Preventive Technologies: Antiretroviral and Vaccine Development

By Tim Horn and Richard Jefferys

The U.S. Food and Drug Administration (FDA) approval of co-formulated tenofovir DF and emtricitabine (Truvada) as preexposure prophylaxis (PrEP) has transformed the HIV prevention landscape, though perhaps more in theory than reality. Uptake of PrEP has been slow, including among men who have sex with men (MSM), but a gradual uptick in U.S. prescriptions is expected with the recent publication of U.S. Public Health Service guidelines providing critical information to help health care providers and at-risk individuals evaluate the suitability of PrEP and to ensure that those who choose this prevention method have the comprehensive and coordinated support they require to remain HIV-negative.¹

Clinical trials of tenofovir DF and emtricitabine have indicated significant efficacy as PrEP—if it is taken daily as prescribed. Adherence has been described as “the single biggest Achilles heel in all the PrEP studies,” as has been evident in the highly variable results from clinical trials reported to date.² There are also toxicity, drug resistance, and cost considerations. As a result, there is profound interest in antiretrovirals in the preventive technologies pipeline, including additional agents for oral use, long-acting injectables, and a robust portfolio of products for vaginal and rectal administration: gels, tablets, rings, films, and nanofibers.

An effective preventive HIV vaccine also remains highly desirable, but frustratingly elusive. The surprising—albeit slight—efficacy seen with a poxvirus vector prime/protein boost (ALVAC/AIDSVAX) in the RV144 trial in Thailand exposed how ill-prepared the HIV vaccine field was to respond to success.³ The RV144 results were announced in 2009, but as yet no confirmatory trials have been launched, largely due to the need to produce a new envelope protein boost to replace the discontinued AIDSVAX.

Efficacy trials aiming to build on RV144 are planned, but hopes that they might begin in 2014 have not been borne out. The estimated start date is now 2016 at the earliest. In the meantime, a variety of other candidates are being evaluated for safety and immunogenicity; whether any will eventually
advance further is unclear. The greatest promise for the future may lie in the accumulating number of broadly neutralizing antibodies (bNABs) that have been discovered, and recent advances in understanding both how these bNABs are generated by the human immune system and how they interact with the HIV envelope to accomplish neutralization. A vaccine capable of inducing bNABs remains the holy grail for the HIV vaccine field, and these developments suggest that it is possible.

**ANTIRETROVIRALS FOR PREVENTION**

Table 1. PrEP and Microbicides Pipeline 2014

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class/Type</th>
<th>Delivery</th>
<th>Manufacturer/Sponsor(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truvada (tenofovir DF/emtricitabine) oral PrEP demonstration projects</td>
<td>Combined nucleoside and nucleotide reverse transcriptase inhibitors</td>
<td>Oral</td>
<td>Gilead/U.S. Centers for Disease Control and Prevention</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Truvada (tenofovir DF/emtricitabine) intermittent/as-needed dosing</td>
<td>Combined nucleoside and nucleotide reverse transcriptase inhibitors</td>
<td>Oral</td>
<td>HIV Prevention Trials Network, French National Agency for Research on AIDS and Viral Hepatitis</td>
<td>Phase III</td>
</tr>
<tr>
<td>dapivirine</td>
<td>Reverse transcriptase inhibitor</td>
<td>Vaginal ring</td>
<td>International Partnership for Microbicides/Microbicide Trials Network</td>
<td>Phase III</td>
</tr>
<tr>
<td>tenofovir</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Vaginal gel</td>
<td>CONRAD</td>
<td>Phase III</td>
</tr>
<tr>
<td>tenofovir</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Rectal gel</td>
<td>CONRAD</td>
<td>Phase II</td>
</tr>
<tr>
<td>maraviroc, maraviroc + tenofovir DF, maraviroc + emtricitabine</td>
<td>CCR5 inhibitor</td>
<td>Oral</td>
<td>HIV Prevention Trials Network, AIDS Clinical Trials Group</td>
<td>Phase II</td>
</tr>
<tr>
<td>GSK1265744</td>
<td>Integrase strand transfer inhibitor</td>
<td>Long-acting injectable</td>
<td>ViiV Healthcare, HIV Prevention Trials Network</td>
<td>Phase II</td>
</tr>
<tr>
<td>rilpivirine</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td>Long-acting injectable</td>
<td>PATH, HIV Prevention Trials Network</td>
<td>Phase II</td>
</tr>
<tr>
<td>dapivirine</td>
<td>Reverse transcriptase inhibitor</td>
<td>Vaginal gel</td>
<td>International Partnership for Microbicides</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>tenofovir</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Vaginal tablets</td>
<td>CONRAD</td>
<td>Phase I</td>
</tr>
<tr>
<td>Agent</td>
<td>Class/Type</td>
<td>Delivery</td>
<td>Manufacturer/Sponsor(s)</td>
<td>Status</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>tenofovir/emtricitabine</td>
<td>Combined nucleoside and nucleotide reverse transcriptase inhibitors</td>
<td>Vaginal tablets</td>
<td>CONRAD</td>
<td>Phase I</td>
</tr>
<tr>
<td>tenofovir</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Vaginal ring</td>
<td>CONRAD</td>
<td>Phase I</td>
</tr>
<tr>
<td>tenofovir DF</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
<td>Vaginal ring</td>
<td>Albert Einstein College of Medicine</td>
<td>Phase I</td>
</tr>
<tr>
<td>maraviroc</td>
<td>CCR5 inhibitor</td>
<td>Vaginal ring</td>
<td>International Partnership for Microbicides/Microbicides Trials Network/NIAID/National Institutes of Mental Health (NIMH)</td>
<td>Phase I</td>
</tr>
<tr>
<td>maraviroc + dapivirine</td>
<td>CCR5 inhibitor, reverse transcriptase inhibitor</td>
<td>Vaginal ring</td>
<td>International Partnership for Microbicides/Microbicides Trials Network/NIAID/NIMH</td>
<td>Phase I</td>
</tr>
<tr>
<td>MZC (MIV-150/zinc acetate/carrageenan) vaginal gel</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td>Vaginal gel</td>
<td>Population Council</td>
<td>Phase I</td>
</tr>
<tr>
<td>dapivirine</td>
<td>Reverse transcriptase inhibitor</td>
<td>Thin film polymer</td>
<td>International Partnership for Microbicides</td>
<td>Phase I</td>
</tr>
<tr>
<td>ibalizumab</td>
<td>Monoclonal antibody</td>
<td>Long-acting injectable</td>
<td>TaiMed/Aaron Diamond AIDS Research Center</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

**Oral Preexposure Prophylaxis (PrEP)**

Following FDA approval of co-formulated tenofovir DF and emtricitabine as PrEP in July 2012, two broad objectives have emerged:

- continued development and implementation of demonstration projects,\(^4\) cost-benefit analyses, guidelines to shepherd prescribing and follow-up practices in a variety of clinical care and community-based settings,\(^5\) and affordable scale-up in the United States and other countries where PrEP has been identified as a potentially useful prevention modality; and

- ongoing research and development of agents and optimized delivery mechanisms to further minimize safety concerns and to maximize adherence and, ultimately, effectiveness.
Tenofvir DF and Emtricitabine

Topline results from the five clinical trials reviewed by the FDA’s Antiviral Drugs Advisory Committee in May 2012 recommending the approval of tenofvir DF/emtricitabine as PrEP against sexual transmission of HIV are summarized in our 2013 Pipeline Report. Three trials demonstrated protective efficacy: iPrEx, which enrolled MSM and transgender women, primarily in Peru and Ecuador; Partners PrEP, involving HIV-serodiscordant heterosexual couples in Uganda and Kenya; and TDF2, a U.S. Centers for Disease Control and Prevention (CDC) study that enrolled single heterosexual men and women in Botswana. Two studies, both of which were limited to women, failed to demonstrate protective efficacy: the FEM-PrEP trial, conducted in Kenya, Malawi, South Africa, and Tanzania; and the VOICE study, the largest of all five studies and conducted in South Africa, Uganda, and Zimbabwe, with final results reported in March 2013.

Results from a clinical trial evaluating daily tenofvir DF as PrEP for people who inject drugs were published soon after the 2013 Pipeline Report went to press. Though the CDC–sponsored Bangkok Tenofovir Study demonstrated a statistically significant reduction in risk of HIV acquisition of 49 percent among 2,413 men and women who inject drugs in Bangkok, Thailand (95% CI: 9.6–72.2; P = .01)—the efficacy was 71 percent among those who opted to receive directly observed therapy (DOT) and 84 percent among those with 97.5 percent adherence, as determined by drug level measurements—the extent to which tenofvir DF truly protected against parenteral exposure to HIV remains a matter of debate.

The Bangkok Tenofovir Study failed to demonstrate efficacy during the first three years of the trial when reported needle sharing was highest among trial participants. Only during the subsequent four years of the trial, when the number of participants presenting for follow-up dwindled and rates of needle sharing declined, was there a divergence in infection rates among those who received tenofvir compared with those on placebo. This led academics and advocacy groups—many of which had long-standing concerns about the study’s ethical practices and the failures of the sponsor and investigators to address activists’ concerns—to question whether tenofvir’s efficacy was more directly related to sexual exposure during the study’s seven-year follow-up period. However, in his oral review of the efficacy and additional adherence data from the trial at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention in July 2013 in Kuala Lumpur, Michael Martin, MD, of the
CDC noted the likelihood of a statistical fluke during the first three years of the study, created in part by the very low HIV incidence in the tenofovir and placebo arms. Additionally, according to a multivariate analysis presented at the conference, sharing needles, a history of incarceration, or being under 30 years of age were the only risk factors associated with HIV infection in the study.

Reporting sex with domestic, casual, or same-sex partners was not associated with HIV infection.

Aside from ongoing tenofovir DF/emtricitabine PrEP demonstration projects, two closely watched clinical trials—the HIV Prevention Trials Network (HPTN) ADAPT study and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) IperGay study—are exploring the efficacy of intermittent dosing of Truvada.

Maraviroc

CCR5-tropic HIV—virus that utilizes the CCR5 coreceptor on CD4 cells to gain entry and establish infection—is responsible for more than 95 percent of new sexually transmitted infections of the virus. In turn, there has been interest in studying the CCR5 antagonist maraviroc (Selzentry) for potential use as PrEP. Compared with tenofovir and emtricitabine, maraviroc may be associated with a reduced risk of adverse events, such as kidney toxicity and bone mineral density depletion. Because its mechanism involves blockade of cellular rather than viral protein functioning, maraviroc may also minimize the risk of developing drug resistance. The drug, administered systemically, also penetrates and concentrates well in cervical, vaginal, and rectal tissues.

Results from preclinical studies involving animals have been mixed. Oral maraviroc prevented HIV infection in a humanized mouse model involving vaginal challenge with the virus. In a study involving macaques, however, maraviroc failed to protect against rectal challenges with simian/human immunodeficiency virus (SHIV), despite high concentrations of the drug in rectal tissue.

Three human studies are under way. The first is NEXT-PrEP, a phase II clinical trial being conducted by the HIV Prevention Trials Network (HPTN 069) and the AIDS Clinical Trials Group (A5305). It has an estimated enrollment of 600 HIV-negative MSM and at-risk women, with an anticipated completion date of July 2015. NEXT-PrEP is primarily a safety and tolerability trial comparing four arms: maraviroc, maraviroc plus emtricitabine, maraviroc plus tenofovir DF, and tenofovir DF plus emtricitabine.
Another study, MARAVIPREX, is being conducted by the Fundació Lluita contra la SIDA in Barcelona and is evaluating the capacity of maraviroc to protect against HIV in samples of rectal mucosa from HIV-negative volunteers.$^{25}$ The third trial is MVC-PREP, which is being conducted at Emory University and is evaluating concentrations of maraviroc in the blood and genital tracts of HIV-negative women.$^{26}$

**Long-Acting Formulations**

A significant challenge in the oral PrEP clinical trials completed to date was adherence, which has been demonstrated to be directly related to levels of protection. For example, in Partners PrEP, the intention-to-treat (ITT) efficacy of tenofovir/emtricitabine was 75 percent, and the estimated adherence, determined using blood measures of drug concentrations, was 75 to 80 percent. In iPrEx, which yielded a more moderate tenofovir DF/emtricitabine efficacy of 44 percent in the ITT analysis, the estimated adherence rate was 51 percent. In the VOICE study, which found that tenofovir DF/emtricitabine wasn’t efficacious, adherence was estimated at 29 percent.$^{27}$

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. A particular focus is the development of long-acting parenteral nanosuspensions of antiretrovirals with PrEP potential, which may allow for monthly or quarterly, rather than daily, dosing. The two long-acting drugs furthest along this development path are GSK1265744 (GSK744 LA), Viiv Healthcare’s integrase strand transfer inhibitor (and dolutegravir analog), and rilpivirine (Edurant; RPV LA), Janssen’s non-nucleoside reverse transcriptase inhibitor.

Data from a study evaluating the protective effects of GSK744 LA in macaques rectally challenged with simian-human immunodeficiency virus (SHIV) were presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in March 2014 in Boston. Chasity Andrews of the Aaron Diamond AIDS Research Center in New York administered single injections of GSK744 LA to 12 macaques (four received placebos) and challenged the animals with SHIV on a weekly basis.$^{28}$ Whereas monkeys that received placebo injections all became infected within seven weeks, the GSK744 LA–treated macaques were protected for six to 17 weeks. No animals were infected as long as the GSK744 drug levels remained three times the concentration inhibiting 90 percent of viral replication (IC90). Interpreting these results in tandem with those from a human pharmacokinetics study presented previously,$^{29,30}$ Andrews noted that 800 mg
injections maintained plasma levels three times the IC90 for 12 to 16 weeks, indicating that quarterly administration should result in high-level protection.

Also presented at CROI 2014 were data from a CDC study that treated six female macaques with GSK744 LA and six with placebo. Three injections, once a month, were administered. Whereas the six placebo-treated monkeys were all infected by week 11 (all but one within five weeks), none of the GSK744 LA–treated macaques were infected during the twelve-week study. Gerardo García-Lerma, presenting for the CDC, cautioned that concentrations of GSK744 were lower in both vaginal (20% lower) and rectal tissues (50% lower) compared with plasma, though he also noted that GSK744 LA’s protection is likely dependent on both systemic and tissue concentrations of the drug.

Encouraging phase I data from a study evaluating the pharmacokinetics of RPV LA in plasma, the genital tract in females, and the rectum in males were reported at the 19th CROI in Seattle.

A phase II study of GSK744 LA is under way. ÉCLAIR, being conducted in the U.S. by ViiV Healthcare, is enrolling 120 at-risk men (60% MSM). Volunteers will receive 30 mg daily oral dosing or placebo for four weeks. Following a one-week washout period, intramuscular (IM) injections of 800 mg GSK744 LA, or placebo, will be administered every 12 weeks for a total of three injections. A second study, HPTN 077, is in development and will enroll 160 at-risk women (60%) and men in the United States, South America, and sub-Saharan Africa. The primary objective of both studies is to assess the safety, tolerability, and acceptability of GSK744 LA.

The safety, tolerability, and acceptability of RPV LA are to be evaluated in a phase II clinical trial: HPTN 076. Following an oral lead-in period, 132 HIV-negative women will receive IM injections of 1,200 mg RPV LA or placebo, once every eight weeks, over a 44-week period. The study is to be conducted at four sites in the United States, South Africa, and Zimbabwe.

Another long-acting agent being explored for its preventive potential is ibalizumab, a monoclonal antibody being developed by TaiMed in collaboration with the Aaron Diamond AIDS Research Center and the Bill & Melinda Gates Foundation. A phase I clinical trial, involving 24 HIV-negative volunteers and evaluating a newly developed subcutaneous formulation of the monoclonal antibody with potential for large-scale administration over the currently available intravenous formulation, has been completed.
Microbicides: Vaginal and Rectal Gels

A gel containing one percent tenofovir continues to undergo confirmatory testing as a vaginal microbicide, following the completion of one clinical trial (CAPRISA 004) demonstrating a 39 percent reduced risk of acquiring HIV—along with a 51 percent reduction in the risk of acquiring herpes simplex virus 2 (HSV-2)—and another trial (VOICE) that failed to demonstrate a statistically significant benefit, likely because of poor adherence.\textsuperscript{36,37}

FACTS 001, a pivotal phase III placebo-controlled clinical trial being conducted by CONRAD in collaboration with the Follow-on African Consortium for Tenofovir Studies (FACTS) and the U.S. Agency for International Development (USAID), has an estimated enrollment of 2,900 HIV-negative women in South Africa, including 899 women in a high-incidence area of KwaZulu-Natal, with preliminary data anticipated by the end of 2014.\textsuperscript{38} As with CAPRISA 004, volunteers are being instructed to use the tenofovir gel or matching placebo within 12 hours before and 12 hours after intercourse (BAT-24 regimen). If the results of FACTS 001 are affirmative, applications for approval are likely to be submitted to regulatory agencies.

There is also CAPRISA 008, an open-label study providing additional safety data and an evaluation of the feasibility and effectiveness of providing one percent tenofovir gel to HIV-negative women through family planning clinics.\textsuperscript{39} The trial is open to CAPRISA 004 participants and women from communities in which the trial was conducted.

A reduced-glycerin one percent tenofovir gel for rectal use is in a phase II study. The new formulation developed by CONRAD has an improved osmolarity profile, meaning that it contains fewer sugars and salts relative to epithelial cells and therefore prevents tissues from purging too much water. This, in turn, may prevent damage to the structural integrity of the rectum’s lining and also help minimize gastrointestinal side effects.\textsuperscript{40} The phase II Microbicide Trials Network (MTN) 017 trial is evaluating the safety and acceptability of daily or episodic (applied before and after receptive anal intercourse) reduced-glycerin one percent tenofovir gel, compared with daily oral tenofovir/emtricitabine, in roughly 186 HIV-negative MSM and transgender women in Peru, South Africa, Thailand, Puerto Rico, and the United States.\textsuperscript{41}
The Population Council is developing a combination gel containing the non-nucleoside reverse transcriptase inhibitor MIV-150, zinc acetate, and carrageenan (MZC). In initial studies of the MZC gel, a single application provided eight hours of protection to macaques challenged vaginally with SHIV.\textsuperscript{42,43} Gels containing zinc acetate and carrageenan have also been shown to protect against HSV-2 vaginal and rectal challenges in mice.\textsuperscript{44} Additionally, carrageenan has activity against human papillomavirus (HPV) infection.\textsuperscript{45,46,47,48}

Most recently, a modified MZC gel—containing buffers, co-solvents and preservatives suitable for human trials—protected macaques against SHIV infection when applied up to eight hours prior to vaginal challenge.\textsuperscript{49} The gel was also protective against rectal challenges in mice, but not in macaques. Protection against HSV-2 as well as HPV-16 (one of the two most common strains associated with precancerous and cancerous cervical and anal disease) has also been documented among MZC gel-treated mice challenged vaginally and rectally.

A phase I safety, pharmacokinetics, and acceptability evaluation of an MZC gel was announced in early 2014 and is expected to begin enrolling approximately 35 HIV-negative women this year.\textsuperscript{50}

Microbicide gels in preclinical stages of development for vaginal or rectal use include:

- one percent raltegravir gel, which recently showed potential for postexposure protection of macaques from vaginal SHIV infection in a study conducted by the CDC in collaboration with Merck;\textsuperscript{51}
- a gel containing 0.25% IQP-0528, a pyrimidinedione analog in development by ImQuest Biosciences;\textsuperscript{52}
- a gel containing griffithsin, an HIV entry inhibitor with activity against CXCR4- and CCR5-tropic virus, being developed by the Population Council;\textsuperscript{53}
- a maraviroc-based gel for rectal use, being developed by the International Partnership for Microbicides; and\textsuperscript{54}
- three combination gels, also being developed by the IPM.\textsuperscript{55} For vaginal use: maraviroc plus dapivirine, and the protease inhibitor darunavir plus dapivirine; for rectal use: maraviroc plus tenofovir.
Microbicides: Vaginal Rings

As with the oral PrEP, ITT efficacy data in clinical trials of microbicide gels have been hobbled by poor adherence rates. In turn, there has been considerable interest in easy-to-administer technologies that can slowly release protective antiretrovirals over the course of weeks or months. Polymeric vaginal rings, similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology and are currently in various stages of clinical and preclinical development.

The most clinically advanced candidate is a silicone elastomer vaginal matrix ring containing 25 mg dapivirine (TMC120), a non-nucleoside reverse transcriptase inhibitor licensed to the International Partnership for Microbicides (IPM) by Janssen Pharmaceuticals. Following the IPM’s successful evaluation of dapivirine in 14 phase I/II safety and acceptability studies, the vaginal ring is now in two large efficacy studies.

Preliminary results from the phase III ASPIRE study, sponsored by the Microbicide Trials Network (MTN 020), are anticipated in late 2014. The study is randomizing 3,500 HIV-negative women to receive the dapivirine ring or matching placebo, replaced once a month for a year. The trial is being conducted at sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe. The Ring Study, a phase II/III evaluation, is comparing the dapivirine ring to a placebo ring, inserted once every week over 24 months, in 1,650 HIV-negative women in South Africa and Rwanda. Data are anticipated in early 2015.

A rationale for developing rings that combine dapivirine with antiretrovirals using different mechanisms—in order to increase the breadth of protection and limit the emergence of drug-resistant HIV—has been established. Results from an IPM and MTN phase I study (MTN 013/IPM 026) evaluating vaginal rings containing 100 mg maraviroc, both with and without 25 mg dapivirine, are mixed. Though all of the rings used in the study of 48 HIV-negative women were generally safe, well tolerated, and acceptable (roughly one in five women said they would prefer not to use the ring during menstruation), only four of the 24 women randomized to receive rings containing maraviroc alone or both drugs had detectable maraviroc in cervical tissue samples. Plasma levels of maraviroc were also below the limits of quantification in most women. The IPM is currently redeveloping the combination ring to achieve protective vaginal and systemic concentrations of maraviroc, with a second phase I study slated for 2015.
Other compounds being evaluated in preclinical and early clinical studies for extended release via vaginal rings include:

- tenofovir DF, currently in a phase I safety and pharmacokinetics study, being conducted by Albert Einstein College of Medicine in New York;\(^{59}\)
- tenofovir, which achieves protective vaginal concentrations in sheep, and to be developed further by CONRAD;\(^{60}\)
- griffithsin and MIV-150, being developed by the Population Council;
- DS003, a gp120-binding entry inhibitor developed by Bristol-Myers Squibb that has been licensed to the IPM; and\(^ {55}\)
- dapivirine plus the protease inhibitor darunavir, also in the preclinical stages of development by the IPM.\(^ {55}\)

## Microbicides: Vaginal Tablets and Films

A number of groups are evaluating the potential utility of dissolvable films and tablets, both of which may be easier to use and associated with reduced manufacturing costs compared with vaginal gels.

CONRAD is evaluating the potential utility of rapidly disintegrating vaginal tablets containing tenofovir and tenofovir plus emtricitabine. Preclinical testing in rabbits and macaques has demonstrated favorable vaginal tissue and fluid concentrations of both drugs.\(^ {61,62}\) A phase I placebo-controlled safety and pharmacokinetics evaluation of vaginal tablets containing, tenofovir, emtricitabine, and a combination of both drugs in 48 HIV-negative women at Albert Einstein College of Medicine and Eastern Virginia Medical School has been completed, the results of which have not yet been reported.\(^ {63}\)

Preliminary results from a phase I clinical trial (FAME-02) comparing the safety, drug absorption, and drug distribution of a dapivirine film to dapivirine gel were reported at CROI 2014.\(^ {64}\) Plasma levels of dapivirine were comparable across the film and gel arms, suggesting that both products can deliver drugs in a similar manner. While the levels of dapivirine in vaginal tissue were higher in gel users than in those who used film, ex vivo laboratory viral-challenge studies demonstrated that both the film and gel protected against HIV.
Vaginal films in preclinical development include:

- a film dosed with 0.1 percent IQP-0528, being developed by ImQuest;\(^{65}\)
- a film containing EFdA, a nucleoside reverse transcriptase inhibitor, being evaluated by the Magee Women’s Research Institute at the University of Pittsburgh;\(^{66}\)
- vaginal films containing maraviroc plus tenofovir and maraviroc plus dapivirine; and\(^ {55}\)
- a vaginal tablet containing DS003, also being developed by the IPM.\(^ {55}\)

### Multipurpose Prevention Technologies

Male and female condoms are the only prophylactic technology available to protect against pregnancy, HIV, and other sexually transmitted infections (STIs). As has been well documented in the development of oral PrEP and microbicides, however, there is a need for options that women can easily control and do not require the cooperation, consent, or knowledge of their sexual partners. In turn, there is tremendous interest in the development of multipurpose prevention technologies (MPTs) that can double as contraception and biomedical prevention against STIs.

Products currently in preclinical development can be categorized as either long-acting or on-demand. Long-acting MPTs include vaginal rings; on-demand products include gels that can be used around the time of intercourse.

At least three vaginal ring MPTs—all of which employ the contraceptive hormone levonorgestrel, a synthetic progestogen with extensive clinical experience and suitable for formulation in matrix rings—are being developed and are in various stages of preclinical testing:

- A dual-reservoir ring that can release steady levels of tenofovir, with its established activity against HIV and HSV-2, and the hormonal contraceptive levonorgestrel over a 90-day period.\(^ {67}\) It is being developed by CONRAD.
- A 30-day ring containing MIV-150, zinc acetate, carrageenan, and levonorgestrel (MZCL) to protect against pregnancy, HIV, HSV-2, and human papillomavirus (HPV). Prototype development and preclinical evaluation by the Population Council is ongoing.
HIV Preventive Technologies

- A 60-day silicone matrix ring that releases dapivirine and levonorgestrel, also in development by the Population Council.

On-demand products include:

- A reformulated one percent tenofovir gel to include sperm-immobilizing agents that can be used with the silicone single-sized SILCS diaphragm. Preclinical work and plans for early clinical development is being undertaken by CONRAD.

- A carrageenan-based gel containing MIV-150, zinc acetate, and levonorgestrel (MZL) being developed by the Population Council.

PREVENTIVE VACCINES

Table 2. HIV Vaccines Pipeline 2014

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class/Type</th>
<th>Manufacturer/Sponsor(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC-HIV vCP1521</td>
<td>Canarypox vector including HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol gene, and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins</td>
<td>Sanofi Pasteur/U.S. HIV Military HIV Research Program (USMHRP)/NIAID</td>
<td>Phase IIb</td>
</tr>
<tr>
<td>pGA2/JS7 DNA + MVA/HIV62</td>
<td>Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B</td>
<td>GeoVax/NIAID</td>
<td>Phase Ila</td>
</tr>
<tr>
<td>HIVIS 03 DNA + MVA-CMDR</td>
<td>Prime: HIVIS DNA including Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) genes Boost: MVA-CMDR including Env (E), Gag (A), and Pol (E) genes</td>
<td>Vecura/Karolinska Institutet/Swedish Institute for Infectious Disease Control (SMI)/USMHRP</td>
<td>Phase II</td>
</tr>
<tr>
<td>LIPO-5</td>
<td>Five lipopeptides comprised of CTL epitopes from Gag, Pol, and Nef proteins</td>
<td>French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)</td>
<td>Phase II</td>
</tr>
<tr>
<td>VICHREPOL</td>
<td>Chimeric recombinant protein comprised of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant</td>
<td>Moscow Institute of Immunology/Russian Federation Ministry of Education and Science</td>
<td>Phase II</td>
</tr>
<tr>
<td>Agent</td>
<td>Class/Type</td>
<td>Manufacturer/Sponsor(s)</td>
<td>Status</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>--------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>DNA-C + NYVAC-C</td>
<td>Prime: DNA vaccine including clade C Env, Gag, Pol, and Nef genes Boost: NYVAC-C attenuated vaccinia vector including clade C Env, Gag, Pol, and Nef genes</td>
<td>GENEART/Sanofi Pasteur/ Collaboration for AIDS Vaccine Discovery (CAVD)</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>MYM-V101</td>
<td>Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env</td>
<td>Mymetics Corporation</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Ad26.ENVA.01</td>
<td>Adenovirus serotype 26 vector including the HIV-1 clade A Env gene</td>
<td>Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard</td>
<td>Phase I Prime-boost phase I w/ Ad35-ENVA</td>
</tr>
<tr>
<td>Ad35-ENVA</td>
<td>Adenovirus serotype 35 vector including the HIV-1 clade A Env gene</td>
<td>Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard</td>
<td>Phase I Prime-boost phase I w/ Ad26.ENVA.01</td>
</tr>
<tr>
<td>Ad35-GRIN/ENV</td>
<td>Two adenovirus serotype 35 vectors, one including HIV-1 clade A Gag, reverse transcriptase, integrase and Nef genes, and the other including HIV-1 clade A Env (gp140)</td>
<td>International AIDS Vaccine Initiative (IAVI)/University of Rochester</td>
<td>Phase I Prime-boost phase I w/ GSK HIV vaccine 732461</td>
</tr>
<tr>
<td>Ad5HVR48.ENVA.01</td>
<td>Hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; includes HIV-1 clade A Env gene</td>
<td>Crucell/NIAID</td>
<td>Phase I</td>
</tr>
<tr>
<td>Cervicovaginal CNS5gp140-hsp70 conjugate (TL01)</td>
<td>HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjuvant, delivered intravaginally</td>
<td>St George’s, University of London/European Union</td>
<td>Phase I</td>
</tr>
<tr>
<td>DCVax + poly ICLC</td>
<td>Recombinant protein vaccine including a fusion protein comprising a human monoclonal antibody specific for the dendritic cell receptor, DEC-205, and the HIV Gag p24 protein, plus poly ICLC (Hiltonol) adjuvant</td>
<td>Rockefeller University</td>
<td>Phase I</td>
</tr>
<tr>
<td>DNA-HIV-PT123, NYVAC-HIV-PT1, NYVAC-HIV-PT4, AIDSVAX B/E</td>
<td>DNA and NYVAC vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE</td>
<td>IPPOX/EuroVacc/HVTN</td>
<td>Phase I</td>
</tr>
<tr>
<td>DNA + Tiantan vaccinia vector</td>
<td>Prime: DNA vector, with or without electroporation Boost: Replication-competent recombinant Tiantan vaccinia strain vector Both encoding Gag, Pol, and Env genes from HIV-1 CNS4</td>
<td>Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/ Peking Union Medical College</td>
<td>Phase I</td>
</tr>
<tr>
<td>Agent</td>
<td>Class/Type</td>
<td>Manufacturer/Sponsor(s)</td>
<td>Status</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>EN41-FPA2</td>
<td>Gp41-based vaccine delivered intranasally and intramuscularly</td>
<td>PXTherapeutics/ European Commission</td>
<td>Phase I</td>
</tr>
<tr>
<td>GEO-D03 DNA + MVA/HIV62B</td>
<td>Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines include Gag, Pol, and Env genes from HIV-1 clade B and produce virus-like particles</td>
<td>GeoVax/NIAID</td>
<td>Phase I</td>
</tr>
<tr>
<td>GSK HIV vaccine 7324G1</td>
<td>Gag, Pol, and Nef proteins in proprietary adjuvant</td>
<td>GlaxoSmithKline</td>
<td>Phase I Prime-boost phase I w/ Ad35-GRIN</td>
</tr>
<tr>
<td>HIV-1 Tat/delta-V2 Env</td>
<td>Tat and oligomeric ΔV2 Env proteins</td>
<td>Istituto Superiore di Sanità/ Novartis Vaccines</td>
<td>Phase I</td>
</tr>
<tr>
<td>MAG-pDNA, Ad35-GRIN/ENV</td>
<td>Multi-antigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system, two adenovirus serotype 35 vectors, one including HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 clade A Env (gp140)</td>
<td>IAVI/Profectus Biosciences/ Ichor Medical Systems Incorporated</td>
<td>Phase I</td>
</tr>
<tr>
<td>MAG-pDNA, rVSV_HIV-1 Gag</td>
<td>Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein</td>
<td>Profectus Biosciences/HVTN</td>
<td>Phase I</td>
</tr>
<tr>
<td>MV1-F4-CT1</td>
<td>Recombinant measles vaccine vector including HIV-1 clade B Gag, Pol, and Nef</td>
<td>Institut Pasteur</td>
<td>Phase I</td>
</tr>
<tr>
<td>MVA.HIVA</td>
<td>MVA vector including a synthetic copy of a major part of HIV’s Gag gene and 25 CD8 T-cell epitopes</td>
<td>Impfstoffwerk Dessau-Tornau (IDT)/University of Oxford/ Medical Research Council/ University of Nairobi/Kenya AIDS Vaccine Initiative</td>
<td>Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative mothers (PedVacc001)</td>
</tr>
<tr>
<td>MVA HIV-B</td>
<td>MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef</td>
<td>Hospital Clinic of Barcelona</td>
<td>Phase I</td>
</tr>
<tr>
<td>Agent</td>
<td>Class/Type</td>
<td>Manufacturer/Sponsor(s)</td>
<td>Status</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>PENNVAX-G DNA + MVA-CMDR</td>
<td>Prime: DNA vaccine including HIV-1 clade A, C, and D Env proteins and consensus Gag protein &lt;br&gt;Boost: MVA-CMDR live attenuated MVA vector including HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins &lt;br&gt;DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device</td>
<td>NIAID/USMHRP/Walter Reed Army Institute of Research</td>
<td>Phase I</td>
</tr>
<tr>
<td>PolyEnv1 EnvDNA</td>
<td>Vaccinia viruses including 23 different Env genes and DNA vaccine with multiple Env genes</td>
<td>St. Jude Children's Research Hospital</td>
<td>Phase I</td>
</tr>
<tr>
<td>pSG2.HIVconsv DNA + ChAdV63.HIVconsv, or MVA.HIVconsv</td>
<td>Prime: DNA vaccine pSG2 &lt;br&gt;Boost: chimpanzee adenovirus vector ChAdV63 or MVA vector &lt;br&gt;All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1</td>
<td>University of Oxford</td>
<td>Phase I</td>
</tr>
<tr>
<td>rAd35 VRC-HIVADV027-00-VP</td>
<td>Adenovirus serotype 35 vector</td>
<td>Vaccine Research Center/NIAID</td>
<td>Phase I</td>
</tr>
<tr>
<td>rVSV_HIV-1 Gag</td>
<td>Attenuated replication-competent vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein</td>
<td>Profectus Biosciences/HIV Vaccine Trials Network (HVTN)</td>
<td>Phase I</td>
</tr>
<tr>
<td>SAAVI DNA-C2, SAAVI MVA-C, clade C gp140/MF59</td>
<td>SAAVI and MVA vectors encoding an HIV-1 clade C polyprotein including Gag-reverse transcriptase-Tat-Nef and an HIV-1 clade C truncated Env Novartis protein subunit vaccine comprising a clade C oligomeric V2 loop-deleted gp140 given with MF59 adjuvant</td>
<td>South Africa AIDS Vaccine Initiative/HVTN/Novartis</td>
<td>Phase I</td>
</tr>
<tr>
<td>SeV-G(NP), Ad35-GRIN</td>
<td>Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, adenovirus serotype 35 vector including HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef genes</td>
<td>IAVI/DNAVEC</td>
<td>Phase I</td>
</tr>
<tr>
<td>LIPO-5, MVA HIV-B, GTU-MultiHIV</td>
<td>Five lipopeptides comprised of CTL epitopes from Gag, Pol, and Nef proteins &lt;br&gt;MVA vector encoding Env, Gag, Pol, and Nef antigens from HIV clade B &lt;br&gt;DNA vector encoding fusion protein of six different HIV genes &lt;br&gt;Given in four different prime-boost combinations</td>
<td>French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)</td>
<td>Phase I, Phase II</td>
</tr>
</tbody>
</table>
The 31 percent reduction in the risk of HIV infection associated with receipt of ALVAC+AIDSVAX in the RV144 trial\(^3\) continues to provide the impetus for the next round of planned efficacy trials. A multi-stakeholder partnership, the Pox-Protein Public-Private Partnership (P5), is leading the research; current P5 members are the Bill & Melinda Gates Foundation, the HVTN, Novartis Vaccines and Diagnostics, Sanofi Pasteur, the South African Medical Research Council, the U.S. Military HIV Research Program, and NIAID/Division of AIDS. The main site of these activities is South Africa, where a two-pronged strategy to follow up on RV144 will unfold under the aegis of the HVTN. One part will involve an evaluation of a regimen closely modeled on the original trial:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class/Type</th>
<th>Manufacturer/Sponsor(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad4-mgag, Ad4-EnvC150</td>
<td>Live, replication-competent recombinant adenovirus serotype 4 vectors encoding HIV-1 clade C Env and HIV-1 mosaic Gag. Formulated either as enteric-coated capsules for oral administration or as an aqueous formulation for tonsillar administration.</td>
<td>NIAID/PaxVax, Inc.</td>
<td>Phase I</td>
</tr>
<tr>
<td>DNA Nat-B env, NYVAC Nat-B env DNA CON-S env, NYVAC CON-S env DNA mosaic env, NYVAC mosaic env</td>
<td>Prime: DNA vector encoding Nat-B, CON-S or mosaic Env antigen Boost: NYVAC vectors encoding Nat-B, CON-S or mosaic Env antigen</td>
<td>HVTN/IPPOX/Center for HIV/AIDS Vaccine Immunology (CHAVI)</td>
<td>Phase I</td>
</tr>
<tr>
<td>CN54gp140 + GLA-AF</td>
<td>HIV-1 clade C gp140 protein and glucopyranosyl lipid adjuvant - aqueous formulation (GLA-AF), delivered intramuscularly</td>
<td>Imperial College London/Wellcome Trust/National Institute for Health Research, UK</td>
<td>Phase I</td>
</tr>
<tr>
<td>DNA, MVA-C, CN54gp140 + GLA-AF</td>
<td>DNA vectors encoding a Gag-Pol-Nef polypeptide and gp140 Env protein, both from clade C MVA-C vector encoding Gag-Pol-Nef and gp120 Env protein from clade C HIV-1 clade C gp140 protein and GLA-AF, delivered intramuscularly</td>
<td>Imperial College London/Medical Research Council/Wellcome Trust</td>
<td>Phase I</td>
</tr>
<tr>
<td>rAAV1-PG9DP</td>
<td>Recombinant AAV vector encoding the PG9 broadly neutralizing antibody</td>
<td>International AIDS Vaccine Initiative/NIAID/Children's Hospital of Philadelphia (CHOP)</td>
<td>Phase I</td>
</tr>
<tr>
<td>GTU-MultiHIV</td>
<td>DNA vector encoding fusion protein of six different HIV genes, administered by intramuscular, intradermal, or transcutaneous routes</td>
<td>Imperial College London/European Commission - CUTHIVAC Consortium</td>
<td>Phase I</td>
</tr>
<tr>
<td>MVA-B</td>
<td>MVA vector encoding Env, Gag, Pol, and Nef antigens from HIV clade B</td>
<td>Hospital Clinic of Barcelona</td>
<td>Phase I</td>
</tr>
</tbody>
</table>
an ALVAC vector adapted to encode antigens from HIV subtype C (ALVAC vCP2438) followed by a boost with a bivalent envelope protein containing antigens from two subtype C isolates, formulated with an MF59 adjuvant. These vaccines will initially be tested in a phase I trial, HVTN 100, involving around 240 participants, slated to begin next year. If all proceeds according to plan, a traditional phase III efficacy study, HVTN 702, will follow in 2016, aiming to recruit 5,400 volunteers at high risk for HIV infection and projected to take six years to complete.

The second prong of the strategy is designated the “correlates program” and features a more complex adaptive clinical trial design including combinations of DNA and NYVAC vectors with envelope protein boosts formulated in one of two different adjuvants. Part A of this study, HVTN 701, comprises a phase I evaluation of safety and immunogenicity, while part B will be a phase IIb test of safety, immunogenicity, and efficacy, with a particular focus on identifying immune correlates of protection against HIV infection. Current estimates indicate a 2015 start date for part A, and 2016 for part B.\(^68,69\) In addition to the work in South Africa, the U.S. Military HIV Research Program, which sponsored RV144, plans to conduct a follow-up trial in Thai MSM at high risk of HIV infection, with 2017 as the possible start date.\(^69\)

In parallel with efforts to launch new trials, researchers are sifting through the available samples from RV144 participants in the hope of gaining a better understanding of how the slight degree of protection against HIV acquisition was achieved. Although the analyses are only exploratory, they have identified an association with IgG antibody responses to the V1/V2 region of the HIV envelope, and suggested that IgA antibody responses may have played a detrimental role.\(^70,71\) The IgG antibodies are not neutralizing, but studies published over the last year indicate that they belong to a subclass (IgG3) associated with the mediation of additional antiviral activities including antibody-dependent cellular cytotoxicity and antibody-dependent phagocytosis.\(^72,73\) Furthermore, in a prior trial of AIDSVAX alone that did not show significant protection against HIV, this type of antibody response was not predominant.

A similar tale has emerged from the most recently conducted HIV vaccine efficacy trial, HVTN 505, which studied a prime-boost combination of a DNA and Ad5 vector that included HIV envelope antigens from multiple clades. The results, published in October 2013, showed that vaccination did not reduce the
risk of acquiring HIV. Subsequent evaluation of samples from HVTN 505 has revealed that the regimen induced only low levels of IgG and IgG3 antibody responses to V1/V2 compared with RV144. Other factors that have been suggested as potential contributors to success in RV144 are the specific innate immune profile associated with ALVAC immunization compared with other poxvirus vectors, and an interaction between vaccination and a particular immune response gene, HLA-A*02. Taken together, these findings may offer important clues about the type of immune responses vaccines will need to induce in order to replicate or improve upon the RV144 results.

Several new HIV vaccine candidates have entered clinical trials over the past year. The first assessments of mosaic HIV antigens, delivered by DNA and NYVAC vectors, are now under way. Mosaic antigens, as their name implies, represent amalgams of components from multiple different HIV isolates, optimized to induce immune responses capable of recognizing the diversity of viruses that are circulating globally. Mosaic antigens have shown some promise for reducing acquisition risk in the SIV/macaque model. Vaccine candidates are also being explored in new combinations with the aim of improving immunogenicity; examples include DNA and MVA vectors plus gp140 protein at Imperial College London and DNA and MVA vectors plus lipopeptides under the sponsorship of the French ANRS.

A vaccine based on adenovirus serotype 4 joins a growing roster of replication-competent vectors under evaluation (the others are vesicular stomatitis virus and the Tiantan vaccinia strain). The rationale is that the capacity to replicate allows a vector to induce a more sustained immune response to the antigens it encodes. However, uncertainty persists about the safety of the adenovirus platform due to evidence that a replication-incompetent serotype 5 (Ad5) vector enhanced the risk of acquiring HIV in two efficacy trials, Step and Phambili. A meta-analysis of the three efficacy trials involving Ad5-based HIV vaccines has confirmed a statistically significant, roughly one-third increase in acquisition risk, although this was entirely driven by results from Step and Phambili and was not seen in HVTN 505 (although this may be because the latter trial featured exclusion criteria intended to minimize risk and included only one immunization with an Ad5 vector as opposed to three). At a mini-summit sponsored by NIAID in September 2013, it was concluded that no further studies of Ad5 vectors in HIV should be conducted. During the discussions at the mini-summit, it was noted that adenovirus vectors derived from other serotypes may also have the potential to enhance HIV acquisition, by boosting numbers of adenovirus-
specific CD4 T cells that are subsequently drawn to mucosal sites when vaccine recipients are exposed to natural adenovirus infections (which are common in nature). Adenovirus-specific CD4 T cells cross-react to antigens from multiple serotypes. A published report from the mini-summit urges vigilance about this possibility in future studies of adenovirus vectors, while stressing that it remains speculative.

At the beginning of this year, the first human trial was launched of a novel approach that straddles territory between gene therapy and vaccination. The aim is to prevent HIV infection with bNAbs. But instead of attempting to induce bNAb production by the immune system, the approach uses an adeno-associated virus (AAV) vector to deliver them into the body. The AAV vector is injected into muscle tissue, where it then acts as a factory churning out a constant supply of bNAbs. The strategy has shown efficacy in both the macaque and humanized mouse models. The phase I trial, which is taking place in the United Kingdom, represents the culmination of extensive, long-term preclinical development by the research group of Philip Johnson at the Children’s Hospital of Philadelphia in close collaboration with (and with sponsorship from) the International AIDS Vaccine Initiative. Results are eagerly anticipated.

Researchers have not given up on trying to solve the difficult problem of inducing the immune system to produce bNAbs with a traditional vaccine. A confluence of developments has renewed optimism that a bNAb-inducing HIV vaccine is achievable. Key among them is the development of a stable version of the three-pronged HIV envelope structure targeted by bNAbs. The HIV envelope trimer, as it is called, proved enormously difficult to reproduce for biological studies due to inherent instability and the frustrating tendency for lab-created mimics to fall apart. The solution of this problem has allowed scientists to conduct structural analyses that reveal how different bNAbs interact with the HIV envelope in order to successfully neutralize diverse viral isolates, providing critical information to aid the design of vaccine immunogens. Complementing this line of research are recent studies describing how bNAb responses are generated in the rare individuals who develop them, which offer insight into how the process might be duplicated with a vaccine.
CONCLUSIONS

The pipeline of antiretrovirals for prevention—agents that can be administered orally, parenterally, vaginally, and rectally, for daily, long-acting, and as-needed use—is robust. Importantly, many of these drugs and formulations are being developed by sponsors who recognize that poor adherence has been a sizeable barrier in clinical trials and, hence, that efforts to improve the acceptability of the preventive methods is a priority.

Continued funding of demonstration projects and implementation research to evaluate facilitators and barriers to PrEP and comprehensive services intended to support adherence and behavioral risk reduction is also essential. Cost-effectiveness evaluations are also needed to drive advocacy in support of strong policies defining comprehensive and coordinated HIV prevention–service delivery under the Affordable Care Act in the United States and through payer programs in low-, middle-, and high-income countries.

On the preventive vaccine front, there are reasons to be optimistic about long-term prospects, but a licensed product is not on the immediate horizon. The question whether the RV144 results can be repeated and improved likely won’t be answered until the end of this decade at the earliest. And even if research progresses fruitfully, it is difficult to envisage a bNAb-inducing vaccine being developed until late into the 2020s. There is one approach that might alter this timeline: the hybrid of gene therapy and vaccination that employs an AAV vector to produce a continuous supply of bNAbss in the body; encouragingly, the first human trial began earlier this year, so it should soon be apparent if this novel idea has the potential to progress into efficacy studies.

The authors wish to acknowledge and thank Jeremiah Johnson for his review of this chapter.
ENDNOTES


