Preventive Technologies: Antiretroviral and Vaccine Development

By Jeremiah Johnson and Richard Jefferys

INTRODUCTION

Recent advances in the research, development, and implementation of biomedical HIV prevention—primarily in the form of treatment as prevention (TasP) and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as pre-exposure prophylaxis (PrEP)—already appear to be bearing fruit in addressing complex HIV epidemics. At this year's Conference on Retroviruses and Opportunistic Infections (CROI), the Centers for Disease Control and Prevention (CDC) presented their first HIV incidence estimates in six years, showing declines in new infections overall, including among white men who have sex with men (MSM).[1] Last year, a *Lancet* article looking at incidence in Danish MSM found that, thanks to very high levels of viral suppression among HIV-positive MSM, new infections have been declining since 1996, nearly reaching the World Health Organization (WHO) elimination threshold by 2013.[2] A 42 percent decline in HIV diagnoses among MSM in London's Dean Street STI clinic, which diagnoses one in four of London's HIV infections, also seems strongly linked to increased testing, treatment, and community advocacy to connect men to PrEP in spite of National Health Service England's ongoing refusal to cover PrEP.[3] Given the persistence of HIV epidemics among MSM, these successes indicate that we may at last have prevention tools that can end some of the most stubborn epidemics.

Not all of the news is rosy, of course. Racial disparities in the United States in new incidence rates—including stagnant rates of infections among black MSM and rising infections in Latino MSM—are a reminder that we are far from dismantling the systemic racism that underlies disparate health outcomes in communities of color. The struggle to firmly establish the visibility of transgender men and women in research and data collection continues to leave gender-nonconforming individuals exceptionally vulnerable compared with other key populations.[4] With over 200 documented new infections, largely attributed to injection drug use, since the end of 2014 in an Indiana town of only 4,200 people, we are reminded of the fragility of earlier victories in epidemics among people who inject drugs.[5] UNAIDS has also sounded the alarm about declining international investments in HIV, which are happening at a time when HIV infections among adults have stopped declining and are rising in some regions.[6] While the science of HIV prevention has never been more productive, unfortunately many of our triumphs continue to be overshadowed by the social, political, and economic barriers that greatly limit access for marginalized communities.

Ongoing HIV prevention research remains hopeful, however, with many possibilities for expanding and improving our current toolbox in the pipeline. A number of highly anticipated studies have launched in the past year to build upon recent exciting breakthroughs related to oral PrEP, long-acting injectable PrEP, and vaginal rings. Gilead Sciences began recruitment in the fall of 2016 to study the efficacy of Descovy, their new tenofovir alafenamide (TAF)-based version of Truvada, as PrEP. After a number of missteps that led community advocates to call for a halt to the study—including lack of transparency and community oversight—the phase III trial is now moving forward with separate community advisory groups being convened for North American and European trial sites. Despite concerns related to the long pharmacokinetics (PK) "tail" observed with long-actingy injectable cabotegravir (CAB LA), a phase III trial looking at its efficacy in MSM and transgender women launched in December of last year. A primary challenge for implementation would be that individuals may need to commit to taking oral PrEP for a year or more following their final injection in order to avoid becoming infected with HIV and developing resistance as a result of the subtherapeutic levels of cabotegravir.

The International Partnership for Microbicides (IPM) is moving ahead with follow-up assessments and analyses related to their vaginal ring containing dapivirine, which last year was reported to reduce new infections in two simultaneous studies by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older and little to no protection among women 21 years of age and younger.[7]

One new concept for prevention of bacterial sexually transmitted infections (STIs) that has gained more attention in recent years has been the use of doxycycline as a PrEP or post-exposure prophylaxis (PEP) for gonorrhea, chlamydia, and syphilis. Although the real-world possibilities for implementation remain unclear, particularly considering ongoing concerns related to drug-resistant gonorrhea, more research is being planned to assess doxycycline for prevention.

A few short years ago, passive immunization—the infusion or injection of antibodies—was the tiniest of blips on the biomedical prevention radar. Today it represents a busy and expanding area of research, due to the discovery and characterization of an ever-increasing number of broadly neutralizing antibodies (bNAbs), which are capable of potently inhibiting diverse HIV variants from multiple global clades.[8] Several bNAbs have been manufactured for clinical testing, and the furthest along the developmental pathway, VRC01, is the subject of two large efficacy trials known as the AMP studies.[9] The rise of passive immunization provides an important example of how a technological breakthrough can revolutionize research: the identification of the new generation of potent bNAbs was made possible by techniques that can isolate and clone the antibodies being produced by individual B cells among many millions sampled from an individual.[10,11,12] The U.S. National Institutes of Health (NIH), whose funding is now under serious threat from the Trump administration, provided the support for much of this critical work. In an example of cross-pollination between biomedical prevention fields, bNAbs are also undergoing evaluation in microbicide formulations.[13]

The immunological process that leads to the generation of bNAbs in some HIV-positive individuals is typically long and complex, proceeding over several years,[14] and reproducing this process with a vaccine—which remains the ultimate goal for researchers—presents a stern challenge. Incremental progress has continued in preclinical studies over the past year, and trials of vaccine constructs that may have the potential to guide B cells along the first steps toward bNAb production are expected to begin in 2018.[15]

In the meantime, vaccine candidates capable of inducing other types of immune responses that might lead to at least some level of protection—based on lessons learned from the RV144 trial in Thailand[16]—have advanced into an efficacy trial in South Africa, HIV Vaccine Trials Network (HVTN) 702, which began enrolling last fall.[17]

Table 1. PrEP and Microbicides Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
ORAL FORMULATIONS				
TAF + FTC	NtRTI/NRTI	Gilead Sciences	Oral PrEP	Phase III
TAF + FTC	NtRTI/NRTI	CONRAD	Oral PrEP	Phase I (in cisgender women)
Genvoya (EVG + COBI + FTC + TAF)	INSTI/NtRTI/NRTI	Emory University	Oral PrEP	Phase I
LONG-ACTING FORMULATIONS				
Cabotegravir	INSTI	ViiV Healthcare	IM	Phase IIb/III
Rilpivirine	NNRTI	PATH	IM	Phase II

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
MICROBICIDE RINGS, GELS, ENEMAS, FILMS, AND OTHER INSERTABLES				
Dapivirine	NNRTI	IPM (vaginal ring and rectal gel also with MTN)	Vaginal ring	Phase IIIb
			Vaginal gel	Phase II
			Rectal gel	Phase I (planned)
			Vaginal film	Phase I
Tenofovir	NtRTI	CONRAD		
			Vaginal ring	Phase I
			Vaginal tablet	Phase I
Tenofovir	NtRTI	Johns Hopkins University	Enema	Phase I
MIV150	NNRTI	MTN	Rectal gel	Phase I (planned)
Elvitegravir	INSTI	MTN	Rectal insert	Phase I (planned)
IQP-0528	NNRTI	ImQuest U19	Rectal gel	Phase I
Griffithsin	Cell-viral fusion–blocking agent	U19 University of Louisville	Rectal gel	Phase I
PC-1005	NNRTI, ZA, CGN	Population Council	Vaginal and rectal gel	Phase I
MVC	EI	IPM	Vaginal and rectal gel	Phase I
MVC + dapivirine	EI/NNRTI	IPM	Vaginal ring	Phase I
MK-2048 + vicriviroc	CCR5 inhibitor/ INSTI	MTN	Vaginal ring	Phase I
Dapivirine + darunavir	NNRTI/PI	CHAARM	Vaginal gel	Phase I
DS003	EI	IPM	Vaginal tablet	Phase I
Dapivirine + DS003	NNRTI/EI	IPM	Vaginal ring	Preclinical
Darunavir	PI	IPM	Vaginal ring	Preclinical
MULTIPURPOSE TECHNOLOGIES				
Tenofovir + levonorgestrel	NtRTI/HC	CONRAD	Vaginal ring	Phase I
Dapivirine + levonorgestrel	NNRTI/HC	IPM + MTN	Vaginal ring	Phase I
MB66	Anti-HIV + anti-HSV antibodies	LeafBio, Inc.	Vaginal film	Phase I

CGN, carrageenan
COBI, cobicistat
EI, entry inhibitor
EVG, elvitegravir
FTC, emtricitabine
HC, hormonal contraception
HSV, herpes simplex virus
IM, intramuscular
IPM, International Partnership for Microbicides
MVC, maraviroc
MTN, Microbicide Trials Network
INSTI, integrase strand transfer inhibitor
NNRTI, non-nucleoside analogue reverse transcriptase inhibitor
NRTI, nucleoside analogue reverse transcriptase inhibitor
NtRTI, nucleotide analogue reverse transcriptase inhibitor
PI, protease inhibitor
PrEP, pre-exposure prophylaxis
TAF, tenofovir alafenamide
ZA, zinc acetate

ORAL FORMULATIONS

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

The advantages of these compounds, which include Gilead's TAF plus FTC (Descovy) and possibly its other TAF-based single-tablet regimen product that includes elvitegravir, cobicistat, and FTC (E/C/F/TAF; Genvoya)—as PrEP remain unclear.[18,19] Possibilities include improved markers of renal and bone safety relative to TDF-inclusive regimens. Although kidney and bone problems remain uncommon and mild and are almost always reversible following drug cessation among long-term TDF/FTC PrEP users in clinical trial and demonstration project cohorts, new oral compounds may prove to be useful for those with other risk factors (e.g., underlying renal insufficiency, baseline bone mineral deficiency, concomitant use of nephrotoxic or bone-mineral-depleting medications, and advancing age).[20,21,22,23,24,25]

Updates for PEP have also been in the works. Last year, the CDC updated its guidelines for non-occupational PEP (nPEP).[26] Researchers are also looking at dolutegravir (Tivicay), elvitegravir/cobicistat/FTC/TDF (Stribild), and E/C/F/TAF as alternative PEP regimens that may improve adherence to and completion of the 28-day course of prophylaxis (see Text Box, page 41). The use of doxycycline as a PrEP and/or PEP for bacterial STIs has also gained interest in recent years, with studies presented at CROI 2015 and 2017 showing an effective reduction in STIs when doxycycline was used among MSM for prevention (see Text Box, page 43).

TAF and FTC

Like TDF, TAF is a prodrug formulation of tenofovir. Unlike TDF, which is converted in the blood to the active drug tenofovir diphosphate (TFV-DP) and then taken up into cells, TAF is primarily metabolized and converted to TFV-DP inside of cells. Using a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90 percent lower but intracellular concentrations that are approximately four- to sevenfold higher.[27,28] The reduced systemic exposure has the potential for fewer renal- and bone-related toxicities compared with TDF. TAF's low-milligram dosing also has the potential for reduced generic production costs and, ultimately, greater affordability versus TDF/FTC in low-income countries. Hence, TAF/FTC is also being eyed as an alternative to Truvada.

Enrollment for a phase III safety and efficacy trial comparing TAF/FTC to TDF/FTC for the prevention of HIV infections in HIV-negative men and transgender women who have sex with men is underway, with an estimated study completion date of September 2020.[29] The DISCOVER trial is being run by Gilead Sciences, the manufacturer of both Descovy and Truvada, and began recruitment in September of 2016 with an estimated 5,000 participants set to be enrolled from across the United States, Canada, and Western Europe. Participants will be randomized to two arms, one receiving active TAF/FTC and placebo TDF/FTC and the other receiving active TDF/FTC and placebo TAF/FTC. Following community pushback, Gilead modified the initial study protocol, which called for a 30-day washout period for individuals already on Truvada for PrEP.[30,31] After at least 96 weeks of blinded treatment, and provided that TAF/FTC shows sufficient efficacy, the study will be unblinded and participants will be offered the option to continue as part of an open-label extension of DISCOVER.

With TDF set to go off patent in the United States at the end of this year and FTC going off patent in 2021, there is little mystery as to why Gilead has taken TAF off the shelf—after development was inexplicably delayed for the past decade[32]—and is now following up on the FDA approval of Descovy

for HIV treatment by aggressively pursuing a phase III trial of F/TAF as PrEP before generics can come to market. If F/TAF is shown to be noninferior, its improved safety profile may give a competitive edge to Descovy over generic TDF/3TC or, eventually, TDF/FTC. Given the already excellent safety profile of TDF/FTC, health care professionals and potential PrEP users should be wary of this scheme. While F/TAF as PrEP will be the better option for some, particularly individuals with decreases in renal function, for the vast majority of PrEP users the additional financial costs of Descovy will greatly outweigh the additional benefits compared with generics.

Researchers are confident that Descovy will be noninferior to Truvada as PrEP, given positive outcomes in nonhuman primate trials. Results from CDC evaluations of TAF plus FTC in rhesus macaques that were rectally challenged with simian-human immunodeficiency virus (SHIV) were published last year and more thoroughly covered in last year's *Pipeline Report*.[33] None of the TAF-treated macaques were infected after 19 exposures—100 percent protection—whereas the previous macaque studies of TDF/FTC suggested 94 percent protection after 14 SHIV exposures.

Making heads or tails of macaque and human tissue studies has been difficult. Despite apparent protection, rectal concentrations of TFV-DP of macaques treated with TAF were lower than those of the macaques treated in previous studies with TDF. In another study presented at CROI 2016 that looked at TFV and TFV-DP concentrations in the mucosal tissues of eight HIV-negative cisgender women, the plasma levels of TFV were 19-fold lower and peripheral blood mononuclear cell levels of TFV-DP were ninefold higher than those seen following single-dose TDF 300 mg dosing in an earlier study.[34] Conversely, intracellular concentrations in biopsied tissues proved to be significantly lower: twofold in cervicovaginal samples and 13-fold in rectal samples. And, compared with TDF, TAF administration resulted in a higher percentage of tissue samples with undetectable drug levels: 63 percent of the rectal and 75 percent of genital tract samples had TFV and TFV-DP concentrations below the level of detection.

While DISCOVER will seek to answer lingering questions and determine efficacy for men and transgender women who have sex with men, CONRAD has launched additional investigation aimed at assessing the pharmacology of TAF in cervicovaginal tissues as a next step for understanding the potential value of TAF as PrEP for cisgender women.[35] The phase I trial is estimated to be completed by October of this year and will give greater insights into whether TAF/FTC is likely to show efficacy in a larger trial.

PEP Updates

A 2014 meta-analysis of randomized and nonrandomized studies reporting completion rates for PEP revealed low levels of completion of PEP in the 28 days following a possible exposure to HIV.[36] Researchers have been looking for alternative regimens that might have better completion outcomes.

Last year, the CDC released an update to its 2005 nPEP guidelines listing TDF/FTC and raltegravir as the preferred regimen for nPEP, with TDF/FTC, darunavir, and ritonavir as possible alternatives.[37] Research has shown, however, that the second daily dose of raltegravir may be challenging for people taking nPEP to remember.[38] Ritonavir, with its well-known gastrointestinal side effects, may also complicate nPEP completion.

A recent study with results published in March of this year found that dolutegravir with TDF/FTC was a safe and well-tolerated option for once-daily PEP in 100 gay and bisexual Australian men in need of PEP.[39] PEP completion was 90 percent (95% confidence interval [CI]: 84–96%). For the 10 men who did not complete dosing, nine were lost to follow-up and one discontinued due to headache. No participant was found to acquire HIV through week 12.

Another study looking at Stribild as PEP published favorable results in November, showing that among 234 participants who effectively received PEP, 215 (92%) completed 28 days of PEP, with only three switching from Stribild to another PEP because of side effects. More than 60 percent of participants reported at least one adverse event, which were mild to moderate. Fatigue and central neurological and abdominal side effects were the most frequently reported.[40] Another study is preparing to evaluate Genvoya, Gilead's TAF-based version of Stribild, as PEP.[41] Researchers are hopeful that these single-tablet regimens will be capable of further improving adherence and completion.

TDF/FTC and Pregnancy

A number of studies are looking at the role of TDF/FTC in the lives of pregnant or postpartum women and for serodiscordant couples looking to conceive. Conception and pregnancy pose unique circumstances for HIV prevention; in women trying to conceive, condoms are obviously not a viable option for protection from HIV infection, and pregnant and postpartum women have been shown to be at increased risk of HIV infection largely due to reduced condom use.[42] While treatment as prevention may itself be enough to protect the HIV-negative partner while trying to conceive,[43] PrEP may contribute to peace of mind and presents a simpler, potentially cheaper, and less invasive solution than methods such as sperm washing or in vitro fertilization. It may also be a safe alternative to condoms for women during and just after pregnancy.

PrEP during pregnancy has not been specifically studied as part of randomized controlled trials; however, the safety of TDF/FTC for pregnant women and fetuses has been fairly well established. For years, HIV-positive women who have become pregnant have safely taken TDF/FTC as part of treatment with no increased likelihood of birth defects or adverse pregnancy outcomes reported in the Antiretroviral Pregnancy Registry.[44] Additionally, researchers in the Partners PrEP study observed no statistically significant pregnancy-related complications among the 288 pregnancies that happened among study participants.[45] Although pregnancy led to discontinuation from the trial and the study was not meant to specifically research PrEP during pregnancy, investigators estimate that fetuses may have been exposed to either tenofovir or TDF/FTC for a maximum of six weeks each. A study presented at HIV R4P last year also found that it was safe to breastfeed while still on PrEP.[46] Still, there has previously been some indication that pregnant women taking TDF/FTC may give birth to slightly smaller babies with reduced bone density,[47] making it preferable to reduce unnecessary exposure to TDF/FTC until better information becomes available.

The Microbicide Trials Network's ongoing EMBRACE study (MTN-016), an HIV prevention agent pregnancy exposure registry that compiles information from pregnancies that occur during biomedical prevention trials, will hopefully shed further light on the effects of TDF/FTC in expectant mothers.[48] In the

meantime, some studies are attempting to develop better screening methodologies that will help limit uptake of PrEP in pregnant women with low risk of seroconversion.[49]

Two ongoing observational studies are looking specifically at PrEP as an option for safer conception.[50,51] One from the University of California, San Francisco will compare uptake, adherence, and efficacy of PrEP, sperm washing, and/or artificial vaginal insemination offered to serodiscordant couples looking to conceive. Results from the study are expected in March 2019. Another study headed up by the University of Washington will look at pregnancy rates and HIV incidence when serodiscordant couples looking to conceive are counseled on TasP, PrEP, and timed condomless sex: results will be forthcoming in summer 2018.

Doxycycline for the Prevention of Bacterial STIs

Bacterial STIs have been shown to increase the likelihood that an individual will acquire or transmit HIV.[52] Traditional STI prevention approaches, including behavior change related to frequency/number of sexual partners and levels of condom use, appear to be largely ineffective from a public health perspective. Syphilis rates among MSM in the United States and Western Europe have also been increasing since before the turn of the century—well before iPrEx demonstrated the efficacy of Truvada as PrEP—adding to the urgency for better, evidence-based options for the prevention of bacterial STIs.[53]

A small pilot study released in 2015 demonstrated that the antibiotic doxycycline provided as a PrEP may be effective in reducing STI incidence.[54] The study was small, with only 30 gay men and transgender women, but it showed a statistically significant 70 percent decrease in STIs when half the participants were assigned doxycycline as PrEP and half the participants were offered financial incentives to avoid infections. Absolute numbers of syphilis, gonorrhea, and chlamydia infections were all lower in the doxycycline arm; however, the study was too small to provide statistically significant reductions when infections were broken down by specific disease.

A study presented at CROI 2017 showed that doxycycline provided as a PEP in oral HIV PrEP users led to a 47 percent reduction in bacterial STIs, with a 70 percent drop in chlamydia and a 73 percent drop in syphilis, but no reduction in gonorrhea.[55] The study randomized 232 MSM from the French Ipergay PrEP study, with half of them being provided with doxycycline for STI PEP. Those in the treatment arm were told to take a 200 mg pill up to 72 hours after each episode, though nearly every participant who took a pill did so within 24 hours. Participants were followed for 8.7 months, with 212 participants-,106 in each arm, completing the study. Notably, STI percentages were extremely high in each arm, though the 38 percent annual STI incidence rate in the doxycycline arm was a significant improvement compared with 70 percent in the control arm.

Two new studies looking at doxycycline for STI prevention are being conducted by the British Columbia Centre for Disease Control.[56,57] One is a smaller pilot study that will look at the feasibility and tolerability of using daily doxycycline for syphilis PrEP in a group of 50 HIV-negative MSM who are also taking Truvada as HIV PrEP. The second study is an early phase

I study to determine whether the daily use of doxycycline is an efficacious and acceptable intervention for syphilis prevention in a group of 288 HIV-positive MSM. The study focusing on HIV-negative men currently has an estimated completion date of December 2017, whereas the study of HIV-positive men is set to run through May 2020.

Antibiotic resistance, specifically in the case of gonorrhea, will be one of the major factors in considering the future of doxycycline as STI PrEP or PEP. Although doxycycline has not been recommended as treatment for gonorrhea for years, the threat of additional resistance remains a concern given that there are so few new antibiotics in the treatment pipeline for gonorrhea.

PrEP Breakthrough Infections

TDF/FTC (Truvada) as PrEP remains the most effective, thoroughly researched, evidence-based option for preventing sexual acquisition of HIV. Out of tens of thousands of individuals taking PrEP to date, only three cases of likely breakthrough infections have been documented, validating earlier mathematical modeling indicating that Truvada was up to 99 percent effective in preventing sexual infections if taken consistently in HIV-negative individuals. However, extremely rare instances of breakthrough infections tend to gain considerable—and disproportionate—media attention when they occur.

The first and most well-documented case of a breakthrough infection was reported in Boston at CROI 2016 regarding a Toronto gay man who reported high adherence to PrEP and consistently maintained three-month checkups with his physician.[58] Dried blood spot (DBS) analysis of tenofovir levels in red blood cells showed excellent adherence leading up to the infection, as did high plasma concentrations of tenofovir at the patient's follow-up visit, though these assessments could not completely rule out the potential for a brief lapse. Despite a high likelihood of consistent adherence, the man tested positive for HIV in April 2015—two years after starting PrEP. Resistance testing indicated that the man's virus was totally resistant to FTC and carried mutations that conferred at least partial resistance to TDF. A similar second breakthrough infection coming out of New York City with convincing, though less conclusive, documentation was reported in October in Chicago at the HIV Research for Prevention (HIVR4P) conference.[59] A gay man taking PrEP with reported good adherence was diagnosed with a strain of HIV resistant to both TDF and FTC. Due to a five-month break between visits, the man's physician was unable to fully assess adherence for the entire period, though DBS testing did indicate excellent adherence over the prior three months. Both cases indicate that TDF/FTC may not be able to prevent infection from extremely rare viruses with resistance to both medications.

A third case reported at CROI 2017, involving a gay man from Amsterdam with a strain of HIV showing no resistance mutations, has raised the possibility that on extremely rare occasions even nonresistant strains might establish infection in spite of evidence of good PrEP adherence.[60] There are many mysteries and questions in this case, however. The infection occurred in the six weeks following the man's last doctor's visit, meaning that a lapse in adherence cannot be ruled out. Also, the man reported two instances of injection drug use over the period in question, though he insisted that he had used sterile equipment.

These three cases stress the importance of routine provider visits while taking PrEP and provide greater insight into the conditions that could potentially lead to breakthrough infection. The extreme rarity of breakthrough infections confirms that although PrEP is not 100 percent effective, it remains the most effective prevention option for sexual acquisition of HIV to date.

IMPLANTS AND INJECTABLE LONG-ACTING FORMULATIONS

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. Investment in subcutaneous implants to deliver antiretrovirals for PrEP has increased in the last year, including significant investment by the NIH and the Bill & Melinda Gates Foundation.[61] Particular focus is also being placed on the development of long-acting nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for doses that are separated by weeks or months. The drug furthest along the development path is CAB LA, ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog); however, the unexpectedly long persistence of CAB LA in a significant minority of ECLAIR trial participants, possibly tied to higher body mass index (BMI), has led to some uncertainty about how to manage the long PK tail in some individuals. A long-acting injectable version of rilpivirine (RPV LA), Janssen's non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), remains on an uncertain course.

As long-acting formulations become more likely candidates for real-world use, it is imperative that researchers and key stakeholders begin actively looking at implementation challenges early. An NIH-funded review article published in 2015 looked at the importance of addressing long-acting formulation implementation issues at three levels: patient, provider, and system.[62] Patient-level factors include targeted education and messaging, tailored supports to enhance acceptability and uptake, and effective strategies for promoting adherence/persistence and retention in care. Provider-level factors include engaging a broad mix of providers while ensuring adequate training and support for patient assessment, counseling, and follow-up. Systems-level factors include optimal delivery modalities, resource allocation, and ensuring access to populations most in need of new prevention options.

CAB LA

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

Last year's Pipeline Report gave a detailed review of the outcomes of the ECLAIR trial.[63] The study randomized 127 HIV-negative men between 18 and 65 years of age and at low risk of acquiring HIV at screening to either CAB (N = 106) or placebo (N = 21). For the first four weeks of the trial, oral CAB (30 mg) or placebo were administered, followed by a seven-day washout period. The injection phase began at week 5 and ended at week 41, with CAB LA 800 mg or saline being administered via intramuscular (IM) injections during visits at weeks 5, 17, and 29. CAB LA was found to be well tolerated in comparison to placebo, although a minority of participants withdrew due to injection tolerability (4%) and a small proportion experienced grade 2 events such as fever, injection site itching, and injection site swelling. Two seroconversions were reported: one in the placebo group at week 23 and one in the CAB LA group at week 53, 24 weeks after the participant's final injection; however, the participant in the CAB LA group who ultimately seroconverted had no detectable CAB in blood plasma at week 53. CAB PK data throughout each 12-week dosing interval were reported. Results showed trough concentrations to be lower than the prespecified ideal at the end of the dosing intervals in approximately two-thirds of participants. On the basis of these findings, a new dosing strategy of 600 mg IM injections every eight weeks has been selected for CAB LA's continued development.

The study also included a follow-up phase with preliminary results presented at the HIVR4P conference in October 2016. There, researchers reported that in 14 out of 86 participants (17%), drug levels of CAB LA remained above the lower limit of quantification but below the protein-adjusted 90% inhibitory concentration (PA-IC90) a year after their last injection.[64] Persistence of CAB LA was associated with a higher range of BMIs, with higher BMIs leading to a longer PK tail. Additional covariate evaluation is warranted; however, these findings raise questions about CAB LA discontinuation and the possibility of drug resistance should individuals become infected with HIV while they maintain subtherapeutic yet quantifiable levels of CAB LA a year or more beyond their last injection.

To better understand the impact of CAB LA's prolonged PK, a companion phase IIa study to ECLAIR, HPTN 077, has been extended by 24 weeks.[65] The study will aim to find out how long measurable drug levels persist and if smaller and more frequent injections of 600 mg every 8 weeks may shorten the tail. HPTN 077 has enrolled approximately 200 HIV-negative volunteers in the United States, South America, and sub-Saharan Africa. The estimated primary completion date is now set for July 2017.

Despite ongoing questions related to CAB LA persistence, HPTN 083, a phase IIb/III head-to-head safety and efficacy trial of CAB LA versus oral TDF/FTC, was launched in December 2016.[66] In step 1 of the trial, lasting five weeks, participants will receive oral TDF/FTC or oral CAB 30 mg daily, depending on the randomization. In step 2, participants will receive a daily oral placebo plus active CAB LA 3 mL injections at two time points four weeks apart and every eight weeks thereafter, or active daily oral TDF/FTC plus placebo injections, for up to 180 weeks. In step 3, to cover the prolonged PK tail associated with CAB LA dosing, all participants will be required to take daily oral TDF/FTC for at least one year, starting no later than eight weeks after the last injection. The HPTN 083 trial has a planned enrollment of 4,500 trangender and MSM individuals 18 years of age and older who are at high risk for sexually acquiring HIV infection. The estimated study completion date is June 2020.

A companion study to HPTN 083, HPTN 084, is in the final stages of development, and a final protocol was posted on the HPTN website in March 2017 with plans to begin recruitment later this year.[67] Approximately 3,200 HIV-uninfected cisgender women from sub-Saharan Africa will be enrolled and randomized 1:1 to active CAB LA and placebo TDF/FTC versus active TDF/FTC and placebo CAB LA in order to measure safety and efficacy of CAB LA in women. The study duration is expected to be 4.6 years. After the study reaches the required number of incident HIV endpoints, participants will begin an open-label daily oral TDF/FTC extension for approximately 48 weeks. As part of HPTN 084, an injectable contraceptive substudy will run simultaneously for 100 evaluable participants to study the effect of CAB LA on depot medroxyprogesterone acetate and norethisterone enanthate.

RPV LA

Encouraging phase I results from the SSAT 040 study evaluating the PK of RPV LA in plasma, the genital tract in women, and the rectum in men were published in 2014.[68] Later that year, however, preliminary data from the MWRI-01 phase I study suggested that RPV LA's activity in rectal versus cervicovaginal tissues may differ considerably.[69] Although RPV levels following single 600 mg and 1,200 mg (2 × 600 mg) doses were higher in vaginal fluids versus rectal fluids, rectal tissues were found to have twice the concentration of RPV compared with vaginal tissues. In fact, rectal cell explants were fully resistant to HIV nearly two months after the 1,200 mg RPV LA injections were given, whereas vaginal and cervical cell explants appeared to be no better protected from HIV following either dose of the RPV LA.

A more recent study characterized the concentrations of RPV needed to prevent HIV infection in mucosal tissue.[70] Although rectal tissue RPV levels appeared to be sufficient to block HIV infection—concentrations were approximately fivefold higher than what would be required to suppress viral infection—2.5-fold more drug was needed in female genital tissue to demonstrate similar inhibition. These data, the authors noted, support the explant findings from MWRI-01, in which HIV infection was suppressed in rectal tissue but not in cervicovaginal tissues.

Still under way is HPTN 076, a phase II safety and acceptability evaluation of RPV LA compared with placebo. The study is set to continue through October 2017, although preliminary results were presented at CROI 2017.[71] A total of 136 (100 African, 36 U.S.) women were enrolled with a median age of 31 years. Among participants, 46 percent were married, 94 percent were black, and 60 percent were unemployed. The women were randomized (2:1) to receive either oral rilpivirine 25 mg or placebo daily for four weeks. In the absence of any safety signals, the participants received either 1,200 mg RPV LA (2 mL IM injections in both gluteal muscles) or placebo every eight weeks for a total of six injections.

Acceptability, safety, and PK data were collected throughout the study. The product was paused for any participant with a grade 2 or greater related adverse event or grade 3 or greater unrelated adverse event. Ten women withdrew (eight RPV vs. two placebo) and four had product discontinued (three RPV vs. one placebo) during the oral phase (weeks 0–4). A total of 122 (80 RPV LA vs. 42 placebo) women received one or more injections; 98 (64 RPV LA vs. 34 placebo) received all six injections. During the injection phase (weeks 4–52), one woman withdrew in the placebo group and 16 product discontinuations (10 RPV LA vs. 6 placebo) occurred. Of the product discontinuations, six (8%) RPV LA and two (5%) placebo were due to adverse events, including one placebo arm participant with prolonged QTc interval. Transient grade 2 or greater liver abnormalities occurred in nine (11%) of the RPV LA participants compared with four (10%) in the placebo arm. Three RPV LA arm participants developed grade 3 or greater injection site reactions compared with none in the placebo arm. No significant difference in adverse events was observed between the two arms. Among participants who received one or more injections, the median trough concentration (Ctrough) of RPV was 68.2 ng/mL. At week 52 (eight weeks after last injection), the Ctrough was 91.9 ng/mL. The concentration two weeks after the first and second injections (at weeks 6 and 14) was 85.5 ng/mL and 113 ng/mL, respectively. At the last injection visit, 61 percent of women strongly agreed that they would definitely use and 73 percent that they would think about using a PrEP injectable in the future.

Overall the injections were safe, well tolerated, and acceptable. The lower-quartile RPV concentrations were consistently above the PA-IC90 at all times through eight weeks post-injection. However, based on the conflicting PK and explant infection data reported to date, compounded by the formulation's need for cold-chain storage, there is no indication of RPV LA moving into phase III trials for PrEP.

Implantable Devices

Intarcia Therapeutics, a Boston-based company developing an implantable minipump about the size of a matchstick to deliver a drug for control of blood sugar in people with type 2 diabetes, has received a $50 million grant from the Bill & Melinda Gates Foundation to develop minipump technology to deliver antiretroviral drugs for PrEP, with an additional $90 million available if they are successful.[72]

Other researchers have looked at extended-release implants containing TAF. The Oak Crest Institute for Science (Monrovia, California) published encouraging animal PK data from a study of a subdermal delivery system similar to that used for removable contraceptive rods (e.g., Norplant).[73] Auritec, a Pasadena drug delivery company, received NIH funding to test an implant containing TAF in dogs.[74] The 40-day study found that the implant maintained drug levels 30 times higher than those needed to protect against HIV infection throughout the study period. The Sustained Long-Acting Protection from HIV (SLAP-HIV) partnership, based at Chicago's Northwestern University and supported by a $17 million NIH grant, is working to develop an implant that can deliver either cabotegravir, rilpivirine, TAF, or the tenofovir analogue tenofovir exalidex.[75]

MICROBICIDES

Intravaginal Rings

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women who are vulnerable to HIV infection, provided that adherence levels that are consistent, there has been considerable interest in more user-friendly and longer-acting technologies. Polymeric intravaginal rings (IVRs), similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology and are currently in various stages of development. IPM's dapivirine ring, which showed limited efficacy in sub-Saharan African women in the ASPIRE and Ring studies, has generated the most excitement; CONRAD has also completed a phase I trial for a tenofovir-containing ring.[76] IPM and CONRAD are also both looking at versions of their rings that also contain the contraceptive levonorgestrel as a multipurpose prevention tool that may better meet the needs of women seeking to avoid both HIV and unwanted pregnancies.

Dapivirine

The most clinically advanced candidate is a silicone elastomer IVR containing 25 mg dapivirine (TMC120), an NNRTI licensed to IPM by Janssen Sciences Ireland UC. Data from two registrational trials, the Microbicide Trials Network's ASPIRE study (MTN-020) and the International Partnership for Microbicides' Ring Study (IPM 027), were reported at CROI 2016, with the final ASPIRE results being simultaneously published in the *New England Journal of Medicine*.[77,78,79]

ASPIRE, a phase III trial conducted at sites in Malawi, South Africa, Uganda, and Zimbabwe, randomized 2,629 HIV-negative women between 18 and 45 years of age to receive the dapivirine IVR or a matching placebo IVR, which were self-inserted and removed once a month for a year. The Ring Study, a phase II/III evaluation at six South African sites and one Ugandan site, compared the dapivirine IVR to a placebo IVR, inserted once every month over 24 months, in 1,959 HIV-negative women between 18 and 45.

Results from both studies, presented more comprehensively in last year's Pipeline Report, suggested that the dapivirine IVR is safe and moderately effective at reducing incident HIV in African women. HIV infection rates were reduced by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older: 56 percent in ASPIRE and 37 percent in the Ring Study, with little to no protection among women 21 years of age and younger—most likely due to lower levels of adherence.

An updated adherence analysis from ASPIRE presented at the 21st International AIDS Conference in Durban, South Africa, found that consistent users of the ring experienced 65 percent fewer infections compared to placebo.[80] Rather than looking at blood levels of dapivirine, which may be influenced by participants reinserting the ring shortly before a follow-up visit, researchers refined their analysis by looking at the level of drug left behind in rings that were returned to researchers. A ring that has been worn for a full month should have 20–21 mg of drug remaining. Any level below 22 mg was treated as indicating medium to high adherence, whereas a ring with 23.5 mg or more indicated nonadherence. Of the 2,629 women enrolled in ASPIRE, 2,359 were included in this analysis. Compared to placebo, higher adherence to the active dapivirine ring was associated with a 65 percent (95% CI 23-84, p=0.009) reduction in HIV-1 risk. Results were similar both for the full-study population and when excluding the two sites with lower adherence/retention (risk reduction 67%, 95% CI: 23–86), and point estimates suggested HIV-1 protection for both women >21 years (risk reduction 72%, 95% CI: 21–90) and ≤21 years of age (risk reduction 50%, 95% CI: -78–86). Partial/low adherence was not significantly associated with HIV-1 protection (relative risk reduction 35%, 95% CI -10–61, P = .12).

Qualitative interviews with 214 participants were also published last year, providing insight into important issues related to adherence.[81] The rings were largely acceptable to women; however, concerns about side effects, the appearance of the rings, and the experimental nature of the rings were highlighted as barriers. At clinical visits, women were asked, "How worried are you about having a vaginal ring inside you every day for at least a year?" While 29 percent of women reported this concern at the start of the study, only four percent of participants did so at their final follow-up clinic visit. Specific concerns related to use, health, hygiene, sexual enjoyment, and social approval also decreased significantly between the start and the end of the study.

Additionally, possible detection by male partners during sex and partner opinions were of importance to the women interviewed. Although fewer than five percent of all ASPIRE study participants reported incidents of intimate-partner-related violence or other social harms, women who did report violence or social harm within a month of the interview were nearly 2.5 times more likely to have low adherence to the ring. Younger age at enrollment, having a new primary partner, and not disclosing study participation or ring use to the primary partner were significantly associated with reporting social harms. Additional new data revealed that a majority of women—64 percent—disclosed the use of the ring to their male partners at the outset of the study, but 13 percent of study participants never revealed that they were using the ring. The investigators found that neither disclosing nor concealing use of the ring affected women's adherence to the product.

IPM plans to submit the dossier of dapivirine IVR evidence required for licensure —ASPIRE and the Ring Study are only a part of an extensive research portfolio—to regulatory agencies. Two open-level evaluations of the dapivirine IVR are in the works.[82,83] MTN-025, the HIV Open-Label Prevention Extension (HOPE) trial, is an ASPIRE follow-on study to assess continued safety and adherence, and it is currently enrolling. IPM hopes to conduct its own open-label extension follow-on study to provide former Ring Study participants with the dapivirine IVR.

Several follow-up safety studies are planned and being implemented. A trial looking at compatibility between the dapivirine ring and an antifungal clotrimazole cream commonly used to treat vaginal yeast infections is ongoing as is a trial to assess the presence of dapivirine in the breast milk of lactating women.[84,85] A trial looking at tampon use and menses in women using the ring has been completed. Plans to investigate the potential impact of bacterial vaginosis on ring efficacy are also underway after a substudy of 41 women from the FAME-04 vaginal microbicide study, presented at CROI 2017, found a significant correlation between higher levels of non-*Lactobacillus* bacteria and lower tenofovir levels in vaginal fluid and cervical tissue.[86]

Rectal Microbicide Gel and Enemas

Researchers are largely moving away from tenofovir-based rectal gels, partially due to concerns with developing an acceptable applicator. Instead, several phase I studies are set to look at other compounds for possible gel, insert, and suppository formulations.

MTN-026/IPM 038 is a phase I, randomized, double-blind, multi-site, placebo-controlled trial designed to evaluate the safety and acceptability of dapivirine gel (0.05%) when administered rectally to healthy, HIV-1–uninfected men and women.[87] Another study, MTN-33/IPM 044, is a planned phase I study looking at the PK of the dapivirine gel when administered rectally via a vaginal applicator and a coital simulation device to healthy, HIV-1–uninfected men and transgender women. Participants will be randomized to administer a single dose of study product using an applicator of up to 10 mL of gel applied as a rectal lubricant using a phallic device to simulate anal sex. Specimens will be collected at multiple time points to assess drug concentrations, ex vivo efficacy, and biomarkers of safety. MTN-037 is a phase I trial looking at a rectal gel formulation for MIV150, a new NNRTI; MTN-039 is a phase I trial set to look at the integrase inhibitor elvitegravir as a rectal gel; and ImQuest is looking at another NNRTI- IQP-0528- in its own phase I study.[88] The cell-viral fusion–blocking agent Griffithsin, which has been shown to inhibit both HIV and herpes simplex virus (HSV) infection, is also being assessed as a possible rectal gel at the University of Louisville.[89]

For at least five years, scientists have been looking at a rectal douche as a possible microbicide delivery system for protection during anal sex. Enemas, already frequently used in preparation for receptive anal sex, have the added benefit of achieving more comprehensive coverage compared with rectal gels. A challenge with developing enemas is finding the right formulation with an osmolarity that is likely to lead to cellular uptake of the ARV. At HIVR4P in October, researchers presented promising results from a nonhuman primate study involving a tenofovir-containing gel that is hypo-osmolar.[90] Four formulations were tested: two were iso-osmolar and two were hypo-osmolar. Two concentrations of tenofovir were tested: 1.76 and 5.28 mg/mL. Nonhuman primates were given a simple dose via rectal insertion and evacuation of the TFV liquid medium; researchers then measured concentrations of tenofovir in their blood and in rectal tissue biopsies an hour, a day, and three days after the dose. Explant challenges with simian immunodeficiency virus (SIV) were also conducted in each case. Hypo-osmolar formulations led to faster uptake of tenofovir, with the higher dose leading to drug concentrations both in blood and inside cells that were 5–11 times higher than any of the other formulations, with no indication of damage to rectal tissues with any formulation. Biopsies taken one hour after dosing with the high-dose hypo-osmolar formulation were completely protected from infection; 24 hours after dosing, two out of six samples became infected, compared with infections in biopsies from all other microbicide doses.

A study out of Johns Hopkins University is moving forward with this concept in humans. DREAM-01 is an early phase I open-label dose-escalation and variable-osmolarity study to compare the safety, PK, pharmacodynamics, and acceptability of three formulations of a TFV enema.[91] Eighteen men will be enrolled, with results expected in October of this year. The goal of the study will be to identify the dose

and osmolarity of a TFV enema for HIV PrEP that achieves the desired tenofovir diphosphate target concentrations in colonic mucosal mononuclear cells that have previously been shown to confer protection from HIV acquisition in MSM.

Vaginal Microbicide Gels

The future of vaginal microbicides remains uncertain following the disappointing data from both the FACTS 001 and VOICE studies evaluating 1% tenofovir gel.[92,93] Given these results, CONRAD is reportedly moving away from tenofovir gels, although IVRs containing tenofovir remain in the pipeline. Although adherence, rather than potency, was believed to be the primary factor associated with poor efficacy in the FACTS 001 and VOICE studies, a number of gel-based microbicides containing alternative compounds—dapivirine, maraviroc, and a broad-spectrum coformulation of MIV-150, zinc acetate, and carrageenan (see below)—are at various stages of early development. Several of these products are also being evaluated for rectal use and protection.

PC-1005

The Population Council is developing PC-1005, a combination gel containing the NNRTI MIV-150, zinc acetate, and carrageenan. PC-1005 potentially offers protection not just against HIV but also against HSV-2 and human papillomavirus. Phase I safety, PK, acceptability, and adherence data were presented at CROI 2016 and published in JAIDS in December of last year.[94,95,96] The trial enrolled 25 HIV-negative women between 19 and 44 years of age. Following a three-day open-label evaluation of PC-1005 in five participants, 20 women were randomized to apply PC-1005 4 mL or placebo once daily for 14 days. Seventeen women completed the randomized phase of the trial (two were lost to follow-up and one withdrew before dosing). There were no severe adverse events or early discontinuations because of adverse events. MIV-150 was absorbed systemically at low levels, and there was no measurable HIV and HPV activity in cervicovaginal lavages. Acceptability was also high: 94 percent of participants reported a willingness to use the gel in the future. Additional data also indicate that PC-1005 inhibits HIV and HSV-2 infection in cervical explants in a dose-dependent manner.

PREVENTIVE VACCINES, PASSIVE IMMUNIZATION, AND ANTIBODY GENE TRANSFER

Table 2. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline 2017

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
ALVAC-HIV (vCP2438) + bivalent clade 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/HVTN/Bill & Melinda Gates Foundation/ South African Medical Research Council/Sanofi Pasteur/GlaxoSmithKline	Phase IIb/III
pGA2/JS7 DNA + MVA/HIV62	Prime: DNA vaccine Boost: 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/MHRP/NIAID	Phase II

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
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/SMI/MHRP	Phase II
LIPO-5	Five lipopeptides composed of CTL epitopes from Gag, Pol, and Nef proteins	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	Ad26 vectors encoding mosaic Env, Gag, and Pol MVA vectors encoding mosaic Env, Gag, and Pol gp140 protein boost	Janssen Vaccines & Prevention B.V./NIAID/MHRP/IAVI/Beth Israel Deaconess Medical Center	Phase I/IIa
ALVAC-HIV (vCP2438) Bivalent clade C gp120/MF59 Bivalent clade C gp120/AS01B	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) with either MF59 or AS01B adjuvant	NIAID/GlaxoSmithKline/Sanofi Pasteur	Phase I/IIa
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/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 + AIDSVAX B/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
Cervicovaginal CN54gp140-Hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with Hsp70 adjuvant, delivered intravaginally	St George's, University of London/European Union	Phase I
DCVax + poly-ICLC + MVA-CMDR	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, followed by a boost with MVA-CMDR encoding Env, Gag, and Pol proteins	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

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
GEO-D03 DNA + MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines encode Gag, Pol, and Env proteins from HIV-1 clade B and produce 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 with Ad35-GRIN
MAG-pDNA, Ad35-GRIN/ENV	Multi-antigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, IL-12 pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system + two Ad35 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, rVSVIN 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 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	IDT/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 protein	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	Ad35 vector encoding HIV-1 clade A Env	Vaccine Research Center/NIAID	Phase I
rVSVIN HIV-1 Gag	Attenuated replication-competent rVSV vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
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-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	SAAVI/HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, Ad35 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
Ad4-mgag, Ad4-EnvC150	Live, replication-competent recombinant Ad4 vectors encoding HIV-1 clade C Env and HIV-1 mosaic Gag proteins 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/CHAVI	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	Crucell/NIAID/Beth Israel Deaconess Medical Center	Phase I
MVA mosaic	MVA vectors encoding HIV-1 mosaic proteins	Crucell/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/ UVRI Uganda Research Unit on AIDS/Centre Hospitalier Universitaire Vaudois	Phase I
Oral Ad26	Orally administered replicating Ad26 vector encoding mosaic Env protein	IAVI/University of Rochester/Beth Israel Deaconess Medical Center	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
HIV VACCINES			
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
IHV01 (FLSC-001)	Full-length single-chain gp120-CD4 complex vaccine	University of Maryland/Bill & Melinda Gates Foundation/Profectus BioSciences, Inc.	Phase I
HIV DNA-C CN54ENV + recombinant HIV CN54gp140	DNA vector encoding HIV-1 clade C Env delivered intramuscularly and intradermally Clade C Env protein boost	Imperial College London	Phase I
Ad26.Mos.HIV + clade C gp140	Ad26 vectors encoding mosaic HIV-1 Env, Gag, and Pol + clade C HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
HIV-1 Nef/Tat/Vif, Env pDNA + HIV-1 rVSV envC	DNA vector encoding HIV-1 Nef/Tat/Vif and Env Attenuated replication-competent rVSV vector encoding HIV-1 clade C Env	NIAID	Phase I
Ad4-mgag, Ad4-EnvC150 + AIDSVAX B/E	Orally administered replication-competent Ad4 HIV vaccine in combination with AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	PaxVax, Inc./NIAID	Phase I
Trivalent Ad26.Mos.HIV, tetravalent Ad26.Mos4.HIV + clade C gp140	Ad26 vectors encoding mosaic HIV-1 Env, Gag, and Pol or Ad26 vectors encoding two mosaic HIV-1 Envs, mosaic Gag, and Pol + clade C HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
Tetravalent Ad26.Mos4.HIV + clade C gp140 ± mosaic gp140	Ad26 vectors encoding two mosaic HIV-1 Envs and mosaic Gag and Pol + clade C HIV Env protein boost ± mosaic HIV Env protein boost	Janssen Vaccines & Prevention B.V.	Phase I
MVA/HIV62B + AIDSVAX B/E	MVA vector encoding Gag, Pol, and Env proteins from HIV-1 clade B to produce VLPs + AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID	Phase I
DNA-HIV-PT123 Bivalent clade C gp120/MF59 Bivalent clade C gp120/AS01B	DNA vaccine encoding HIV-1 clade C Gag, gp140, and Pol-Nef + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120) with either MF59 or AS01B adjuvant	NIAID	Phase I
DNA-HIV-PT123 + clade C gp120/ MF59	DNA vaccine encoding HIV-1 clade C Gag, gp140, and Pol-Nef + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120) in MF59 adjuvant		
PASSIVE IMMUNIZATION			
VRC01	Monoclonal bNAb administered intravenously	NIAID/HVTN/HPTN	Phase IIb
10-1074	Monoclonal bNAb administered intravenously	Rockefeller University	Phase I
3BNC117 + 10-1074	Monoclonal bNAbs administered intravenously	Rockefeller University	Phase I
P2G12	Monoclonal neutralizing antibody administered intravenously	St George's, University of London	Phase I
PGT121	Monoclonal bNAb administered intravenously	IAVI	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Status
VRC01	Monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I (adults and HIV-exposed infants)
VRC01LS	LA monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I
VRC07-523LS	LA monoclonal bNAb administered intravenously or subcutaneously	NIAID	Phase I
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/CHOP	Phase I

AAV, adeno-associated virus
Ad4, adenovirus serotype 4
Ad26, adenovirus serotype 26
Ad35, adenovirus serotype 35
BNAb, broadly neutralizing antibody
CAVD, Collaboration for AIDS Vaccine Discovery
CHAVI, Center for HIV/AIDS Vaccine Immunology
CHOP, Children's Hospital of Philadelphia
CMDR, Chiang Mai double recombinant
CTL, cytotoxic T lymphocyte
GLA-AF, glucopyranosyl lipid adjuvant (aqueous formulation)
GM-CSF, granulocyte-macrophage colony–stimulating factor
Hsp70, heat shock protein 70
HVTN, HIV Vaccine Trials Network
IAVI, International AIDS Vaccine Initiative
IDT, Impfstoffwerk Dessau-Tornau
IL, interleukin
INSERM-ANRS, French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis
LA, long-acting
MHRP, U.S. Military HIV Research Program
MVA, modified vaccinia Ankara strain
NIAID, U.S. National Institute of Allergy and Infectious Diseases
Poly-ICLC, polyinosinic-polycytidylic acid with polylysine and carboxymethylcellulose
rVSV, recombinant vesicular stomatitis virus
SAAVI, South Africa AIDS Vaccine Initiative
SMI, Swedish Institute for Infectious Disease Control
UVRI, Uganda Virus Research Institute
VLP, virus-like particle

PASSIVE IMMUNIZATION/ANTIBODY GENE TRANSFER

The Antibody-Mediated Prevention (AMP) trials represent a collaborative effort between the NIH-funded HVTN and the HPTN. The efficacy of the bNAb VRC01 will be assessed in two populations: HVTN 704/HPTN 085 aims to enroll 2,700 MSM and transgender individuals who have sex with men at sites in Brazil, Peru, and the United States, whereas HVTN 703/HPTN 081 will recruit 1,500 sexually active women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe. The antibody is delivered by inpatient infusion every eight weeks, which is not ideal, but a key goal of the studies is to define protective bNAb levels and thus inform the development of potentially more potent and convenient bNAb formulations. Results are anticipated by 2022.

In addition to these large efficacy trials, there are a growing number of early-phase studies of more recently discovered bNAbs that have been demonstrated to have greater breadth and potency than VRC01. These include 3BNC117[97], 10-1074[98], PGT121[99], and VRC07-523LS.[100]

A combination of 3BNC117 and 10-1074 is also being tested, which may be an augury of the future because resistance to individual bNAbs could limit their efficacy when used alone. VRC07-523LS represents a derivative of a parent bNAb, VRC07, modified to enhance potency, breadth, and persistence in the body, thereby reducing dosing frequency—another strategy that may become more common as researchers seek ways to make passive immunization with bNAbs more user-friendly. The phase I VRC07-523LS trial is evaluating both intravenous and subcutaneous delivery.

Over the past several years, there has been considerable attention given to a potential one-shot bNAb delivery approach known as antibody gene transfer. The method draws from gene therapy research, employing adeno-associated virus (AAV) vectors modified with the genetic code for producing the bNAb of interest. Upon injection into muscle tissue, the AAV vector acts as a factory for persistent generation of the bNAb.[101] Promising results have been reported in the SIV/macaque model,[102,103] and the first human trial—a collaboration between the scientist Phil Johnson and the International AIDS Vaccine Initiative (IAVI)—is ongoing, involving the bNAb PG9. A recent macaque study has illuminated a potential downside, however—the approach can induce the production of antibodies against the bNAbs, significantly reducing the levels that are maintained.[104] Additional research will be required to better understand this problem and develop ways to address it.

Several research groups are exploring the possibility of administering bNAbs in microbicide formulations. A combination of three of the earliest generation of bNAbs to be discovered, 4E10, 2F5, and 2G12, has been evaluated in a phase I clinical trial and found to be safe.[105] Antibody levels capable of inhibiting HIV were detectable in cervicovaginal secretions for up to eight hours after administration, and no systemic absorption was observed. A first-in-human trial launched last year is testing the bNAb VRC01 and an antibody against HSV[106] delivered in a vaginal film (see table 1); the product is named MB66, and the antibodies are being produced in a new system using genetically modified tobacco plants.[107] The potential for delivering MB66 via vaginal ring is also under investigation.[108] A separate group of researchers has also used tobacco plants to produce a version of the 2G12 antibody designated P2G12; a single vaginal administration has been shown to be safe,[109] and an ongoing trial at St George's, University of London is now assessing intravenous delivery.

HIV VACCINES

The most significant recent news for the vaccine field has been the launching of HVTN 702, the first HIV vaccine efficacy trial to be conducted in seven years.[110] Led by principal investigator Glenda Gray, the protocol plan is to enroll 5,400 men and women between the ages of 18 and 35 years who are at risk for HIV infection at 15 sites in South Africa. Participants will be randomized to receive placebo or ALVAC vCP2438 (a canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease) plus a boost consisting of two clade C HIV gp120 proteins in MF59 adjuvant. The ALVAC vector is administered alone at baseline and after one month, and then in combination with the gp120 boost at months 3, 6, and 12.

The rationale for the study is derived from RV144, a large efficacy trial conducted in Thailand, which demonstrated that vaccination with similar candidates led to a small but statistically significant 31.2 percent reduction in risk of HIV acquisition.[111] Of potential importance, the final boost in RV144 was given at six months, and there is evidence that protection may have peaked at around 60 percent after one year of follow-up and then declined as vaccine-induced immune responses waned—this has led to the inclusion of an additional booster after 12 months in HVTN 702.

The vaccine regimen has been tailored for the South African setting, where HIV-1 clade C is prevalent. A preparatory trial conducted in South Africa, HVTN 100, evaluated whether the vaccines induced the types of immune responses that were associated with protection in RV144 in the majority of South African recipients, in order to decide whether the larger efficacy trial was justified. As reported at the International AIDS Conference in Durban last year, the immune response criteria—which included binding antibodies to clade C gp120 antigens, V1V2 antibodies to clade gp70 scaffold antigens, and CD4+ T-cell responses to HIV Env—were all met.[112]

There is one aspect of HVTN 702 that has proven slightly controversial, and that is the selection of the adjuvant for the gp120 protein boost. The purpose of adjuvants is to help stimulate the induction of immune responses against the antigens in the vaccine, and in RV144 the gp120 protein boost was delivered with the common adjuvant alum. In HVTN 702, a proprietary squalene-based adjuvant developed by Novartis Vaccines (since acquired by GlaxoSmithKline) named MF59 is being used.

The controversy derives from a macaque experiment conducted by the research group of Genoveffa Franchini at the U.S. National Cancer Institute, which aimed to recapitulate the RV144 results in animals. The researchers reported that while the RV144 vaccine regimen showed some protective efficacy against an SIV challenge, this was not seen in a group of macaques that received the gp120 protein boost with MF59 instead of alum.[113] Analyses also indicated that the alum adjuvant had activated particular genes related to innate immunity and that this was linked to protection against SIV challenge. However, these were post hoc findings because the experiment was not designed or statistically powered to compare the adjuvants, and a subsequent macaque study with an alum adjuvant (albeit not precisely the same) did not duplicate the results.[114] Other researchers, including HVTN director Lawrence Corey, have pointed out that protection against SHIV infection has been reported in some macaque studies employing MF69 as a vaccine adjuvant,[115] countering Franchini's suggestion that it could have a negative effect.[116] The debate has not altered the design of HVTN 702, but it is possible the issue could be revisited if no protection is observed; regular interim evaluations will be carried out by a data safety monitoring board, and the trial can be halted early if there is evidence the vaccines are failing or harmful.

An update on the status of HVTN 702 was provided on a webinar hosted by AVAC on May 8, 2017, by protocol co-chair Fatima Laher from Chris Hani Baragwanath Hospital in Soweto. The first immunizations began in October 2016 and, as of April 2017, 526 participants have been enrolled. Laher noted that the protocol has undergone a revision, with version 2 including additional details on the HIV prevention package offered to participants, including updated information related to obtaining access to PrEP. Collection of DBS samples from participants using PrEP has also been added in order to obtain data on Truvada drug levels.[117]

PrEP in Biomedical Prevention Trials

The efficacy of Truvada PrEP has raised difficult questions regarding how it should be integrated into trials of biomedical prevention interventions, whether vaccines, passive immunization, microbicides, or alternative forms of PrEP. Current UNAIDS/WHO guidelines[118] recommend that clinical trials provide access to proven "state of the art" HIV prevention modalities for clinical trial participants, and an experimental intervention is tested to find out whether it can further reduce the risk of HIV acquisition when given in addition to these modalities. But Truvada PrEP is so efficacious that if all trial participants were to use it consistently as part of a background prevention package, evaluating whether a new experimental intervention has any significant effect on HIV risk would become extremely challenging—perhaps impossible.

PrEP is not necessarily ideal for everyone, however, and this means that there remains a need to develop other user-friendly biomedical prevention technologies and also that trial participants who choose not to use PrEP (or for whom PrEP is not recommended) can ethically be included as participants in clinical trials. The HVTN 704/HPTN 085 AMP trial offers one

example of how the issue of PrEP provision is currently being addressed: Truvada PrEP is being offered free of charge to all participants. Those participants based in the United States who choose to receive Truvada PrEP are referred to a program that integrates provision of the drug into their primary health care. Participants in Peru and Brazil, where Truvada is not yet licensed for PrEP, will be referred to demonstration projects.

In contrast, the HVTN 703/HPTN 081 AMP trial is offering information on Truvada PrEP and referrals to access programs where possible but is not providing the drug itself. The protocol explains that this approach is based on differing recommendations for PrEP use in women and the lack of local regulatory approvals, but it acknowledges HIV prevention standards are continually evolving and states "arrangements for provision of PrEP in this trial will take into account current evidence regarding PrEP efficacy in the populations to be enrolled in this trial, community consultation, guidance from international/regional/national/local and other regulatory authorities, and advice from persons/groups with bioethics and human subjects protection expertise."

The differences between the protocols—both of which were reviewed and approved by multiple stakeholders, including community members and regulators—highlight the current gray areas regarding PrEP provision in biomedical prevention trials, which have been a topic of extensive discussion in the scientific literature.[119,120,121] These discussions are likely to continue for the foreseeable future.

In addition to HVTN 702 and the work surrounding it, there is a second major thrust in HIV vaccine research being driven by Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. The company is sponsoring multiple studies involving combinations of two viral vectors—adenovirus serotype 26 (Ad26) and modified vaccinia Ankara strain (MVA)—and clade C gp140 Env protein boosts, with the goal of launching a first proof-of-concept efficacy trial in the near future. A key element of the program is the use of mosaic HIV antigens designed to induce immune responses capable of recognizing diverse viral variants. The research is being carried out in collaboration with Beth Israel Deaconess Medical Center/Harvard, the Bill & Melinda Gates Foundation, HVTN, IAVI, the U.S. Military HIV Research Program, the National Institute of Allergy and Infectious Diseases, and the Ragon Institute.

Several of the HIV vaccine trials that have begun over the past year are related to the Janssen program. Ad26 vectors are being administered as the priming immunizations in trivalent and tetravalent mixtures: the former includes two mosaic Gag-Pol antigens and a mosaic Env, and the latter adds a second mosaic Env. Booster immunizations comprise the same Ad26 mixtures or MVA vectors encoding two mosaic Gag-Pol-Env antigens and/or a soluble gp140 Env trimer protein (the trimeric form of Env more closely mimics the natural HIV Env protein). In some cases a second mosaic version of the gp140 Env protein[122] is also included.

The groundwork for the effort was laid by experiments in the macaque model demonstrating significant protective efficacy against both SIVmac251 and SHIV-SF162P3 challenges.[123] The highest degree of protection has been observed in recipients of Ad26 prime followed by Ad26 plus gp140 protein boost; the regimen was associated with a 94% reduction in per-exposure risk of infection, and eight out of a

group of 12 macaques (66%) remained uninfected after six SHIV-SF162P3 challenges.[124] Correlates of protection included binding antibodies against the Env protein, Env-specific T-cell responses, and functional antibodies capable of inducing antibody-dependent cellular phagocytosis, a process in which antibodies promote the killing of virus-infected cells.[125]

If all goes according to plan and immune response targets are met in the preparatory studies, a placebo-controlled efficacy trial (HPX2008/HVTN 705) will be launched in late 2017 or early 2018. The aim is to enroll 2,600 sexually active women aged between 18 and 35 at sites in South Africa, Zambia, Zimbabwe, Malawi, and Mozambique. The likely regimen would be the tetravalent Ad26 vector mix administered at months 0, 3, 6, and 12, with soluble gp140 Env trimer protein boosts added at months 6 and 12. The Env protein will be delivered in an alum adjuvant, so the trial may be able to contribute information to the discussion regarding the importance of alum to the protection documented in RV144.

The fate of the diverse collection of other experimental HIV vaccine candidates in the pipeline will almost certainly be significantly influenced by the outcomes of HVTN 702 and the Janssen program. No extant candidate is capable of inducing bNAbs, which remains the holy grail for the vaccine field, and so more information is required regarding the protective potential of non-neutralizing immune responses in order to rationally assess the relative promise of the current crop of contenders. That does not diminish the importance of continuing to develop vaccine candidates in order to have options for future efficacy trials as the science advances. Over the past year, updates have been offered on a variety of approaches, including intranasally administered Sendai virus vectors,[126] DNA/MVA regimens[127,128,129] (including constructs developed by Geovax designed to encode virus-like particles[130]), and a NYVAC plus Env protein combination.[131] Planning is also underway to conduct a first-in-human trial of a CMV vector,[132] which has generated considerable interest due to evidence that it led to clearance of a highly pathogenic SIV when administered prophylactically to macaques.[133,134]

CONCLUSION

Despite encouraging signs that available prevention options may be diminishing HIV incidence in some areas, the need for increased global access and additional, more user-friendly biomedical prevention tools—particularly an effective vaccine—remains dire. The current pipeline is diverse but heavily dependent on increasingly constrained public and philanthropic funding.

The political climate in the United States, which is by far the largest financer of scientific research, is extremely concerning—the Trump administration has demonstrated a distinct antiscience bent, exemplified by its budget proposals that slash support for the NIH and CDC. The instability of the administration and the countervailing views of many congressional leaders may lessen the likelihood that these cuts will manifest, or at least reduce their severity, but vigilance is essential regarding the potential impact on biomedical HIV prevention research.

RECOMMENDATIONS

- Research sponsor and investigator adherence to Good Participatory Practice (GPP) guidelines[135] is essential in all biomedical prevention trials, particularly in the post-iPrEx era. Gilead ran into extensive pushback after developing the study protocol for the DISCOVER trial without sufficiently engaging community advocates. The trial initially required a 30-day washout period for any interested participant already taking Truvada as PrEP, which raised several ethical red flags for community advocates. Had Gilead worked with an existing trial network with more experience in working with the community, or had they initially engaged the community in a way that was in line with GPP guidelines, several complications could have been avoided.

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

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