darunavir In Development	PI	IPM	Vaginal ring	Preclinical

### Multipurpose Technologies

Tenofovir + levonorgestrel NCT03279120	NtRTI/HC	CONRAD	Vaginal ring	Phase I
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- CONRAD: Multi-center, Phase I, 90-day safety, PK, and pharmacodynamics study of the tenofovir/levonorgestrel IVR (TFV/LNG IVR). (NCT03279120). Estimated completed date: third quarter of 2019
- CDC and CONRAD are collaborating on a Phase IIa, 90-day safety, adherence, and acceptability study of IVRs releasing tenofovir with and without levonorgestrel among women in western Kenya. Estimated completion: fourth quarter of 2019

Dapivirine + levonorgestrel NCT02855346	NNRTI/HC	IPM	Three-month vaginal ring	Phase I
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- Phase 1 study evaluating PK and safety of a vaginal ring containing DPV and LNG. Study completed at the end of 2017, results expected in mid-2018.
- Add in about MTN-044 and three-month ring evaluation

MB66 NCT02579083	Anti-HIV + anti-HSV antibodies	LeafBio, Inc.	Vaginal film	Phase I
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- Phase 1 study evaluating the safety of a monoclonal antibody (MB66) vaginal insert to reduce transmission of HSV and HIV. Estimated study completion date of October 2018.

## Conclusion

### Conclusion

Undoubtedly, the signs that TDF/FTC PrEP and treatment as prevention are leading the way in finally reducing the number of new infections in jurisdictions such as New South Wales, Australia are a reason for celebration. In addition, advancement of long-acting formulations of both oral and injectable PrEPs, and ongoing successes with the dapivirine vaginal ring may once again renovate the HIV prevention landscape in the not-so-distant future.

Nonetheless, the need for increased global access and additional, more user-friendly biomedical prevention tools—particularly an effective vaccine—remains dire. Recent signs that microbicide research is likely to be increasingly scarce at the NIH runs contrary to addressing the human need for choices in addressing sexual health. More broadly, the future of the HIV response remains in danger in the hostile political climate of the U.S. Until political change comes to the U.S., the HIV research, prevention, and treatment will be threatened by anti-science political forces that continue to try to slash support for key research at the NIH and CDC and dramatically reduce access to healthcare by repealing the Affordable Care Act. Community advocates, particularly in the U.S., have a key role to play in helping to shift the ongoing political nightmare and continuing to push for full funding of HIV prevention research.

### Recommendations

- With the rising success of the dapivirine ring, the value of ongoing microbicide investment is apparent. The NIH must continue to invest in preventive options that work for diverse communities with diverse needs, including choices for individuals for whom pills and injections are understandably undesirable.
- In anticipation of long-acting injectable technologies, a recent NIH-funded review article looked at what would be necessary to fully implement these new modalities and bring them to scale. Community advocates and other stakeholders have an urgent need to convene meetings and help develop guidelines for the implementation of injectable PrEP and ARV treatment, as these modalities prepare to move into real world scale-up. This should be standard practice for any prevention technology that seems likely to be approved for broader use; addressing implementation as an afterthought leads to significant delays in access, particularly for the marginalized communities that are most in need of new options.
- Research sponsor and investigator adherence to Good Participatory Practice (GPP) guidelines<sup>106</sup> is essential in all biomedical prevention trials, particularly in the post-iPrEx era. Gilead ran into extensive pushback after developing the study protocol for the DISCOVER trial without sufficiently engaging community advocates. The trial initially required a 30-day washout period for any interested participant already taking Truvada as PrEP, which raised several ethical red flags for community advocates. Had Gilead worked with an existing trial network with more experience in working with the community, or had they initially engaged the community in a way that was consistent with GPP guidelines, several complications could have been avoided.

- Researchers, key stakeholders, and community advocates must urgently establish basic ethical standards for the provision of Truvada as PrEP in HIV prevention trials. All parties involved have an obligation to determine the best way to ethically offer PrEP to participants in a way that doesn't lead to impossibly large clinical efficacy trials for new technologies. Prevention studies need to be designed with flexible control arms to allow the best prevention standard of care when new preventive technologies are added to guidelines. Ethical recruitment guidelines for clinical trials are needed for the post-PrEP era. A number of potential recruitment pitfalls need to be considered: explicitly advertising the possibility of PrEP access in recruitment materials for a randomized controlled trial testing the efficacy of an unproven technology or misrepresenting the trial as a PrEP access study are just a few potentially unethical scenarios that arose with the launch of the DISCOVER trial.
- Clinical trials continue to underrepresent a number of priority populations, including youth and transgender men and women. In the U.S., underrepresentation of people of color is a chronic problem in research. Researchers and funding entities should consistently require plans for recruitment of these key priority populations as part of study protocol or be required to explain why they do not find that specific recruitment is necessary or feasible. Studies should include individuals from priority populations at numbers that allow for the possibility of statistically significant outcomes. Recruiting only a handful of transgender women and then including that population in the title of the study is misleading and inadequate.
- As new technologies come closer to market, prices set for novel preventive technologies should be judged not only in terms of potential out-of-pocket costs for key populations, but also by the likely system-wide costs and the anticipated burden on the health care system. Pricing products solely based on what the market will bear—as Gilead did when it set the price of its hepatitis C cure at \$96,000 for a standard course of treatment—forces private and public payers to either explicitly or implicitly ration access via arbitrary restrictions or create unnecessary hurdles. When bringing a product to market, companies should be required to provide a plan for ensuring easy, unfettered universal access, particularly when public funding has gone into any portion of the foundational research.
- Despite a moderately improved safety profile of TAF/FTC compared with TDF/FTC, healthcare providers and community members should be wary of paying higher prices for Descovy as PrEP and of discouraging uptake of potential generic PrEP options. Should Descovy prove to be non-inferior as PrEP, it will be of enormous benefit for potential PrEP users with compromised renal function, but it will not be worth the additional cost for the majority of individuals.

## Endnotes

## Endnotes

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