Preventive Technologies: Antiretroviral and Vaccine Development

By Tim Horn and Richard Jefferys

Though global HIV incidence has declined by an estimated 33% since 2001, more than 2 million people continue to be infected with the virus every year – approximately 6,000 new infections every day.[1] Efforts to reduce infectiousness through the scale-up of testing, engagement in care and supportive services, and access to safe and effective antiretroviral therapy can be credited, in large part, to the annual reductions in new infections that have been observed in many (but certainly not all) regions and populations. And though efforts to optimize HIV care continuum outcomes continue both domestically and internationally, the need for biomedical interventions to protect those most vulnerable to the virus is indisputable.

The development and implementation of, and continuing research on, pre-exposure prophylaxis (PrEP) have brought us significantly closer to a watershed in efforts to end HIV as a global epidemic. Current antiretroviral-based biomedical prevention tools, including approved oral PrEP and microbicide gels in late-stage trials, are not without significant challenges – adherence among them. However, the efficacy data are encouraging, even those limited to subsets of study volunteers: antiretroviral-based biomedical prevention can be highly effective if it is used consistently and correctly.

To address these challenges, which also include potential safety issues, ease of administration, and products that may not be scalable due to cost, there is tremendous interest in antiretrovirals in the preventive technologies pipeline, including agents for oral use, long-acting injectables, and a robust portfolio of products for vaginal and rectal administration: gels, tablets, rings, films, and nanofibers. Knowledge and support of this work are critical, not only because of its epidemic-shifting potential, but because much of it is being led by nongovernmental organizations and academic institutions, both of which are dependent on limited public and philanthropic funding.

An effective HIV vaccine could undoubtedly make a massive contribution to curtailing new infections, but a potentially licensable candidate remains a decade away at best. Recent good news is that key steps have been taken toward an efficacy trial designed to build on the slight but significant success obtained in the RV144 study, which showed a 31% reduction in HIV incidence associated with receipt of a prime-boost vaccine regimen. The new trial will take place in South Africa, and a long-awaited preparatory clinical evaluation of the vaccine components got under way in that country in February.

In a significant development for the field, a collaboration known as the mosaic HIV vaccine research program – involving subsidiaries of a major pharmaceutical company, Johnson & Johnson – is also planning efficacy trials of a combination strategy involving viral vectors and a new, improved gp140 envelope protein boost. As the name of the collaboration indicates, the vectors will encode mosaic HIV antigens, which amalgamate components from diverse viral variants.

As yet, no vaccine has proved capable of inducing the production of broadly neutralizing antibodies (bNAbs), which is the most desired goal. There are potential workarounds, however: an increasing number of highly potent bNAbs have been discovered, and there is great excitement about the possibility of delivering these antibodies by intermittent subcutaneous injections or infusions, an approach called passive immunization. Another idea currently under evaluation is the use of a gene therapy–type strategy described as antibody gene transfer, in which an adeno-associated virus (AAV) vector is employed to deliver a gene encoding a bNAb (or bNAbs) into muscle tissue. The aim is to have the vector churn out a constant supply of the bNAb into the circulation after just a single injection.

Antiretrovirals for Prevention

Table 1. PrEP and Microbicides Pipeline 2015

Agent	Class/Type	Delivery	Manufacturer/Sponsor(s)	Status
Truvada (tenofovir DF/emtricitabine) oral PrEP demonstration projects	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Oral	Gilead/U.S. Centers for Disease Control and Prevention	Phase IV
dapivirine (TMC120)	Reverse transcriptase inhibitor	Vaginal ring	International Partnership for Microbicides/ Microbicide Trials Network	Phase III
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal gel	CONRAD	Phase III
Truvada (tenofovir DF/emtricitabine) event-driven dosing	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Oral	HIV Prevention Trials Network/French National Agency for Research on AIDS and Viral Hepatitis	Phase III
GSK1265744	Integrase strand transfer inhibitor	Long-acting injectable	ViiV Healthcare/HIV Prevention Trials Network	Phase II
maraviroc, maraviroc + tenofovir DF, maraviroc + emtricitabine	CCR5 inhibitor	Oral	HIV Prevention Trials Network/AIDS Clinical Trials Group	Phase II
rilpivirine (TMC278)	Non-nucleoside reverse transcriptase inhibitor	Long-acting injectable	PATH/HIV Prevention Trials Network	Phase II
tenofovir	Nucleotide reverse transcriptase inhibitor	Rectal gel	CONRAD	Phase II
dapivirine	Reverse transcriptase inhibitor	Vaginal gel	International Partnership for Microbicides	Phase I/II
dapivirine	Reverse transcriptase inhibitor	Thin film polymer	International Partnership for Microbicides	Phase I
maraviroc	CCR5 inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicides Trials Network/U.S. National Institute of Allergy and Infectious Diseases (NIAID)/U.S. National Institute of Mental Health (NIMH)	Phase I
maraviroc + dapivirine	CCR5 inhibitor, reverse transcriptase inhibitor	Vaginal ring	International Partnership for Microbicides/Microbicides Trials Network/NIAID/NIMH	Phase I
MZC (MIV-150/zinc acetate/carrageenan) vaginal gel	Non-nucleoside reverse transcriptase inhibitor	Vaginal gel	Population Council	Phase I
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal ring	CONRAD	Phase I
tenofovir	Nucleotide reverse transcriptase inhibitor	Vaginal tablets	CONRAD	Phase I
tenofovir DF	Nucleotide reverse transcriptase inhibitor	Vaginal ring	Albert Einstein College of Medicine	Phase I
tenofovir/emtricitabine	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Vaginal tablets	CONRAD	Phase I
tenofovir + SILCS diaphragm	Reverse transcriptase inhibitor	Vaginal gel, barrier contraception	CONRAD	Phase I

Oral PrEP

Following U.S. Food and Drug Administration (FDA) approval of co-formulated tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) as PrEP in July 2012, two broad objectives have emerged:

- Continued development and implementation of demonstration projects;[2] cost-benefit analyses; educational and messaging campaigns to increase awareness among populations and individuals most at risk for the virus; training and guidelines to shepherd expert and culturally competent prescribing and follow-up practices in a variety of clinical care and community-based settings;[3] 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, drug concentrations in blood and tissues, and, ultimately, effectiveness – the primary focus in this chapter.

TDF/FTC (Truvada)

Topline results from several clinical trials, reported in previous editions of the *Pipeline Report*, have demonstrated the safety and efficacy of co-formulated TDF and FTC as PrEP among men and transgender women who have sex with men, HIV-discordant heterosexual couples, and high-risk HIV-negative heterosexual individuals.[4,5,6,7] These data formed the basis of the July 2012 FDA approval of TDF/FTC as PrEP to reduce the risk of sexually acquired HIV and, along with results from other pivotal clinical trials, the foundation of U.S. clinical practice guidelines supporting PrEP for the prevention of sex- and injection drug use–associated transmission of the virus.[8,9,10]

Though TDF/FTC is available in many countries for the treatment of HIV, it has received regulatory approval as PrEP only in the United States. Applications for approval have been filed in Australia, Brazil, South Africa, and Thailand. In other countries, including those that participated in the regulatory trials that led to U.S. approval (e.g., Botswana, Canada, Ecuador, France, Germany, Kenya, Peru, Tanzania, Uganda, and the United Kingdom), formal requests for regulatory approval have not yet been filed.[11] In the United Kingdom, based in part on the high degree of PrEP efficacy demonstrated in the recently reported PROUD study involving 545 men and transgender women who have sex with men attending sexual health clinics in England (86% efficacy; 90% CI: 58%–96%; P = .0002), advocacy efforts pushing for TDF/FTC's availability as PrEP through the National Health Service are now under way.[12] Encouraging (and superimposable) results from the French National Agency for AIDS Research IPERGAY study have also prompted groups to press the French Agency for the Safety of Health Products to approve a temporary recommendation for the use of TDF/FTC as PrEP.[13]

IPERGAY was a pilot investigation of a somewhat novel dosing strategy for TDF/FTC as PrEP: "event-driven" use, in which two TDF/FTC tablets are taken two to 24 hours before anticipated sexual activity and continued every 24 hours until 48 hours after the last sexual experience.[14] The randomized, placebo-controlled study, which enrolled 414 men and transgender women who have sex with men – 70% of whom reported condomless anal sex within two months prior to study entry – began in 2012 and was unblinded in November 2014 following a favorable interim review of the data. During the nine-month median follow-up, there were two infections in the TDF/FTC group (an annual incidence of 0.94%) and 14 infections in the placebo group (an annual incidence of 6.75%), which translated into an 86% relative reduction in the incidence of HIV infection (95% CI: 40%–99%; P < .002).

On average, IPERGAY volunteers used 16 TDF/FTC (or placebo) tablets a month, or roughly three to four tablets every week; approximately 35% used between 18 and 30 pills a month, or roughly five to seven pills a week. This observation is consistent with data from the iPrEx open-label extension study, which found that PrEP was 100% effective in volunteers using TDF/FTC at least four times a week.[15] In effect, it remains unclear to what extent event-driven oral PrEP is effective in lowering HIV infection risk among men and transgender women who have sex with men and use TDF/FTC less frequently.

Also available are preliminary data from the ADAPT study (HPTN 067).[16] The randomized, open-label trial is exploring three TDF/FTC PrEP dosing schedules: daily use of TDF/FTC; time-driven, involving twice-weekly dosing along with post-sex dosing; and event-driven, involving dosing before and after sex. All three dosing strategies followed a four-week period of once-weekly directly observed dosing. The study has enrolled approximately 500 men, transgender women, and non-transgender women who have sex with men.

The data reported at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) – limited to TDF/FTC coverage, adherence, and tolerability outcomes – come from the cohort of South African non-transgender women enrolled in the trial. Daily dosing resulted in better full coverage of sex acts (75%) and adherence (76%) compared with time-driven (56% and 65%, respectively) and event-driven (52% and 53%, respectively) dosing. There has been one infection in the daily dosing group and two infections each in the time-driven and event-driven groups; these differences are not statistically significant ($P = 0.87$). The authors suggested that daily dosing may foster better habit formation and provide the most forgiveness for missed doses at observed adherence levels, ultimately supporting current recommendations for daily use of TDF/FTC PrEP in non-transgender women.

Analyses of the other ADAPT study cohorts are ongoing.

Maraviroc (Selzentry)

CCR5-tropic HIV – virus that utilizes the CCR5 coreceptor on CD4 cells to gain entry and establish infection – is responsible for more than 95% of new sexually transmitted infections of the virus.[17,18] Thus, there has been interest in studying the CCR5 antagonist maraviroc for potential use as PrEP. Compared with TDF/FTC, 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.

Findings from laboratory research exploring maraviroc's potential activity as PrEP have been mixed. Administered systemically, the drug penetrates and concentrates well in cervical, vaginal, and rectal tissues.[19,20] A microbicide gel formulation of maraviroc has also been found to be approximately 85% effective at blocking HIV infection of rectal tissues, with drug concentrations similar to those achieved following standard oral dosing.[21] And while oral maraviroc has been reported to prevent HIV infection in a humanized mouse model involving vaginal challenges with the virus,[22] a macaque study did not find that maraviroc protected against rectal challenges with SHIV, despite high concentrations of the drug in rectal tissue.[23] More recently, single doses of maraviroc taken by HIV-negative study volunteers failed to inhibit replication in biopsied rectal tissues incubated with the virus – protection was documented in only a subset of vaginal tissues – as determined by measurements of p24 antigen levels (the validity of which remains unclear).[24]

Three clinical trials of maraviroc 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).[25] It has an estimated enrollment of 600 HIV-negative men who have sex with men and at-risk women, with an anticipated completion date of November 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.

The second trial is MVC-PREP, which is being conducted at Emory University and is evaluating concentrations of maraviroc in the blood and genital tract of HIV-negative women.[26]

The third study, MARAVIPREX, has been concluded, though data are not yet available. It was conducted by the Fundació Lluita contra la SIDA in Barcelona and evaluated the capacity of maraviroc to protect against HIV in samples of rectal mucosa from HIV-negative volunteers.[27]

Tenofovir Alafenamide Fumarate (TAF)/FTC

TAF is a prodrug formulation of tenofovir. Unlike the currently approved 300 mg TDF, another prodrug converted in the blood to the active drug tenofovir diphosphate (TDF-DP) and then taken up into cells, TAF is primarily metabolized and converted to TDF-DP inside cells. Thus, at a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90% lower but intracellular concentrations that are approximately four to seven times higher.[28,29] The reduced systemic elimination has the potential for fewer renal- and bone-related toxicities compared with TDF. Though these have not emerged as common or severe adverse events among people using TDF/FTC as PrEP,[30,31] co-formulated TAF/FTC is being eyed as a potentially valued alternative to Truvada.

Gilead Sciences has been primarily focused on developing TAF as a component of co-formulated multidrug tablets for the treatment of HIV. Its TAF/FTC co-formulation, for use in combination with other antiretrovirals for treatment purposes, is being evaluated in a phase III study, with a new drug application (NDA) filed with the FDA in early April requesting approval of the tablet.

Evaluations of TAF/FTC's pharmacokinetics (PK) and pharmacodynamics (PD) as PrEP in animals are being conducted, and data from these studies are expected sometime in the second half of 2015.[32] Information pertaining to TAF/FTC's development is expected from the company following the release of the animal data.

Also of interest is a subdermal implant – a sustained-release delivery system similar to that used for insertable contraceptive rods (e.g., Norplant) – containing TAF. It is being developed by the Monrovia, California–based Oak Crest Institute for Science, with encouraging animal PK data – including TFV-DP concentrations in peripheral blood mononuclear cells that are 30 times higher than those associated with oral daily TDF/FTC PrEP dosing in humans – recently published.[33]

Long-Acting (LA) Formulations

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 nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for monthly or quarterly, rather than daily, dosing. The drugs furthest along this development path are long-acting cabotegravir (CAB LA), ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog), and long-acting rilpivirine (RPV LA), Janssen's non-nucleoside reverse transcriptase inhibitor. Both are administered via intramuscular (IM) injection.

Four nonhuman primate studies have demonstrated CAB LA's protective effects against repeated intrarectal and intravaginal SHIV challenges.[34,35,36,37] Two of the four studies have confirmed a relationship between plasma drug concentrations (specifically the protein-adjusted 90% inhibitory concentration) and protection against intrarectal and intravaginal protection.[36,37] In humans, concentrations of CAB in vaginal, cervical, and rectal tissues following both oral dosing and long-acting IM injections are significantly reduced, compared with plasma levels, and plasma concentrations can vary based on body weight and sex (the drug is more rapidly eliminated from men's versus women's bodies).[38] It is not expected that these findings will affect CAB LA's protective effects; an 800 mg dose (two 400 mg IM injections) every 12 weeks – the dose currently being

evaluated in PrEP clinical trials – results in drug levels that are significantly higher than the concentration plasma targets previously established for protection.[39]

Two phase II studies of CAB LA are ongoing. ÉCLAIR, being conducted in the United States by ViiV Healthcare, enrolled approximately 120 at-risk men (60% men who have sex with men).[40] Volunteers are receiving 30 mg daily oral dosing or placebo for four weeks. Following a one-week washout period, IM injections of 800 mg CAB LA or placebo will be administered every 12 weeks for a total of three injections. The second study, HPTN 077, is currently enrolling approximately 176 HIV-negative volunteers – 60% of the participants will be women – in the United States, South America, and sub-Saharan Africa and will be evaluating three 800 mg IM injections 12 weeks apart.[41] The primary objective of both studies is to assess the safety, tolerability, and acceptability of CAB LA; only men and women at low to minimal risk of HIV infection are being recruited.

Encouraging phase I results from a study evaluating the PK of RPV LA in plasma, the genital tract in women, and the rectum in men were published last year.[42] More recently, however, preliminary data reported at the 2014 HIV Research for Prevention conference in Cape Town suggest that RPV LA's activity in rectal versus cervicovaginal tissues may differ considerably.[43] Though RPV levels following single 600 mg and 1,200 mg (2 $\times$ 600 mg) doses were higher in vaginal fluids versus rectal fluids, rectal tissues were found to have twice the concentrations of RPV compared with vaginal tissues. In fact, biopsied rectal cells were fully resistant to HIV nearly two months after the 1,200 mg RPV LA injections were given, whereas the vaginal and cervical cells appeared to be no better protected from HIV following either dose of the drug.

The implications of these findings, particularly those based on ex vivo pharmacodynamic testing, are not clear. It is possible that women require multiple doses to achieve cervicovaginal tissue concentrations required for protection. A phase II clinical trial being conducted by the HIV Prevention Trials Network (HPTN 076) and now open to enrollment will therefore need to proceed cautiously.[44] Following an oral lead-in period, 132 HIV-negative women considered to be at low risk for HIV infection will receive IM injections of 1,200 mg RPV LA or placebo, once every eight weeks, over a 40-week period. The study is to be conducted at four sites in the United States, South Africa, and Zimbabwe.

Microbicides: Vaginal and Rectal Gels

Phase III testing of a gel containing 1% tenofovir – the only vaginal microbicide to reach late-stage clinical trials – has yielded disappointing results. The preliminary data from FACTS 001, which was conducted to confirm the results from the phase IIb trial CAPRISA 004 demonstrating a 39% reduction in HIV risk among women using the gel,[45] were reported at the 2015 CROI in Seattle.[46]

The FACTS 001 trial was conducted by CONRAD in collaboration with the Follow-on African Consortium for Tenofovir Studies (FACTS) and the U.S. Agency for International Development (USAID). The trial enrolled 2,059 women at increased risk for HIV in South Africa. The median age at study entry was 23 years; 89% of participants were unmarried; 42% were seropositive for herpes simplex virus 2 (HSV-2); roughly 30% reported having used condoms consistently in the four weeks prior to their baseline visit; and 62% lived with their parents. As in CAPRISA 004, FACTS 001 volunteers were instructed to use the tenofovir gel or matching placebo within 12 hours before and 12 hours after intercourse (BAT-24 regimen); the VOICE study required daily microbicide use, which may have contributed to the poor adherence outcomes and null findings.[47]

A total of 123 HIV infections occurred: 61 in the tenofovir group and 62 in the placebo group (incidence rate ratio: 1.0; 95% CI: 0.7–1.4). Both groups had a 4% incidence rate of infection (95% CI: 3.1%–5.2%).

Participants used the gel during an average of 50%–60% of sex acts per month, based on returned applicators and self-reported number of sex acts, with 13% of participants using the gel during intercourse more than

80% of the time. A substudy analysis of 214 women in the tenofovir-treated group showed that detection of drug in genital fluids – notably a drug level consistent with having used the microbicide within the past 10 days – was associated with a 52% reduction in HIV acquisition (hazard ratio: 0.52; 95% CI: 0.27–0.99; P = .04). Participants with no tenofovir detected in genital samples were five times more likely to become infected. Thus, while it is possible to conclude that the gel was effective for those who used it consistently, use in the overall study population was too low to confirm the gel's effectiveness in the gold-standard intention-to-treat analysis.

Some scientists have argued that these results call into question the practicality and acceptability of gel-based microbicides and may signal the end of the line for the approach.[48]

Additional results from FACTS 001 are anticipated, including HSV-2 transmission risk data; in CAPRISA 004 and VOICE, 1% tenofovir gel use was associated with a 51% and 46% reduced risk of acquiring HSV-2, respectively.[45,49] Also forthcoming are data from CAPRISA 008, an open-label study providing additional safety data and an evaluation of the feasibility and effectiveness of providing 1% tenofovir gel to HIV-negative women through family planning clinics in KwaZulu-Natal, South Africa.[50]

A reduced-glycerin 1% 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 help minimize gastrointestinal side effects.[51] The trial is evaluating the safety and acceptability of daily or episodic (applied before and after receptive anal intercourse) reduced-glycerin 1% tenofovir gel, compared with daily oral tenofovir/emtricitabine, in 105 HIV-negative men who have sex with men and transgender women in Peru, South Africa, Thailand, Puerto Rico, and the United States.[52] Results, along with plans for an efficacy trial, are expected in early 2016.

The Population Council is developing PC-1005, 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.[53,54] Gels containing zinc acetate and carrageenan have also been shown to protect against HSV-2 vaginal and rectal challenges in mice and human cervical tissue samples.[55,56] Additionally, carrageenan has activity against human papillomavirus (HPV) infection.[57,58,59,60]

A phase I safety, PK, and acceptability evaluation of PC-1005, compared with a placebo gel, is under way with an estimated enrollment of 35 HIV-negative women.[61]

Compounds in preclinical development include a gel containing griffithsin (University of Pittsburgh), a lectin derived from algae that has activity against HIV and HSV; SR-2P (Stanford Research Institute), a gel composed of two polymers and containing tenofovir and the antiherpetic acyclovir; and IQP-0528, a pyrimidinedione analogue with non-nucleoside reverse transcriptase and entry inhibitor activities (ImQuest BioSciences).

Microbicides: Intravaginal Rings (IVRs)

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women vulnerable to HIV infection, provided that adherence levels consistent with protection can be achieved, there has been considerable interest in more user-friendly technologies. Polymeric IVRs, 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 IVR containing 25 mg dapivirine (TMC120), a non-nucleoside reverse transcriptase inhibitor licensed to the International Partnership for Microbicides (IPM)

by Janssen Pharmaceuticals. IPM has studied the compound in 16 phase I/II clinical trials in Africa, Europe, and the United States. In all studies, dapivirine has been found to be safe and well tolerated, providing the basis for larger studies that will determine whether IPM's dapivirine IVR is safe and effective in preventing HIV.

Two late-stage clinical trials are fully enrolled and ongoing: the Microbicide Trials Network's ASPIRE study (MTN 020) and the IPM's Ring Study (IPM 027).[62,63] ASPIRE, a phase III trial being conducted at sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe, has randomized approximately 3,500 HIV-negative women to receive the dapivirine IVR or a matching placebo IVR, which is replaced once a month for a year. The Ring Study, a phase II/III evaluation taking place in South Africa and Uganda, is comparing the dapivirine IVR to a placebo IVR, inserted once every week over 24 months, in nearly 2,000 HIV-negative women in South Africa and Rwanda. Open-label extensions of ASPIRE and the Ring Study are expected to begin after both trials are completed next year.

A rationale for developing IVRs 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.[64] 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, were mixed, due largely to unsatisfactory levels of maraviroc in cervical tissues and plasma samples.[65] The IPM has been redeveloping the combination IVR with plans for a second phase I study.

More recently, there have been encouraging data from the European Combined Highly Active Antiretroviral Microbicides (CHAARM) program's preclinical evaluations of silicone elastomer IVRs containing dapivirine or the protease inhibitor darunavir.[66] In macaques, all drugs were detectable in blood and vaginal fluid samples, as well as all tissue samples, with the highest concentrations in vaginal and cervical tissues and the lowest concentrations in uterine and rectal tissues. Based on these results, and given the continued progress of the dapivirine vaginal IVR, the authors recommended continued development of a co-formulated dapivirine/darunavir ring as a second-generation HIV microbicide candidate.

Antiviral IVRs in various stages of preclinical development include those containing tenofovir and acyclovir (Auritec Pharmaceuticals); tenofovir and IQP-0528; and griffithsin and carrageenan (Population Council).

Microbicides: Vaginal Tablets, Films, and Nanofibers

Groups are evaluating the potential utility of vaginal tablets and novel delivery systems, such as dissolvable films and nanofibers, which may be easier to use and cheaper to manufacture than 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.[67,68,69] A phase I placebo-controlled safety and PK 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 is ongoing.[70]

Preliminary results from a phase I clinical trial (FAME 02) comparing the safety, drug absorption, and drug distribution of a dapivirine film with dapivirine gel were reported at CROI 2014.[71] Plasma levels of dapivirine were comparable across the film and gel arms, suggesting that both products can deliver drugs with similar efficacy. 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.[71]

A cellulose-based film containing tenofovir is in a phase I trial (FAME 04).[72] The study, being conducted by CONRAD in collaboration with investigators at Magee-Womens Hospital of the University of Pittsburgh Medical Center, is evaluating 10 mg and 40 mg formulations of the film compared with 1% tenofovir gel, matching placebo gel, and matching placebo film. Approximately 80 women are to be enrolled in the trial.

The University of Washington, in collaboration with the Population Council, is evaluating the potential utility of biodegradable electrospun nanofibers containing agents including tenofovir, griffithsin, or carrageenan with activity against HIV, HSV, and HPV.

Contraceptive-Inclusive Multipurpose Prevention Technologies (MPTs)

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 cross-protective options that women can easily use and that do not require the cooperation, consent, or knowledge of their sexual partners. In turn, there is tremendous interest in the development of MPTs that can double as contraception and biomedical prevention against HIV and other 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 two MPT IVRs – all of which employ the contraceptive hormone levonorgestrel, a synthetic progestogen that has been studied and used extensively and is therefore considered 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 (MZCL) over a 90-day period: it is being developed by CONRAD.[73] A phase I safety, PK/PD, and acceptability study is under way.[74]
- A vaginal ring containing MIV-150, zinc acetate, carrageenan, and levonorgestrel to protect against pregnancy, HIV, HSV-2, and human papillomavirus (HPV): preclinical evaluations by the Population Council are ongoing, with one recent analysis finding that the four-way ring protected 11 of 12 macaques against SHIV challenges and resulted in a 30% reduction in HSV-2 infection.[75]

On-demand products include:

- A reformulated 1% 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 are being undertaken by CONRAD.
- Polyphenylenecarboxymethylene (PPCM), a polymer-based gel being developed by Scottsdale, Arizona–based Yaso Biotech, has activity against HIV, HSV, HPV, chlamydia, and gonorrhea and has contraceptive activity as a nonsurfactant spermicide.[76,77,78] It has been in preclinical development for several years.

Providing PrEP in Prevention Trials

The clear efficacy of PrEP has implications for the conduct of clinical trials of HIV prevention interventions. The approach up until now has been for all participants to be offered a standard-of-care prevention package including counseling and condoms, and the effect of a given intervention is evaluated against this background. The question of how to incorporate PrEP into the standard of care now needs to be considered.

When the first PrEP efficacy data emerged, researchers conducting an ongoing vaccine efficacy trial, HVTN 505, initiated extensive consultations with community and other stakeholders, and ultimately, "the preferred option was to reintensify education and counseling about PrEP and develop a referral system rather than to provide the drug directly at trial sites as part of the study."[79] Ethicists have since suggested that PrEP should be offered as part of the standard-of-care prevention package,[80] and investigators planning future vaccine trials have indicated that this will be the case as long as agreement can be obtained from relevant local health authorities.[81]

Issues also arise for the design of trials aiming to assess the efficacy of biomedical alternatives to TDF/FTC PrEP. Researchers have suggested that noninferiority trial designs would be feasible but would probably require large sample sizes, and the results could be challenging to interpret.[82] The same authors note that in some settings where TDF/FTC efficacy has been reported to be low, it may be possible to evaluate the superiority of alternatives.

Preventive Vaccines, Passive Immunization, and Antibody Gene Transfer

Table 2. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline 2015

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES			
pGA2/JS7 DNA + MVA/HIV62	**Prime:** DNA vaccine **Boost:** modified vaccinia Ankara strain (MVA) vector Both encoding Gag, Pol, and Env proteins from HIV-1 clade B	GeoVax/NIAID	Phase IIa
ALVAC-HIV vCP1521	Canarypox vector encoding HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol protein, and a synthetic polypeptide encompassing several known CD8+ T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. Military HIV Research Program (MHRP)/NIAID	Phase II
AIDSVAX B/E	AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	U.S. Army Medical Research and Materiel Command	Phase II
HIVIS 03 DNA + MVA-CMDR	**Prime:** HIVIS DNA encoding Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) proteins **Boost:** MVA-CMDR encoding Env (E), Gag (A), and Pol (E) proteins	Vecura/Karolinska Institutet/Swedish Institute for Infectious Disease Control/ MHRP	Phase II
LIPO-5	Five lipopeptides composed of cytotoxic T lymphocyte (CTL) epitopes from Gag, Pol, and Nef proteins	French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (INSERM-ANRS)	Phase II
VICHREPOL	Chimeric recombinant protein composed of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/ Russian Federation Ministry of Education and Science	Phase II
Ad26.Mos.HIV MVA-Mosaic gp140 protein	Adenovirus serotype 26 (Ad26) vectors encoding mosaic Env, Gag, and Pol MVA vectors encoding mosaic Env, Gag, and Pol gp140 protein boost	CruceII/NIAID/MHRP/International AIDS Vaccine Initiative (IAVI)/Beth Israel Deaconess Medical Center	Phase I/IIa
ALVAC-HIV (vCP2438) + bivalent subtype C gp120/MF59	Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120)	NIAID/HIV Vaccine Trials Network (HVTN)/Bill & Melinda Gates Foundation/South African Medical Research Council/Sanofi Pasteur/ Novartis Vaccines	Phase I/II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
DNA-C + NYVAC-C	**Prime:** DNA vaccine encoding clade C Env, Gag, Pol, and Nef proteins **Boost:** NYVAC-C attenuated vaccinia vector encoding clade C Env, Gag, Pol, and Nef proteins	GENEART/Sanofi Pasteur/Collaboration for AIDS Vaccine Discovery (CAVD)	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics	Phase I/II
DNA-HIV-PT123 AIDSVAXB/E	DNA 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	NIAID	Phase Ib
Ad26.ENVA.01	Adenovirus serotype 26 vector encoding the HIV-1 clade A Env protein	CruceII/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost Phase I w/ Ad35-ENVA
Ad35-ENVA	Adenovirus serotype 35 vector encoding the HIV-1 clade A Env protein	CruceII/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost Phase I w/ Ad26.ENVA.01
Ad35-GRIN/ENV	Two adenovirus serotype 35 vectors, one encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, the other encoding HIV-1 clade A Env (gp140)	IAVI/University of Rochester	Phase I Prime-boost Phase I w/ GSK HIV vaccine 732461 (F4)
Ad5HVR48.ENVA.01	Hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; encodes HIV-1 clade A Env	CruceII/NIAID	Phase I
Cervicovaginal CN54gp140-Hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjuvant, delivered intravaginally	St George's, University of London/ European Union	Phase I
DCVax + poly ICLC	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	Rockefeller University	Phase I
DNA-HIV-PT123, NYVAC-HIV-PT1, NYVAC-HIV-PT4, AIDSVAX B/E	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	NIAID/IPPOX/EuroVacc/HVTN	Phase I
DNA + Tiantan vaccinia vector	Prime: DNA vector, with or without electroporation Boost: Replication-competent recombinant Tiantan vaccinia strain vector Both encoding Gag, Pol, and Env proteins from HIV-1 CN54	Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/Peking Union Medical College	Phase I
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PX'Therapeutics/European Commission	Phase I
GEO-D03 DNA + MVA/HIV62B	**Prime:** DNA vaccine with granulocyte-macrophage colony–stimulating factor (GM-CSF) adjuvant **Boost:** MVA vector Both vaccines encode Gag, Pol, and Env proteins from HIV-1 clade B and produce virus-like particles (VLPs)	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461 (F4)	Gag, Pol, and Nef fusion protein in proprietary adjuvant AS01	GlaxoSmithKline	Phase I Prime-boost Phase I w/ Ad35-GRIN

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV-1 Tat/delta-V2 Env	Tat and oligomeric ΔV2 Env proteins	Istituto Superiore di Sanità/Novartis Vaccines	Phase I
MAG-pDNA, Ad35-GRIN/ENV	Multiantigen DNA vaccine encoding 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 encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, and the other encoding HIV-1 clade A Env (gp140)	IAVI/Profectus Biosciences/ Ichor Medical Systems	Phase I
MAG-pDNA, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine encoding 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 encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector encoding HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector encoding HIV-1 clade A Gag protein and 25 CD8+ T-cell epitopes	Impfstoffwerk Dessau-Tornau/ University of Oxford/Medical Research Council/University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative (PedVacc001) mothers
MVA HIV-B	MVA vector encoding HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
PENNVAX-G DNA + MVA-CMDR	**Prime:** DNA vaccine encoding HIV-1 clade A, C, and D Env proteins and consensus Gag protein **Boost:** MVA-CMDR live attenuated MVA vector encoding HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/MHRP/Walter Reed Army Institute of Research	Phase I
PolyEnv1 EnvDNA	Vaccinia viruses encoding 23 different Env proteins and DNA vaccine encoding multiple Env proteins	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA + ChAdV63.HIVconsv or MVA.HIVconsv	**Prime:** DNA vaccine pSG2 **Boost:** chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
Ad35-ENVA	Adenovirus serotype 35 vector encoding HIV-1 clade A Env	Vaccine Research Center/NIAID	Phase I
$rVSV_{IN}$ HIV-1 Gag	Attenuated replication-competent rVSV vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
SAAVI DNA-C2, SAAVI MVA-C, clade C gp140/MF59	SAAVI DNA and MVA vectors encoding an HIV-1 clade C polyprotein including Gag, reverse transcriptase, Tat, and 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	South Africa AIDS Vaccine Initiative/ HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, adenovirus serotype 35 vector encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef	IAVI/DNAVEC	Phase I
LIPO-5, MVA HIV-B, GTU-MultiHIV	Five lipopeptides comprising CTL epitopes from Gag, Pol, and Nef proteins MVA vector encoding Env, Gag, Pol, and Nef proteins from HIV clade B DNA vector encoding fusion protein comprising elements from six different HIV proteins Given in four different prime-boost combinations	INSERM-ANRS	Phase I Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Ad4-mgag, Ad4-EnvC150	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	NIAID/PaxVax	Phase I
DNA Nat-B Env, NYVAC Nat-B Env DNA CON-S Env, NYVAC CON-S Env DNA mosaic Env, NYVAC mosaic Env	**Prime:** DNA vector encoding Nat-B, CON-S, or mosaic Env proteins **Boost:** NYVAC vectors encoding Nat-B, CON-S, or mosaic Env proteins	HVTN/IPPOX/Center for HIV/AIDS Vaccine Immunology (CHAVI)	Phase I
CN54gp140 + GLA-AF	HIV-1 clade C gp140 protein and glucopyranosyl lipid adjuvant (aqueous formulation) (GLA-AF), delivered intramuscularly	Imperial College London/Wellcome Trust/National Institute for Health Research, U.K.	Phase I
DNA, MVA-C, CN54rgp140 + GLA-AF	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	Imperial College London/Medical Research Council/Wellcome Trust	Phase I
GTU-MultiHIV	DNA vector encoding fusion protein comprising elements from six different HIV proteins, administered by intramuscular, intradermal, or transcutaneous routes	Imperial College London/European Commission - CUT'HIVAC Consortium	Phase I
DNA Nat-B Env DNA CON-S Env DNA mosaic Env MVA-CMDR	**Prime:** DNA vector encoding Nat-B, CON-S, or mosaic Env proteins **Boost:** MVA vector encoding Env (E), Gag (A), and Pol (E) proteins	NIAID/ CHAVI/IPPOX/MHRP/HVTN	Phase I
Trimeric gp140	Protein vaccine consisting of a trimeric gp120	CruceII/NIAID/Beth Israel Deaconess Medical Center	Phase I
MVA mosaic	MVA vectors encoding HIV-1 mosaic proteins	CruceII/MHRP/NIAID/Beth Israel Deaconess Medical Center	Phase I
DNA-HIV-PT123 AIDSVAXB/E	DNA 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	EuroVacc/IAVI/Uganda Medical Research Council/Uganda Virus Research Institute Uganda Research Unit on AIDS/Centre Hospitalier Universitaire Vaudois	Phase I
Oral Ad26	Orally administered replicating adenovirus serotype 26 vector encoding mosaic Env protein	IAVI/University of Rochester/Beth Israel Deaconess Medical Center	Phase I
PENNVAX-GP HIV-1 DNA vaccine IL-12 DNA adjuvant	DNA vector encoding Gag, Pol, and Env proteins + DNA vector encoding IL-12 adjuvant, delivered via intradermal or intramuscular electroporation	NIAID	Phase I
PASSIVE IMMUNIZATION			
VRC01	Monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I (adults and HIV-exposed infants)
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/Children's Hospital of Philadelphia	Phase I

HIV Vaccines

When HIV was first identified more than three decades ago, it was initially thought that the road to a vaccine might be relatively short and straightforward. Instead, it has proved long and winding, with many sharp, disorienting turns and deceptive cul-de-sacs. But important lessons have been learned en route, and, in 2015, a variety of possible approaches are proceeding toward the hoped-for destination of an effective, licensable product.

Leading the way is the relative juggernaut of the Pox-Protein Public-Private Partnership (P5), which includes the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network (HVTN), Novartis Vaccines and Diagnostics, Sanofi Pasteur, the South African Medical Research Council, the U.S. Military HIV Research Program, and the U.S. National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS. The P5 was established to build on the borderline but significant 31% reduction in the risk of HIV acquisition observed in the RV144 trial, which tested a prime-boost combination of an ALVAC canarypox vector and AIDSVAX, a gp120-based protein vaccine, in over 16,000 Thai individuals.[83] A particular focus is whether it might be possible to duplicate or even improve an apparently higher efficacy of 60% that was evident early on in RV144, at one year of follow-up. After an excruciatingly long period of preparation (partly due to the need to manufacture a new gp120 protein boost to replace AIDSVAX), the work of P5 is now approaching the point where new efficacy trials can be launched.

Recently, two key milestones have been reached: a study of the RV144 regimen completed in South Africa – the site chosen for the follow-up efficacy trials – found that it induced similar immune responses, with evidence of slightly higher response rates than in the Thai study population.[84] And in February of this year, a trial began that will evaluate adapted versions of the RV144 vaccines designed specifically for use in South Africa: an ALVAC vector encoding a gp120 envelope protein from the prevalent clade C virus (in addition to gp41, Gag, and protease from clade B) and an envelope protein boost comprising two gp120s derived from clade C HIV isolates formulated with the MF59 adjuvant.[85] The trial is designated HVTN 100, and, if several key immune response targets are met,[81] it will set the stage for a far larger 5,400-person phase III efficacy trial (HVTN 702) with the potential to lead to licensure if the regimen works well enough. The current hope is to start HVTN 702 in 2016.

P5 is also conducting a program that aims to identify correlates of vaccine-induced protection against HIV acquisition, and a key part of this effort involves a complex phase I/IIa adaptive trial (HVTN 701) that currently has an estimated start date of 2018 and intends to assess the efficacy of multiple prime-boost combinations.[86]

The identification of correlates of protection would provide much-needed guidance to the HIV vaccine field. In their absence, there is uncertainty about whether any of the vaccines in the current pipeline might be effective. None has shown an ability to induce antibody responses capable of potently neutralizing a broad array of HIV isolates from different clades (bNAbs), which is still the ideal goal of vaccination.

An alternative mechanism of HIV prevention is elimination of virus-infected cells before systemic infection takes hold. The task is challenging; recent studies in the SIV/macaque model have shown that the long-lived virus reservoir is established in less than three days.[87] Evidence from RV144 suggests that this may have been achieved by antibody-mediated effector activities such as antibody-mediated cellular cytotoxicity (ADCC) and antibody-mediated cellular phagocytosis (ADCP)[88,89] (processes involving antibodies binding to infected cells and flagging them for destruction by natural killer cells or monocytes). The possible role of non-neutralizing antibody effector mechanisms in the RV144 outcome has spurred intense interest in the topic, and researchers are now exploiting new technologies to identify antibody properties associated with different effector functions.[90,91] This work promises to help identify vaccine candidates most likely to induce potent ADCC and ADCP.

There is evidence from animal models that the presence of effector CD8+ T cells at sites of virus exposure might also be capable of controlling and, in some cases, extinguishing infection. This salutary outcome has been observed in studies of replicating cytomegalovirus (CMV) vector.[92] Although CMV has yet to be adapted for use in humans, several other replicating virus vectors are in clinical trials, and a new addition this year is an orally administered adenovirus serotype 26 (Ad26) vaccine being tested at the University of Rochester, in collaboration with the International AIDS Vaccine Initiative (IAVI) and Beth Israel Deaconess Medical Center (BIDMC).[93] The construct is one of many now incorporating mosaic HIV antigens, which are distilled from multiple viral variants and have shown promise in macaque experiments; interestingly, evidence suggests that antibody effector functions are involved.[94]

IAVI and BIDMC are partners in a larger collaborative endeavor informally known as the mosaic HIV vaccine research program, which aims to conduct a comprehensive assessment of whether the mosaic antigen approach can contribute to protection in humans. The other contributors are Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, the U.S. Military HIV Research Program (MHRP), the Ragon Institute, and NIAID. The current goal is to test Ad26 and modified vaccinia Ankara (MVA) strain vectors encoding mosaic HIV antigens along with a gp140 envelope protein in various prime-boost combinations. The gp140 is designed to better mimic the natural structure by preserving its trimeric form. Another new vaccine trial that began during the past year is the first evaluation of this trimeric gp140 in humans.[95]

Depending on the outcome of immunogenicity studies in humans and challenge experiments in macaques, the mosaic HIV vaccine research program's aim is to conduct two phase IIb/III efficacy trials in high-risk populations, one in Africa and Asia and the other in the United States, Latin America, and Europe, possibly beginning as early as 2017.[96]

While news of plans for efficacy trials in addition to the P5 program is welcome for the vaccine field, the inclusion of an adenovirus vector might raise some eyebrows. Receipt of an Ad5 vector was associated with a significant increase in the risk of HIV infection in two previous studies,[97] and no definitive explanation for this adverse outcome exists[98] (an issue discussed in the *2014 Pipeline Report*). Alternative-serotype vectors such as Ad26 have been developed based on the idea that the problem was restricted to Ad5, but the evidence is equivocal, and there is a theoretical possibility that it could extend to other adenoviruses. Researchers affiliated with the MHRP have recently shown that Ad5-specific CD4+ T cells are particularly susceptible to HIV infection and argued that responses to alternative vectors should be similarly analyzed in vitro and carefully evaluated in animal models in order to gain a better understanding of whether they might also increase acquisition risk.[99] Offering some preliminary reassurance, results from a phase I trial of the Ad26 vector have demonstrated no significant increases in vector-specific CD4+ T cells in blood or mucosal tissue.[100]

Early safety and immunogenicity results from several other adenovirus vector trials have been published or presented over the past year, including Ad35 and a hybrid of Ad5 and Ad48 (Ad5HVR48.EnvA.01).[101] The overall theme is that the vaccines are safe and immunogenic, but, given the lack of clarity about correlates of protection, further work will be needed to parse which candidates and combinations might be most worthy of further evaluation. Ad35 has been combined with a new replicating Sendai virus vector, with no safety issues emerging; the order of administration was found to significantly influence whether primarily T-cell or antibody responses were induced.[102] In a separate study in which Ad35 was combined with a fusion protein named F4 (developed by GlaxoSmithKline), both T-cell and antibody responses were invoked, and there was some evidence of CD8+ T cell–mediated inhibition of HIV replication as measured by an in vitro assay, albeit not to levels typically observed in HIV controllers.[103]

Elsewhere in the pipeline, the laboratory of Thomas Lehner in the United Kingdom has been working for many years on a novel strategy that aims to inhibit HIV via induction of chemokines and the antiviral restriction factor APOBEC3G. The vaccine links CN54gp140, an envelope protein from a clade C HIV isolate, with a

heat shock protein 70 (Hsp70) adjuvant (heat shock proteins are naturally produced by cells under conditions of stress). Results from a first phase I trial involving nontraumatic intravaginal administration were published late last year, and the researchers report evidence of chemokine-mediated CCR5 downregulation along with induction of APOBEC3G. An in vitro assessment of the ability of participants' peripheral blood mononuclear cells to support HIV replication indicated that vaccination was associated with reduced infectivity.[104]

Another unconventional vaccine approach that has received attention recently involves the use of a probiotic to deliver virus antigens, leading to the development of immune responses that dampen antiviral activity rather than enhance it. The brainchild of Jean-Marie Andrieu, the vaccine has demonstrated a surprisingly high degree of protection against SIV challenges in macaque studies.[105,106,107] The mechanism appears to relate to the inhibition of CD4+ T cell activation, which deprives the virus of susceptible target cells. The researchers have developed a version to test in humans and hope to launch a trial by the end of the year.[108,109]

An ongoing collaboration between researchers in Nairobi, Kenya, and Oxford, United Kingdom, is investigating whether vaccination might be able to enhance protection against HIV transmission to infants through breastfeeding. The group has recently published results demonstrating that administration of an MVA vector encoding clade A HIV antigens was safe and feasible but not immunogenic when given alone.[110] Future studies aim to explore newer prime-boost regimens and the potential for dual immunization against both HIV and tuberculosis.

Passive Immunization

The discovery of a new generation of highly potent bNAbs has opened up the possibility of testing the efficacy of passive immunization as a preventive strategy. The Vaccine Research Center (VRC) at the U.S. National Institutes of Health is developing the bNAb VRC01 for this purpose and is conducting phase I safety and PK studies of subcutaneous and intravenous delivery in both uninfected and HIV-positive adults. Preliminary results suggest that concentrations shown to be effective in macaque studies are achievable in humans with monthly dosing, and no significant safety issues have emerged.[111] The VRC is working toward conducting clinical trials of VRC01 in infants, as an addition to maternal ART to prevent breastfeeding HIV transmission, and in adults at high risk of HIV acquisition. These plans include a preparatory study in a small number of HIV-exposed infants in collaboration with the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network and an assessment of various dosing regimens in adults in collaboration with the HVTN.

The VRC is also pursuing modifications to bNAbs that would allow less frequent dosing,[112,113] and it has initiated manufacturing of two candidates, VRC01-LS and VRC07-523-LS (VRC07 is similar to VRC01 but even more potent and broadly active). Research conducted with antibodies to respiratory syncytial virus indicates that the modifications may allow dosing as infrequently as every six months to one year.[114]

Another bNAb being evaluated for use as passive immunization is 3BNC117. This year saw the publication of highly anticipated first results from a clinical trial that administered 3BNC117 as a single infusion to HIV-positive individuals.[115] At the upper end of the range of doses evaluated, 3BNC117 caused significant declines in viral load that persisted up to 28 days in some cases. However, one participant had high-level resistance to 3BNC117 at baseline, highlighting the fact that even the best bNAbs are unlikely to be able to inhibit all HIV variants when administered as single agents. Researchers intend to explore combinations of bNAbs, and recently Dan Barouch presented encouraging laboratory data showing that just two highly potent bNAbs – PGT121 and PGDM1400 – can together inhibit 98%–99% of a large panel of different HIV variants from across the globe.[116]

Antibody Gene Transfer

An alternative to passive immunization with bNAbs is antibody gene transfer or vectored immunoprophylaxis. AAV vectors, which have been used with some success to supply factor IX in human trials for hemophilia,[117] are employed to deliver the gene encoding a bNAb into muscle tissue, essentially acting as a persistent factory for bNAb production. The approach has shown promise in macaque[118] and humanized mouse[119] models, and a human trial of an AAV vector encoding the bNAb PG9 is ongoing in the United Kingdom.[120] Results are pending, but the investigator Phil Johnson stated in a recent presentation that dose escalation is proceeding according to plan, with the third dosing group now enrolling.[121] Several research groups are interested in pursuing AAV as a vehicle for delivering bNAbs or other HIV inhibitors (such as a recently described and highly potent protein named eCD4-Ig[122]), so the progress of this initial trial is being closely watched.

Conclusion

An astonishing array of antiretroviral-based modalities continue to make their way down the HIV biomedical prevention pipeline, though progress remains slow, with several promising candidates and new technologies still in the same phases of preclinical development reported in the "Preventive Technologies" chapter of the *2014 Pipeline Report*. However, new data continue to emerge at a steady clip – made increasingly accessible through biomedical prevention–focused sessions at longstanding congresses such as CROI and new conferences such as HIV Research for Prevention (HIVR4P) – to help facilitate the development of candidates that are likely to be not only potent and safe but also acceptable (and, indeed, desirable) to vulnerable populations who need them most.

Progress in preventive vaccines, and the related approaches of passive immunization and antibody gene transfer, promises to complement and extend the successes that have been obtained with antiretroviral-based strategies. As long as the research continues to be supported, the tidal wave of new HIV infections promises to be not only stemmed but also reduced to a level that could finally end the epidemic.

Indeed, there appears to be a decline in global funding for HIV prevention research and development, despite an increase in encouraging basic science, preclinical research, and proof-of-concept studies involving antiretroviral-, vaccine-, passive immunotherapy–, and antibody gene transfer–based technologies. According to a recent resource tracking report published by AVAC, funding for HIV prevention R&D declined by US$50 million, or four percent, in 2013 (US$1.26 billion), compared with 2012 (US$1.31 billion). This follows a four-year increase in funding between 2009 (US$1.22 billion) and 2012. The decrease is attributed primarily to a decline in investments by the U.S. public sector – which remains the largest funder of HIV prevention R&D – by US$38 million between 2012 (US$925 million) and 2013 (US$887 million) – along with a 10% decline in investments by European public-sector agencies between 2012 (US$86 million) and 2013 (US$77 million).[123]

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HIV R4P: HIV Research for Prevention Conference
ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy
IAC: International AIDS Conference (World AIDS Conference)
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