Preventive Technologies: Antiretroviral and Vaccine Development

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With the continued rollout and implementation of global, national, and regional HIV incidence targets and timelines, one thing has become abundantly clear: reducing HIV rates below endemic and epidemic levels in all vulnerable populations and subpopulations everywhere in the world will require not only a monumental scale-up of care and antiretroviral therapy for those living with the virus, but also fierce commitment to primary biomedical prevention. This isn't simply rhetoric, but rather a public health mandate that is supported by a growing body of epidemiological and other scientific data.[1,2,3,4]

However, only a fraction of adolescents and adults vulnerable to HIV are accessing one on the most important evidence-based additions to the prevention toolbox: coformulated tenofovir disoproxil fumarate and emtricitabine (Truvada; TDF/FTC) as a pre-exposure prophylaxis (PrEP). In the U.S. alone, where TDF/FTC has been approved as PrEP since July 2012, of the 1.2 million adults with indications for PrEP—a likely conservative estimate from the U.S. Centers for Disease Control and Prevention (CDC)—only an estimated 4% have used it, even briefly.[5,6] For PrEP to have a population-level effect in the U.S., however, a substantial increase in PrEP uptake will be required: 40% use among high-risk men who have sex with men, 10% use among people who inject drugs, and 10% use among high-risk heterosexuals would be in the absence of any improvements in clinical care engagement and viral load suppression rates among people living with HIV, necessary to prevent approximately 48,000 new infections between 2015 and 2020.[7]

Significant barriers to PrEP uptake exist, with the most egregious examples being achingly slow product registration and national health plan inclusion—the high cost of TDF/FTC, along with limited cost-effectiveness data, are considerable factors[8]—in many high-, middle-, and low-income countries. Even where PrEP has been approved, myriad access challenges exist. Examples in the U.S. include restrictions in CDC and other federal agency funds to pay for TDF/FTC; reluctance to expand Medicaid in many states, particularly those with high HIV prevalence and incidence estimates; and lags in awareness of PrEP and best screening, prescribing, and monitoring practices among primary care providers. Implementation strategies to overcome these structural hindrances, on top of myriad social and behavioral barriers, will be critical for PrEP's success.

Success also depends on expanding the toolbox of biomedical prevention modalities that can extend the very high level of adherence-dependent protection associated with oral TDF/FTC to individuals and populations with unique safety, dosing, and affordability needs.[9] Additional oral antiretroviral regimens, including maraviroc (MVC)- and tenofovir alafenamide (TAF)-based combinations, are in various stages of development. Although no generic contenders have yet entered clinical trials, the scientific and economic basis for fast-track evaluations of TDF (which loses its patent at the end of 2017) and 3TC can potentially hasten global scale-up of oral PrEP before coformulated TDF/FTC's patent expires in 2021.

Interest in long-acting (LA) products also continues to grow. An injectable nanoformulation of cabotegravir is now entering its efficacy phase of development. Another intriguing contender, much further back in the pipeline, is MK-8591, Merck's nucleoside reverse transcriptase inhibitor, which may allow for injectable dosing separated by several months (see "The Antiretroviral Pipeline," page 21).

Researchers and advocates for women's health are also working to wrap their heads around long-awaited data from ASPIRE and the Ring Study, two phase III investigations of the dapivirine intravaginal ring reported at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) earlier this year in Boston and

reviewed in detail below. Both trials suggest that the dapivirine ring has the potential to be at least moderately effective, but that significant utilization challenges exist, particularly for young sub-Saharan African women—a highly vulnerable population in dire need of an acceptable primary prevention option.

Also inching forward is a cache of other products for vaginal and rectal administration: gels, tablets, and films, along with an array of other intravaginal rings that combine drug and hormonal products for broad-spectrum antiviral and contraceptive protection.

Passive immunization involves the infusion of antibodies that are capable of inhibiting a large swathe of HIV variants, and represents another potential biomedical prevention option that is now being vigorously pursued. The launching of the first efficacy trials of the approach in adults was announced recently.[10] Known as the antibody-mediated prevention (AMP) studies, they will test bimonthly infusions of the VRC01 antibody in populations that are at high risk of HIV infection.

Inducing protective antibody responses with a vaccine remains a stubborn challenge for researchers, but progress continues in the pre-clinical realm, and there is hope that candidates capable of leading the immune system down the road toward the generation of effective antibodies will enter clinical trials in the next year or two.[11,12]

In the interim, the major news for the HIV vaccine field is that the first efficacy trial in nearly a decade will begin later this year.[13] The trial, HIV Vaccine Trials Network (HVTN) 702, is designed to try and duplicate or improve on the slight, but statistically significant, 31.2% reduction in risk of HIV acquisition that was observed in RV144, a large-scale evaluation of a prime-boost vaccine regimen that was conducted in Thailand and reported results in 2009.[14] HVTN 702 will take place in South Africa and, if all goes according to plan, results are anticipated by 2020.

ANTIRETROVIRALS FOR PREVENTION

Table 1. Antiretroviral-based PrEP and Microbicides Pipeline 2016

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
ORAL FORMULATIONS				
TAF + FTC	NtRTI/NRTI	Gilead Sciences	Oral	Phase III (planned)
MVC	EI	HPTN/ACTG	Oral	Phase II
LONG-ACTING FORMULATIONS				
Cabotegravir	INSTI	ViiV Healthcare	IM	Phase IIb/III
Rilpivirine	NNRTI	PATH	IM	Phase II
MICROBICIDE RINGS, GELS, FILMS, AND OTHER INSERTABLES				
Dapivirine	NNRTI	IPM	Vaginal ring	Phase IIIb
			Vaginal gel	Phase II
			Rectal gel	Phase II
			Vaginal film	Phase I
Tenofovir	NtRTI	CONRAD	Vaginal gel	Phase IIIb
			Rectal gel	Phase II
			Vaginal ring	Phase I
			Vaginal tablet	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
MICROBICIDE RINGS, GELS, FILMS, AND OTHER INSERTABLES (continued)				
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
Dapivirine + darunavir	NNRTI/PI	IPM	Vaginal gel	Phase I
DS003	EI	IPM	Vaginal tablet	Phase I
MULTI-PURPOSE TECHNOLOGIES				
Tenofovir + levonorgestrel	NtRTI/HC	CONRAD	Vaginal ring	Phase I
Dapivirine + levonorgestrel	NNRTI/HC	IPM	Vaginal ring	Phase I

ACTG, AIDS Clinical Trials Group; CGN, carrageenan; EI, entry inhibitor; FTC, emtricitabine; HC, hormonal contraceptive; HPTN, HIV Prevention Trials Network; IM, intramuscular; IPM, International Partnership for Microbicides; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide fumarate; 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—two additional oral products continue to make their way down the biomedical prevention pipeline.

The advantages of these compounds—which include ViiV's MVC and Gilead's TAF plus FTC—as PrEP remain unclear. 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).[15,16,17,18,19,20]

MVC (Selzentry)

CCR5-tropic HIV—HIV 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.[21,22] Thus, there has been interest in studying the CCR5 antagonist MVC for its potential use as PrEP. Not only might MVC be associated with a reduced risk of adverse events, its unique mechanism of blockading cellular rather than viral protein function may also be associated with a reduced risk of developing drug resistance.

Preliminary data from the phase II NEXT-PrEP study (HPTN 069/ACTG A5305) suggest that MVC is well tolerated and is potentially efficacious as PrEP in transgender women and men who have sex with men (TG/MSM), although it is likely more effective as a component of a multi-drug regimen.[23] Results from the study's cohort of 200 women vulnerable to HIV infection enrolled in NEXT-PrEP will be reported at the 2016 International AIDS Conference in Durban.

The TG/MSM cohort comprises 406 participants randomized to receive either MVC alone, MVC plus FTC, MVC plus TDF, or standard-of-care TDF/FTC. All participants had a history of condomless anal intercourse

with at least one HIV-positive or unknown serostatus man within 90 days of study entry. The median age at baseline was 30 years; 2% were transgender, 28% black/African American, 22% Latino, and 62% white.

There were 34 sexually transmitted infections (STIs) diagnosed among 31 participants (8%) at study entry. During the 48-week follow-up period, 115 additional STIs were diagnosed.

Adherence rates, based on plasma drug concentrations in a random subset of 160 participants across the four study groups, were 83% at week 24 and 77% at week 48.

There were 67 grade 3–4 adverse events, with no differences in occurrence rates or severity among the four study arms. Hypophosphatemia (17%) and upper respiratory tract infections (11%) were the most common grade 2 or higher adverse events. Other than increased creatinine being documented in 1% of study volunteers in the MVC/FTC group, renal safety results were limited. Additional safety data, including bone mineral density findings, are forthcoming.

Five new HIV infections were documented during the study, for an annual incidence rate of 1.4% (95% confidence interval (CI): 0.8%–2.3%). Four of the five infections occurred in participants in the MVC monotherapy group; one occurred in the MVC/TDF group, but this participant had undetectable plasma drug concentrations at every study visit.

One of the participants in the MVC monotherapy group who became infected had a plasma drug concentration at the time of seroconversion (145 ng/mL) that was significantly above the median pre-dose state of 32 ng/mL expected in individuals with 100% adherence. His MVC plasma concentrations were highly variable prior to HIV detection at week 16, however, indicating that adherence was inconsistent. The second and third participant in the MVC monotherapy group to become infected had suboptimal drug concentrations on their documented seroconversion dates: 6.7 and 0.7 ng/mL; both individuals also had a history of drug concentrations consistent with poor adherence. The fourth participant in the MVC group to become infected had undetectable drug concentrations at the time of seroconversion and throughout the duration of the study.

Adherence observations aside, the imbalance in new infections among those in the MVC monotherapy group raises questions about the potential for stand-alone MVC as PrEP and the likely need for MVC-inclusive combinations to ensure efficacy.

A substudy of NEXT-PrEP underscores this concern.[24] It was conducted to explore MVC's association with increased gut-associated lymphoid tissue (GALT) T cell activation as well as increased CCR5 expression[25,26]—observations in HIV-positive people that would be undesirable in HIV-negative individuals who are already vulnerable to the virus—and to determine whether MVC is associated with suppression of colorectal explant HIV infection.

There were no significant differences in CD4+ cell activation phenotypes between baseline and week 24 or 48 samples collected from the 55 TG/MSM participants selected at random from the four study groups. Nor were there increases in CCR5 phenotype in the substudy. And although significant viral suppression was seen between baseline and week 24 with all of the PrEP study regimens in the explant infection study, no significant suppression was seen at week 48 in samples from substudy participants receiving MVC alone.

The reason(s) for MVC's diminished suppression of explant HIV infection are not clear. The study investigators noted that a limitation of explant research is that MVC disassociates, or loses its affinity for, tissue in culture—findings that don't necessarily mirror what happens in vivo. Pharmacokinetic (PK) and pharmacodynamics (PD) data are pending and may help to explain the lack of efficacy.

The next steps for MVC's development as oral PrEP, or a component thereof, are currently being discussed.

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% 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 coformulated with FTC—approved as Descovy in the U.S. and other countries, but indicated only for the treatment of HIV infection—is also being eyed as an alternative to Truvada.

Results from CDC evaluations of TAF plus FTC in rhesus macaques that were rectally challenged with simian-human immunodeficiency virus (SHIV)—a model and methodology that were used previously to establish the potential efficacy of TDF and TDF/FTC as PrEP—were reported at CROI 2016.[29] The first of the two-part study established TAF 1.5 mg/kg as the macaque dose required to achieve intracellular concentrations that were comparable to those typically seen in humans receiving TAF 25 mg. The second part of the study treated 12 macaques with either TAF or placebo and then challenged them weekly for up to 19 weeks.

None of the TAF-treated macaques were infected after 19 exposures—100% protection, whereas the previous macaque studies of TDF/FTC suggested 94% protection after 14 SHIV exposures—and all six of the placebo-treated macaques were infected by their tenth exposure to the virus. Of note, macaque rectal concentrations of TFV-DP were lower with TAF than those of the macaques previously treated with TDF.

Some questions about the interchangeability of TAF for TDF as PrEP have arisen following a second report at CROI 2016, this time from a study evaluating concentrations of TFV and TFV-DP in mucosal tissues from eight HIV-negative women who received a single dose of TAF 25 mg.[30] Consistent with PK data used to support TAF's use as a treatment, the plasma levels of TFV were 19-fold lower and peripheral blood mononuclear cell (PBMC) levels of TFV-DP were ninefold higher than those seen following single-dose TDF 300 mg dosing in an earlier study.

The investigators hypothesized that TFV-DP levels following TAF administration would also be significantly higher in cervical, vaginal, and rectal cells compared with TDF. 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% of the rectal and 75% of genital tract samples had TFV and TFV-DP concentrations below the level of detection.

Making heads or tails of the macaque and human tissue studies is especially difficult in light of the fact that pharmacologic correlates of protection and surrogate/biologic markers of prophylactic efficacy have not yet been fully validated. The research teams from both studies agree that additional study will be necessary before any conclusions about the efficacy of F/TAF can be made, particularly in comparison with a coformulated regimen that has not only been proven to be highly effective and well tolerated as PrEP, but will be coming off of patent in five years.

Additional investigations aimed at determining the pharmacology of TAF in mucosal tissues are expected, as are large-scale registrational trials conducted by Gilead Sciences.

Of additional interest are 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).[31] Also in early development is a biodegradable thin-film polymer device containing TAF that can be administered subcutaneously.[32]

LONG-ACTING (LA) FORMULATIONS

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. Particular focus is being placed on the development of LA 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 LA cabotegravir (CAB LA), ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog) entering phase III trials. On a less certain course is a LA injectable version of rilpivirine (RPV LA), Janssen's NNRTI.

Cabotegravir LA

Long-awaited preliminary data from the phase IIa ÉCLAIR trial were reported at CROI 2016.[33] The study, designed to assess safety and tolerability, 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 five and ended at week 41, with CAB LA 800 mg or saline being administered via IM injections during visits on weeks 5, 17, and 29. The study also included a follow-up phase, for a total of 81 weeks.

The median age at baseline was 30 years. Approximately 57% were white, 33% were black/African American, and 14% were Hispanic/Latino. Approximately 76% in the placebo group, compared with 85% in the CAB group, listed sex with other men as their risk factor for HIV (compared with heterosexual contact for 29% and 21%, and occupational exposure for 5% and 2%, respectively).

Adverse events leading to withdrawal during the oral phase (N = 7) included three events of neutropenia, three events of increasing creatine phosphokinase (CPK), and one event of fatigue—all of which occurred in the CAB group. For participants who entered the injection phase, a similar proportion (93% for CAB LA, 95% for placebo) completed all three injection cycles. Injection intolerability led to withdrawal in 4% of CAB LA participants. One participant in the placebo group seroconverted and subsequently withdrew from the study.

The number of grade 2–4 adverse events in the CAB group was higher than in the placebo group during the injection phase (80% for CAB LA, 48% for placebo). Grade 2 events in the injection phase that were not related to injection site pain included fever (7% versus 0%, respectively), injection site itching (6% versus 0%, respectively), and injection site swelling (6% versus 0%, respectively).

CAB PK data throughout each 12-week dosing interval were reported. Results showed trough concentrations to be lower than the prespecified ideal (fourfold higher than the protein-adjusted 90% inhibitory concentration [4× PA-IC90] of 0.664 mg/mL) at the end of the dosing intervals in approximately two-thirds of participants; 15% to 31% had trough concentrations below 1× PA-IC90 at the end of the dosing intervals. 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.

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. The participant in the CAB group who ultimately seroconverted had no detectable CAB in blood plasma at week 53 and was one of the individuals who had CAB trough concentrations below 1× PA-IC90 on two occasions during the injection phase of the study.

A second phase IIa trial, HIV Prevention Trials Network study 077 (HPTN 077), is currently enrolling approximately 176 HIV-negative volunteers—60% of the participants will be women—in the U.S., South America, and sub-Saharan Africa.[34] It is designed similarly to ÉCLAIR, with its primary objectives being safety, tolerability, and acceptability assessments in participants at low-to-minimal risk of HIV infection.

Currently in the final stages of development is HPTN 083, a phase IIb/III head-to-head safety and efficacy trial of CAB LA versus oral TDF/FTC.[35] 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 receive daily oral TDF/FTC for approximately one year, starting no later than eight weeks after the last injection.

HPTN 083 trial has a planned enrollment of 4,500 TG/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.

Rilpivirine 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.[36] 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.[37] 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 drug.

A more recent study characterized the concentrations of RPV needed to prevent HIV infection in mucosal tissue.[38] Although rectal tissue RPV PK 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, with an expected completion date of October 2017, is HPTN 076, a phase II safety and acceptability evaluation of RPV LA, compared with placebo, in approximately 132 HIV-negative women between 18 and 45 years of age in Cape Town, South Africa; Harare, Zimbabwe; Newark, New Jersey; and Bronx, New York.[39] The women have been randomized (2:1) to receive either daily oral rilpivirine 25 mg or placebo for four weeks. In the absence of any safety signals, the participants will receive 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.

Based on the conflicting PK and explant infection data reported to date, compounded by the formulation's need for cold-chain storage, RPV LA is not expected to move into phase III trials for PrEP.[40]

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 with protection can be achieved, 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.

Dapivirine

The most clinically advanced candidate is a silicone elastomer IVR containing 25 mg dapivirine (TMC120), a NNRTI licensed to the International Partnership for Microbicides (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.[41,42,43]

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 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, highlighted in table 2, suggest 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% in ASPIRE and 37% in the Ring Study, with little to no protection among women 21 years of age and younger.

In ASPIRE, women 22 years of age and older appeared to use the ring more consistently. In the Ring Study, there was a trend toward higher efficacy with more consistent use. In discussing the ASPIRE results, principal investigator Jared Baeten, MD, of the University of Washington reiterated that strong relationships between adherence and HIV protection are expected in all biomedical prevention studies. However, unlike post hoc PK analyses from oral TDF/FTC PrEP trials, which have demonstrated strong adherence is associated with protection approaching 100%, inferences regarding maximum possible protection using the dapivirine IVR are not yet possible. Further analyses are required to define whether there is a threshold of dapivirine IVR use for protection against HIV, and to ferret out both behavioral and possible biologic effects that may have contributed to the lack of HIV protection in the youngest women in both studies.

Table 2. ASPIRE and The Ring Study

	ASPIRE (MTN 020)		Ring Study (IPM 027)	
	Dapivirine IVR (N = 1,313)	Placebo IVR (N = 1,316)	Dapivirine IVR (N = 1,300)	Placebo IVR (N = 650)
Median age	26 years		26 years	
Married	41%		11%	
Primary sex partner	>99%		>98%	
RETENTION AND ADHERENCE				
Person-years follow-up	4,280		2,805	
Expected protocol-specified visits	91%		82%	
Ring adherence	82% to 84%		83%	
HIV-1 PROTECTION				
Number of seroconversions, overall	71	97	77 (5.9%)	56 (8.9%)
Number of seroconversions, sites exclude**	54	85		
HIV-1 incidence, overall (per 100 patient-years [P/Y])	3.3	4.5	4.1	6.1
HIV-1 incidence, sites excluded (per 100 P/Y)**	2.8	4.4		

	ASPIRE (MTN 020)		Ring Study (IPM 027)	
	Dapivirine IVR	Placebo IVR	Dapivirine IVR	Placebo IVR
HIV-1 PROTECTION (continued)				
Protection effectiveness, overall, all ages	**27%** (95% CI: 1% to 46%); P = 0.007		**31%** (95% CI: 0.9% to 51%); P = 0.040	
Protection effectiveness, sites excluded, all ages**	**37%** (95% CI: 12% to 56%); P = 0.007			
Protection effectiveness, ≤21 years of age	**–27%** (95% CI: –133% to 31%)		**15%** (95% CI: –60% to 55%)	
Protection effectiveness, ≥22 years of age	**56%** (95% CI: 31% to 71%); P < 0.001		**37%** (95% CI: 3% to 59%)	
SAFETY				
Serious adverse events	4%	4%	3%	1%
Metrorrhagia			26%	28%
Genital infection			22%	18%
Menorrhagia			20%	10%
NNRTI mutations	12%	10%	18%	16%

*Dapivirine plasma concentrations >95 pg/mL (indicating at least 8 hours of continuous use); residual dapivirine <23.5 mg in returned rings (indicating at least some use during the month)
**Excluding data from two sites with recruitment and monitoring difficulties

Additional dapivirine IVR results reported at CROI 2016 included data from a phase IIa PK, safety, adherence, and acceptability study in 96 postmenopausal women in the U.S (MTN-024/IMP 031).[44,45] The women—the mean age at baseline was 56.8 years; 66% were white and 31% were black/African American, 61% had a primary sexual partner, and 66% were sexually active—were randomized 3:1 to monthly IVRs containing dapivirine 25 mg or placebo for 12 weeks.

IVRs were safe and well tolerated. Only two women chose not to continue using the rings as a result of adverse events. There was no difference in the number of women with related grade 2 or higher adverse events in the two groups (8% versus 13% in the dapivirine and placebo groups, respectively), and no statistical significantly differences in grade 3 or higher adverse events (6% versus 0%, respectively). One grade 3 adverse event (vaginal pain) was deemed to be related to study product. Adherence rates were also high, with most women (99%) saying the IVR was very easy/easy to use, 96% indicating that it never interfered with daily activities, 91% reporting they either liked or very much liked the IVR, and 65% preferring VR to condoms.

Two cost-effectiveness analyses were also reported at CROI 2016.[46,47] According to one analysis using a deterministic HIV transmission model of South Africa, the dapivirine IVR could avert 125,000–175,000, 265,000–364,000, or 427,000–588,000 infections at 25%, 50%, and 75% efficacy, respectively, from 2017–2050 under the different counterfactual scenarios.[46] This represents 1.1% to 7.0% of total HIV infections in this period at corresponding cost-effectiveness of US$1,000 to US$1,300, US$370 to US$520, and US$160 to US$260 per disability-adjusted life year (DALY) averted.

As for next steps, two open-level evaluations of the dapivirine IVR are planned. MTN-025, the HIV Open-Label Prevention Extension (HOPE) trial, is an ASPIRE follow-on study to assess continued safety and adherence, and is scheduled to begin this summer. IPM hopes to conduct its own open-label extension follow-on study to provide former Ring Study participants with the dapivirine IVR.

IPM plans to submit the dossier of dapivirine IVR evidence—ASPIRE and the Ring Study are only a part of an extensive research portfolio (table 3)—required for licensure to regulatory agencies beginning in early 2017.

Table 3. Dapivirine IVR Study Portfolio

Study	Description	N	Status
IPM 007	Seroconverter protocol	n/a	Ongoing
IPM 013	IVR safety & PK	48	Completed
IPM 015	IVR safety	280	Completed
IPM 024	IVR safety & PK	16	Completed
IPM 027	The Ring Study	1,959	To be completed 12/2016; preliminary data reported at CROI 2016
IPM 028	Drug-drug interaction	36	Completed
IPM 029	Male condom functionality	70 couples	Completed
MTN-020	Phase III ASPIRE trial	2,629	Completed; reported at CROI 2016 and published
MTN-023/IPM 030	IVR safety (adolescent girls)	96	Ongoing
MTN-024/IPM 031	IVR safety & acceptability (postmenopausal women)	96	Reported at CROI 2016
IPM 033	Female condom functionality	80 couples	Data analysis
IPM 034	IVR extended PK	40	Completed
IPM 035	Menses & tampon use	32	Ongoing
IPM 036	Drug-drug interactions	36	Ongoing
MTN-029/IPM 039	PK (lactating women)	16	Enrolling
MTN-031/IPM 043	Financial Incentives and ring adherence	450	In development
MTN-034/IPM 045	IVR and oral TDF/FTC crossover in adolescent girls	300	In development
MTN-036/IPM 047	PK & safety of three dapivirine ring formulations	36	In development
MTN-025	Phase IIIb open-label (HOPE) ASPIRE follow-on trial		Planned

Source: Microbicide Trials Network, International Partnership for Microbicides

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.[48,49] Additional data are anticipated, however. These include results from the phase IIIb CAPRISA 008—currently being analyzed by CONRAD investigators—an open-label follow-on study of the phase IIb CAPRISA 004 trial to collect additional safety and data and to evaluate the feasibility and effectiveness of providing 1% tenofovir gel to HIV-negative women through family planning clinics in KwaZulu-Natal, South Africa.[50]

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, MVC, 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, in addition to a reduced-glycerin 1% tenofovir gel, are also being evaluated for rectal use and protection.

Reduced-Glycerin 1% Tenofovir Gel

The reduced-glycerin 1% tenofovir gel (RG 1% TFV), 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 may in turn prevent damage to the structural integrity of the rectum's lining and help to minimize the gastrointestinal side effects documented in earlier 1% tenofovir gel studies.[51,52]

MTN-017 is a phase II safety and acceptability study of RG 1% TFV in 195 HIV-negative MSM and transgender women in the U.S., Peru, Thailand, and South Africa.[53] It was designed as a follow-up trial to the phase I MTN-007 rectal study, the data from which were published last year.[54]

The study employed a crossover design that required all study participants to cycle through three eight-week regimens: RG 1% TFV used daily, RG 1% TFV used episodically before and after receptive anal intercourse, and TDF/FTC taken orally daily.

Most side effects from study products in MTN-017 were minor, with roughly a third of participants experiencing grade 2 or higher adverse events using the three regimens: 34% for TDF/FTC, 33% for daily RG 1% TFV, and 30% for episodic RG 1% TFV.

Overall, participants were highly adherent in MTN-017, which was defined as >80% of expected doses taken and assessed by convergence scoring of daily texts and study product returns. Episodic RG 1% TFV and daily oral TDF/FTC dosing were associated with >80% adherence among 93% and 94% of study participants, respectively, compared with 83% adherence to daily RG 1% TFV dosing. Using qualitative plasma PK testing, the investigators also noted that 94.3% TFV-positive samples were associated with oral TDF/FTC, compared with 80.2% with daily RG 1% TFV dosing.

With respect to acceptability, participants reported they would be less likely to use the daily RG 1% TFV regimen (odds ratio [OR]: 0.38, $P < 0.001$), but would be just as likely to use the episodic RG 1% TFV regimen (OR: 0.70, $P = 0.23$), for HIV protection compared with oral TDF/FTC dosing. Overall liking of the regimens also favored oral TDF/FTC compared with either daily (OR: 0.28, $P < 0.28$) or episodic (OR: 0.37, $P < 0.002$) RG 1% TFV dosing.

Additional data from MTN-017, including quantitative PK testing data to shed additional light on adherence in the trial, are forthcoming.

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 herpes simplex virus-2 (HSV-2) and human papillomavirus.

Phase I safety, PK, acceptability, and adherence data were presented at CROI 2016.[55] 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 measurable HIV and HPV activity in cervicovaginal lavages (CVLs). Acceptability was also high: 94% of participants reported a willingness to use the gel in the future.

Additional data presented at CROI 2016 indicate that PC-1005 inhibits HIV and HSV-2 infection in cervical explants in a dose-dependent manner.[56]

CONTRACEPTIVE-INCLUSIVE MULTIPURPOSE PREVENTION TECHNOLOGIES

As has been well documented in the development of oral PrEP and microbicides, there is a need for biomedical prevention options that protect against not just HIV (and other STIs), but also unwanted pregnancies. For women vulnerable to both, the development of multipurpose prevention technologies (MPTs) is of tremendous interest.

Products currently in preclinical development can be categorized as either LA or on-demand. LA MPTs include IVRs, and on-demand products include gels that can be used around the time of intercourse.

LA MPTs that are currently in phase I studies include IVRs containing levonorgestrel—a synthetic progestogen that has been studied and used extensively, and is therefore considered to be suitable for formulation in matrix IVRs—combined with either tenofovir or dapivirine. Data from CONRAD's phase I evaluation of the safety, PK, and acceptability of its IVR containing tenofovir and levonorgestrel are being analyzed.[57] A phase I safety and PK study of IPM's matrix IVR containing dapivirine and levorgestrel is still being finalized in partnership with the Microbicide Trials Network.

PREVENTIVE VACCINES, PASSIVE IMMUNIZATION, AND ANTIBODY GENE TRANSFER

Table 4. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline

Agent	Class/Type	Manufacturer/Sponsor(s)	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/HIV Vaccine Trials Network (HVTN)/Bill & Melinda Gates Foundation/South African Medical Research Council/Sanofi Pasteur/ Novartis Vaccines	Phase IIb/III
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. HIV 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 (SMI)/MHRP	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
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	Crucell/NIAID/MHRP/IAVI/Beth Israel Deaconess Medical Center	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/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 + 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
Ad26.ENVA.01	Adenovirus serotype 26 vector encoding the HIV-1 clade A Env protein	Crucell/International AIDS Vaccine Initiative (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	Crucell/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	Crucell/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

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
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 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
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	Multi-antigen 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, interleukin-12 (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 (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 mothers (PedVacc001)
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

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
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 recombinant vesicular stomatitis virus (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-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
Ad4-mgag, Ad4-EnvC150	Live, replication-competent recombinant adenovirus serotype 4 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/Center for HIV/AIDS Vaccine Immunology (CHAVI)	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
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 glucopyranosyl lipid adjuvant (aqueous formulation [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 glycoprotein140 (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 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 Interleukin-12 (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 and 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	Adenovirus serotype 26 (Ad26) vectors encoding mosaic HIV-1 Env, Gag, and Pol + clade C HIV Env protein boost	Crucell Holland BV	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
HIV-1 Nef/Tat/Vif, Env pDNA + HIV-1 rVSV envC	DNA vector encoding HIV-1 Nef/Tat/Vif and Env Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector encoding HIV-1 clade C Env	NIAID	Phase I
Ad4-mgag, Ad4-EnvC150 + AIDSVAX	Orally administered replication-competent adenovirus serotype-4 HIV vaccine in combination with an AIDSVAX B/E boost	PaxVax, Inc./NIAID	Phase I
Trivalent Ad26.Mos.HIV, tetravalent Ad26.Mos4.HIV + clade C gp140	Adenovirus serotype 26 (Ad26) vectors encoding mosaic HIV-1 Env, Gag, and Pol or Ad26 vectors encoding two mosaic HIV-1 Envs, and mosaic Gag, and Pol + clade C HIV Env protein boost	Crucell Holland BV	Phase I
PASSIVE IMMUNIZATION			
VRC01	Monoclonal broadly neutralizing antibody (bNAb) administered intravenously	NIAID/HVTN/HPTN	Phase IIb
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
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/Children's Hospital of Philadelphia (CHOP)	Phase I

PASSIVE IMMUNIZATION/ANTIBODY GENE TRANSFER

HIV is notorious for its ability to evade antibody responses, and for a long period the number of antibodies known to be capable of significantly inhibiting the virus could be counted on one hand. But the landscape has changed dramatically in recent years as a result of technological advances that have allowed the identification of an ever-growing list of antibodies that can neutralize a broad array of HIV isolates from multiple different clades. Many of these broadly neutralizing antibodies (bNAbs) are extremely potent, meaning that they can neutralize the virus even when present at relatively low concentrations.[58]

The burgeoning armamentarium of bNAbs has spurred researchers to develop and manufacture candidates for testing in people, both in the prevention and treatment contexts. The furthest along is VRC01, a bNAb that was discovered toward the end of the last decade by scientists at the Dale & Betty Bumpers Vaccine Research Center (VRC) at the U.S. National Institutes of Health.[59] Phase I trials showed favorable safety and pharmacokinetic profiles,[60] leading to the recent initiation of the AMP studies, two large-scale phase IIb efficacy evaluations that represent collaborations between the HVTN and the HPTN:

- HVTN 704/HPTN 085 will enroll approximately 2,700 men and transgender people who have sex with men at sites in Brazil, Peru, and the U.S.
- HVTN 703/HPTN 081 will enroll approximately 1,500 sexually active women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.

Participants will be randomly assigned to receive either placebo or VRC01 at one of two doses: 30 mg/kg or 10 mg/kg. Infusions are scheduled every eight weeks. The primary endpoints are safety and efficacy, with secondary analyses including assessments of VRC01 levels, markers of protection, and antibody effector functions. If the trials proceed as expected, results are likely to become available around 2022.

It is currently unclear whether VRC01 might be developed commercially if significant efficacy is demonstrated. Since VRC01 was discovered, several other broader and more potent bNAbs have been identified, and certain dual combinations have been reported to neutralize over 98% of circulating HIV isolates from multiple clades[61]—theoretically, at least, these newer bNAbs may be better candidates for advancing toward possible licensure.

Delivery is another issue for passive immunization approaches, and ongoing work is aiming to produce LA bNAb formulations that would be amenable to subcutaneous injection (as opposed to the inconvenient method of inpatient intravenous infusion being used in the AMP studies). A phase I trial of a LA version of VRC01, VRC01LS, was started earlier this year.[62]

The question of whether the expense of manufacturing bNAb may be an impediment to making passive immunization a real-world prevention option has been the subject of some debate. In a presentation at the Cent Gardes HIV vaccine conference last October, John Mascola from the VRC noted that the current cost to manufacture a bNAb is about US$100 per gram, which equates to US$1,200 per year for a bimonthly 30 mg/kg dose administered to a 70 kg adult. However, according to Mascola, progress in improving potency, half-life, and manufacturing efficiency could conceivably bring this figure down to as low as US$10 per person per year.[63]

Antibody gene transfer, also known as vectored immunoprophylaxis, is a potential alternate method of bNAb delivery that is similar to gene therapy. The approach utilizes adeno-associated virus (AAV) vectors that are modified to encode genes for producing bNAbs. When injected into muscle tissue, the AAV vectors can act as factories for the persistent generation of bNAbs. A first human trial of an AAV vector encoding the bNAb PG9 began in the UK in 2014, but results have not yet been published.[64] The VRC is aiming to start a trial of an AAV vector encoding another bNAb, VRC07, before the end of the year.[65,66]

HIV VACCINES

For the past several years, TAG's annual *Pipeline Report* has been covering the incremental progress toward the next round of HIV vaccine efficacy trials. This year represents a milestone because, on May 18, it was announced that the first of these trials, HVTN 702, is scheduled to begin before the end of the year.

HVTN 702 is the culmination of a huge amount of work conducted by the Pox-Protein Public-Private Partnership (P5), a collaboration involving the HVTN, the Bill & Melinda Gates Foundation, 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 goal of P5 is to duplicate or improve on the results of the RV144 trial in Thailand, which demonstrated a significant 31.2% reduction in the risk of HIV acquisition being associated with receipt of a prime-boost vaccine regimen consisting of a canarypox vector encoding HIV antigens (vCP1521) and an HIV envelope protein (AIDSVAX). Notably, vaccine efficacy appeared to be higher after one year of follow up in RV144, at around 60%, but subsequently waned—this has led to the incorporation of additional booster immunizations in the design of HVTN 702. Versions of the vaccines used in RV144 have also been developed and tailored to the prevalent clade C HIV that is circulating in South Africa, where HVTN 702 will take place.

The trial will enroll a total of approximately 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 immunizations or ALVAC vCP2438 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 (in RV144, the final boost was at month 6).

The decision to begin HVTN 702 was based on results from an ongoing study in South Africa, HVTN 100, which tested the same vaccine regimen to establish whether it induced HIV-specific antibody and CD4+ T cell immune responses comparable or superior to those that were associated with protection from HIV infection in RV144. The specific criteria included:

- Prevalence of binding antibodies to clade C gp120 antigens in the vaccine that approach 90%
- Prevalence of V1V2 antibodies to clade gp70 scaffold antigens of >57% at week 28
- CD4+ T cell responses to HIV Env of ~60%

Based on the results of RV144, the above immune responses would predict vaccine efficacy of at least 50% at two years of follow up.[67] The data from HVTN 100 have not yet been presented publicly, but the announcement that HVTN 702 has been given the green light indicates that all of the immune response criteria were met.

In terms of anticipating results, three interim analyses of HVTN 702 are planned, two in 2018 and one in 2019, which will assess whether the trial should continue or be stopped early as a result of either evidence of efficacy or futility (a finding that, if the trial were to proceed, it would not be able show a difference between vaccines and placebo). If the trial proceeds, the final efficacy analysis will take place in 2020.

Although it is hoped that HVTN 702 may confirm and extend the results of RV144, there are also some reasons to be cautious about expectations. The study population in South Africa is at a higher risk for HIV infection than was the case for the Thai participants in RV144, and there is evidence in the original trial that higher HIV risk is associated with lower or absent vaccine efficacy.

In addition, background levels of immune activation and inflammation have been reported to be higher on the African continent than other geographic locales,[68,69] and this is likely linked to higher rates of HIV transmission as a result of the virus's predilection for targeting activated immune cells. In a microbicide trial conducted in South African women, genital tract inflammation was found to be a significant correlate of risk for HIV acquisition.[70,71] It is not known whether inflammation or other factors (such as coinfections) could act as countervailing forces capable of undermining otherwise protective vaccine-induced immune responses, but this is one of the questions that HVTN 702 has the potential to address.

In addition to the P5 program, another large collaborative effort (involving the International AIDS Vaccine Initiative, the Beth Israel Deaconess Medical Center, the U.S. Military HIV Research Program, the Ragon Institute, NIAID, and Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson) is continuing to test various adenovirus and modified Vaccinia Ankara strain (MVA) vectors, as well as HIV Env protein boosts, with the goal of starting efficacy trials of selected vector/protein prime-boost combinations toward the end of this decade.[72,73,74,75]

An array of other HIV vaccine candidates loiter in the waiting room of early-stage clinical testing, uncertain whether they'll ever be called on to pass through the doorway to further development. Results from efficacy trials such as HVTN 702 should help to shed additional light on what types of immune responses are associated with protection against HIV infection, which in turn should help to identify which of the various vaccine concepts in the pipeline have promise.

Relatively few clinical trials of new experimental HIV vaccines have begun over the past year, but among them is a candidate that has been in the works for many years. The creation of George Lewis and colleagues at Robert Gallo's Institute for Human Virology in Maryland, the vaccine is comprised of elements of both the HIV gp120 protein and the human CD4 protein. The goal is to generate immune responses to HIV antigens that are typically only briefly exposed as the virus binds to the CD4 protein on target cells, and the vaccine has shown some success in macaque challenge studies.[76] There have been concerns that including parts of CD4 could result in the induction of autoimmune responses, but this was not observed in a recently published macaque study[77], and a dose-escalation trial is now underway in humans.

The 2015 *Pipeline Report* mentioned plans to study a new oral, probiotic-based HIV vaccine developed by Jean-Marie Andrieu, which had shown a surprising degree of protective efficacy in the SIV/macaque model[78] and drawn considerable press coverage.[79] Unfortunately, an attempt to confirm the macaque results by the laboratory of Guido Silvestri at Emory University produced very disparate findings, with no evidence of protection documented.[80] Andrieu and colleagues believe that the use of macaques of Indian rather than Chinese origin may explain the divergent outcomes because of differing immune response genes,[81] but it seems likely that further research will be needed before the candidate can advance into clinical trials.

CONCLUSION

Several antiretroviral-based modalities, along with numerous active and passive immunization strategies, continue to make their way down the HIV biomedical prevention pipeline. Although there have been no registrational approval filings for any primary prevention products other than coformulated TDF/FTC anywhere in the world, immunologic, antiviral activity, PK/PD, safety, and efficacy data from clinical trials of new products continue to accumulate.

Testaments to this include entire abstract sessions dedicated to biomedical prevention at longstanding HIV congresses. In fact, the bulk of data reported in this year's *Pipeline Report* chapter come from standing-room-only presentations at CROI in Boston earlier this year. There is also the biennial HIV Research for Prevention (HIVR4P) conference, the second of which will be held in Chicago in October.

However, with the advancement of several antiretroviral compounds, biologics, and vaccines, as well as new delivery technologies—compounded by the real-world scale up of TDF/FTC PrEP as a cornerstone of primary prevention services—a number of product registration challenges are becoming increasingly apparent.

One issue is how to incorporate PrEP into background standard-of-care options in vaccine and prevention-based immunotherapy clinical trials. In HVTN 702, for example, South African study participants will receive referrals to local programs where they may obtain TDF/FTC, as opposed to active provision of PrEP as a component of prevention services (e.g., free condoms and lubricant, counseling, and access to STI testing and treatment). This is similar to the standard-of-care approach being employed in the VRC01 AMP Study (HVTN 704/HPTN 085), although in that case U.S. participants have access to a specific referral program that allows their primary care provider to offer TDF/FTC PrEP free of charge.

It has been argued that TDF/FTC should be offered through these trials themselves.[82] This is, however, a difficult issue to wrestle with, as active provision of PrEP may substantially increase the person-years of follow-up required—and, with it, the study's population size and expense—to reach the statistically sound number of seroconversion events needed for efficacy analyses. Indeed, the local Institutional Review Boards and both local and global Community Advisory Boards responsible for reviewing and approving both HVTN 702 and the AMP Study appear to have found the practice of referring participants to external sources of PrEP to be acceptable, at least at the current time.

A second related issue involves registrational trial methodologies that are necessarily rigorous in their design, yet feasible for the sponsors of new biomedical prevention candidates—a large number of which are not-for-profit programs that are dependent on finite public and philanthropic support. A major factor influencing study designs is the ethical principle of beneficence, which requires the abandonment of placebo comparisons and the inclusion of proven interventions, such as oral TDF/FTC, in control groups. Regulatory agencies, however, still want proof that an experimental PrEP regimen is more effective than placebo. This in turn requires reliable background incidence estimates, which have repeatedly proven to be difficult to come by in PrEP clinical trials. Also required are many person-years of follow up—and, by extension, extremely large, long, and expensive clinical trials—to yield the number of seroconversions necessary for standard non-inferiority comparisons, particularly with a highly efficacious regimen such as TDF/FTC.[83,84]

Close attention to these issues, particularly as an increasing number of products enter phase II and III stages of development, is critical. A stringent, but amenable, regulatory climate is necessary to ensure the availability of necessary safety, efficacy, and acceptability data, without being prohibitively costly and ultimately deterring critical investments by product sponsors, particularly those heavily dependent on limited public and philanthropic funding.

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