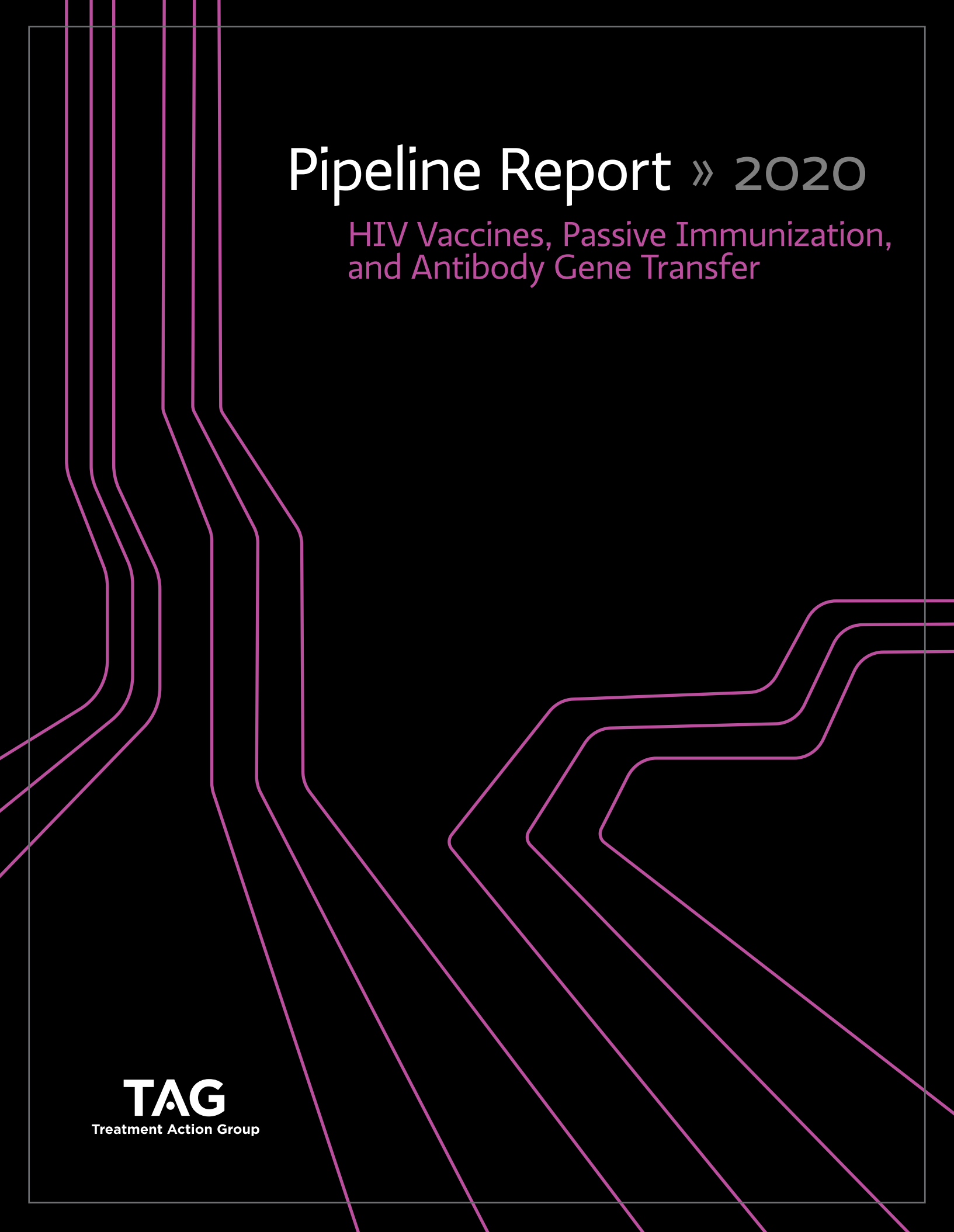
Pipeline Report » 2020

HIV Vaccines, Passive Immunization, and Antibody Gene Transfer



TAG
Treatment Action Group

HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline 2020

By Richard Jefferys

Early in 2020, the HIV vaccine field received disappointing news from HIV Vaccine Trials Network (HVTN) 702 (Uhambo), a key efficacy trial. The research aimed to replicate—or improve upon—the marginal 31.2% reduction in HIV acquisition risk reported in the RV144 trial in Thailand (the only study to date to offer any evidence of vaccine-induced protection against HIV). An announcement on February 3 revealed that HVTN 702's prime-boost regimen of an ALVAC canarypox vector and gp120 envelope proteins had failed to have any impact on HIV incidence. The trial itself was not a failure, as it successfully answered a critical question about the generalizability of the RV144 findings in a South African population at high risk for HIV acquisition. But the answer was not what the world was hoping for.

HVTN 702 had recruited 5,407 sexually active, HIV-negative men and women aged between 18 and 35 years. The announcement of the results came after the Data Safety Monitoring Board (DSMB) performed an interim analysis involving 5,383 participants—2,694 in the vaccine arm and 2,689 in the placebo arm—and found 129 HIV infections among vaccine recipients and 123 in those who received the placebo. The DSMB recommended cessation of further immunizations because there was no possibility of the vaccine showing a significant effect on HIV acquisition.

Considerably more women than men enrolled in the trial, and investigators also compared HIV incidence rates based on participant sex at birth. Again, no significant effect of vaccination was observed. The analysis was based on 1,886 female vaccine recipients, 1,886 female placebo recipients, 808 male vaccine recipients, and 803 male placebo recipients. At month 24, 114 HIV infections had occurred in females in the vaccine arm, 107 in females in the placebo arm, 14 in males in the vaccine arm, and 14 in males in the placebo arm. HIV incidence was approximately fourfold higher in females, consistent with population-level data in South Africa, emphasizing the urgent need to develop effective prevention interventions for this population.

Glenda Gray, the principal investigator of HVTN 702, has noted that a significant difference with the RV144 trial is the far greater rate of exposure to HIV among women—approximately 14 times higher in the South African versus Thai trial populations. There is, as yet, no evidence that the divergent outcomes are related to the magnitudes of the immune responses induced by the vaccines. In preparatory studies, the HVTN 702 vaccine regimen proved slightly more immunogenic in South Africa compared with results reported from RV144.

An issue that may deserve exploration is geographic differences in levels of background immune activation, which can potentially influence susceptibility to HIV. A study comparing genital tract immune activation among women in the United States and Kenya found significantly higher levels in the latter group. The results echoed a previous study that analyzed blood samples of individuals living in Uganda or Europe. However, no direct comparisons of background immune activation levels in South Africa and Thailand have been published.

An outlying possibility is that the RV144 results were a statistical fluke. There was an extremely wide confidence interval (CI) associated with the borderline statistically significant 31.2% reduction in HIV acquisition risk reported in the trial (95% CI 1.1 to 52.1). One published analysis concluded that "the RV144 data provide moderate evidence of low-level positive VE [vaccine efficacy] – with ≥22% chance remaining for no efficacy under a range of prior assumptions." Countervailing evidence includes data on immune correlates of protection from the study, which have been supported by some macaque studies. HVTN 702 researchers are prioritizing the investigation of immune responses that correlated with reduced HIV risk in RV144.

HVTN 702 is ongoing despite the cessation of immunizations. Investigators have unblinded participants to their assignment (vaccine or placebo) and invited them to consent to 12 months of further follow-up to evaluate safety. A more complete reporting of results is expected to occur at the HIV Research for Prevention (R4P) conference, originally slated to take place in October 2020 but now rescheduled to January 2021 due to the COVID-19 pandemic.

Efforts to determine why the HVTN 702 vaccines failed will likely be important for deciding the fates of a number of other prime-boost regimens that induce similar immune responses but have yet to undergo efficacy testing.

Two large HIV vaccine efficacy trials remain ongoing: HVTN 705/HPX2008 (Imbokodo) and HVTN 706/HPX3002 (Mosaico). Both are evaluating a prime-boost approach being developed by Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. The priming components are adenovirus serotype 26 (Ad26) vectors encoding four different HIV 'mosaic' antigens that are amalgams derived from multiple virus clades. The boost contains the HIV gp140 envelope protein in alum adjuvant. In Imbokodo, the gp140 boost is from a clade C virus, while Mosaico is using a bivalent clade C and mosaic gp140 protein construct. The goal is to induce immune responses capable of recognizing multiple global HIV clades.

Imbokodo is fully enrolled with 2,637 women in South Africa, Malawi, Mozambique, Zambia, and Zimbabwe. In response to the COVID-19 pandemic, the HVTN has issued guidance for trial investigators "specific to the particular circumstances of participating countries and study sites." In some cases, the guidance may recommend temporarily pausing vaccinations.

Mosaico aims to enroll 3,800 cisgender men and transgender individuals who have sex with cisgender men and/or transgender individuals. Sites include the United States, Argentina, Brazil, Italy, Mexico, Peru, Poland, and Spain. The trial was only just getting underway when COVID-19 struck, so all new screening, enrollment, and vaccination visits have been temporarily paused. HVTN is assessing the situation periodically.

There are key differences between these trials and HVTN 702, including the mosaic antigens and the use of an Ad26 viral vector as opposed to ALVAC. Another distinction is that the justification for launching efficacy studies does not derive primarily from RV144 but rather from promising results in animal models involving exposure of macaques to SHIVs (hybrids of simian and human immunodeficiency viruses).

One additional trial being designed to assess efficacy is PrEPVacc, which involves a novel design that will compare pre-exposure prophylaxis (PrEP) with Truvada versus Descovy in addition to two different prime-boost vaccine regimens versus a placebo control. Sites include Uganda, Tanzania, Mozambique, and South Africa. Recruitment is delayed until at least 2021 because of COVID-19.

The randomized PrEP portion of the study runs for the first 26 weeks, during the period when the first three immunizations are administered. The vaccine regimens are DNA-HIV-PT123 and AIDSVAX B/E or DNA-HIV-PT123 and CN54gp140 followed by MVA-CMDR and CN54gp140. The vaccine efficacy assessment occurs after the first six months and involves the use of a statistical methodology known as the averted infections ratio.

Earlier-phase vaccine testing is now predominantly focused on the evaluation of carefully designed HIV envelope protein structures intended to guide the B-cell response toward the development of broadly neutralizing antibodies (bNAbs). The successful induction of safe, protective bNAbs remains the ultimate aspiration for HIV vaccine researchers. The challenge is daunting because bNAbs are typically complex and result from multiple rounds of gene rearrangements in B cells (a process called somatic hypermutation). Teasing B cells along the correct gene-shuffling pathway will be difficult, and the vaccines currently undergoing testing represent just the first steps toward this goal.

Passive Immunization

The advent of technologies that allow vast numbers of human B cells to be sampled and assessed for production of antibodies that potently inhibit HIV has revolutionized the field of passive immunization. The approach involves directly administering bNAbs, an alternative to trying to induce them via vaccination. Researchers are discovering an ever-growing number of bNAbs, with many being developed and manufactured to allow testing in clinical trials.

The antibody-mediated prevention (AMP) studies are the only ongoing efficacy trials of passive immunization, evaluating infusions of VRC01, one of the first bNAbs to be discovered. A collaborative effort between the HVTN and the HIV Prevention Trials Network (HPTN), the two trials are fully enrolled, totaling 4,625 participants. HVTN

703/HPTN 081 recruited women, whereas HVTN 704/HPTN 085 recruited men and transgender persons who have sex with men. HVTN's COVID-19 update notes that VRC01 infusions have been discontinued but sufficient data have been accrued to meet the study objectives. Results are anticipated later this year.

The first combination bNAb trial in young South African women, CAPRISA 012A, is underway. The study is looking at subcutaneous dosing of VRC07-523LS and/or PGT121 as a step toward selecting a candidate for coformulation with a potent bNAb targeting clade C HIV—CAP256-VRC26.25LS—and ultimately launching an efficacy trial.

The earlier-phase passive immunization pipeline contains an alphabet soup of more recently identified bNAbs, many with broader and more potent activity than VRC01. There is an increasing trend toward the clinical evaluation of longer-acting bNAbs (typically designated with an appended "-LS" to denote a structural modification) administered by either intravenous or subcutaneous injection.

Antibody Gene Transfer

Currently, clinical research into antibody gene transfer for HIV prevention is experiencing a hiatus. The approach borrows from gene therapy, delivering the genetic code for bNAbs or antibody-based HIV inhibitors via adeno-associated virus (AAV) vectors. An initial clinical study sponsored by IAVI failed to generate detectable levels of the bNAb PG9, likely because of the induction of anti-PG9 antibodies.

At the 2020 Conference on Retroviruses and Opportunistic Infections (CROI 2020), Joseph P. Casazza reported results from a small therapeutic trial of VRC07 delivered by an AAV8 vector that achieved greater success, demonstrating detectable levels of the bNAb in most participants. However, the highest blood concentrations that were achieved fell considerably below those reported to suppress viral load in people with HIV (~1 microgram versus over 10 micrograms). The investigators are not planning prevention studies.

Preclinical work continues, with the research group of Michael Farzan reporting preventive efficacy against SHIV infection in macaques using an AAV-delivered eCD4-Ig entry inhibitor that has broad activity against HIV (see CROI 2020 presentation). Farzan and colleagues hope to eventually progress to clinical testing.

Table: HIV Vaccines and Passive Immunization Pipeline 2020 (Active Clinical Trials)

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
HIV VACCINES				
Ad26.Mos4.HIV, clade C Mosaic gp140 HIV/ alum	Ad26 vectors encoding four mosaic Env, Gag, and Pol antigens (Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol, Ad26.Mos1. Env, Ad26.Mos2S.Env) Clade C and mosaic gp140 protein in alum adjuvant	NCT03964415 (HPX3002/HVTN 706)	Janssen Vaccines & Prevention B.V.	Phase III
■ Stieh DJ, Callewaert K, Sarnecki M, et al. Primary analysis of TRAVERSE: a phase 1/2a study to assess safety/tolerability and immunogenicity of 2 different prime/boost HIV vaccine regimens (Abstract OA02.06LB). Paper presented at: R4P; 2018 October 21–25; Madrid, Spain.				
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)	NCT02968849 (HVTN 702)	NIAID/HVTN/ Bill & Melinda Gates Foundation/ South African Medical Research Council/ Sanofi Pasteur/ GlaxoSmithKline	Phase IIb/III
■ Gray G. Presentation of HVTN 702 study data. Presented at: CROI; 2020 March 10; Boston, MA. ■ NIAID (Press Release). Experimental HIV vaccine regimen ineffective in preventing HIV. 2020 February 3.				
DNA-HIV-PT123 AIDSVAX B/E DNA-HIV-PT123 MVA CMDR CN54gp140/MPLA-L Descovy or Truvada PrEP	DNA vaccines encoding clade C ZM96 Gag, clade C ZM96 Env, and CN54 Pol-Nef Bivalent HIV gp120 glycoprotein including clade B (MN) and clade E (A244) proteins Recombinant CN54gp140 Env protein from the clade C 97/CN/54 isolate in MPLA-L adjuvant MVA encoding envgp160, CM235 clade E and gag and pol CM240 clade A	NCT04066881	MRC/UVRI Uganda Research Unit on Aids	Phase IIb
■ Joseph S, Kaleebu P, Ruzagira E, et al. OC 8491 PREPVACC: a Phase III, MAMS adaptive prophylactic HIV vaccine trial with a second randomisation to compare F/TAF with TDF/FTC PrEP. BMJ Global Health. 2019;4:A10.				
Ad26.Mos4.HIV clade C gp140/alum	Ad26 vectors encoding four mosaic Env, Gag, and Pol antigens (Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol, Ad26.Mos1. Env, Ad26.Mos2S.Env) Clade C gp140 protein	NCT03060629 (HPX2008/HVTN 705)	Janssen Vaccines & Prevention B.V.	Phase IIb
■ NIH (Press Release). NIH and partners launch HIV vaccine efficacy study. 2017 November 30.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
HIV DNA-rTV	DNA prime and replication-competent Tiantan vaccinia virus vector boost encoding Gag, Pol, and Env proteins from HIV-1 CN54	ChiCTR1900021422	Beijing Youan Hospital, Capital Medical University/Center for STD/AIDS Prevention, and Control of China CDC/Beijing Bioproducts Research Institute Company, Ltd.	Phase IIa
■ Shao Y, Li T, Wolf H, et al. The safety and immunogenicity of HIV-1 vaccines based on DNA and replication competent vaccinia vector in phase I clinical trial (Abstract P14-15 LB). Retrovirology. 2009;6(Suppl 3):P404. doi: 10.1186/1742-4690-6-S3-P404.				
ALVAC-HIV vCP1521 AIDSVAX B/E	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 AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NCT01931358 NCT01435135	U.S. Army Medical Research and Materiel Command	Phase II
■ Akapirat S, Karnasuta C, Vasan S, et al. Characterization of HIV-1 gp120 antibody specificities induced in anogenital secretions of RV144 vaccine recipients after late boost immunizations. PLoS One. 2018 Apr 27;13(4):e0196397. doi: 10.1371/journal.pone.0196397. ■ Rerks-Ngarm S, Pitisuttithum P, Excler JL, et al. Randomized, double-blind evaluation of late boost strategies for HIV-Uninfected vaccine recipients in the RV144 HIV vaccine efficacy trial. J Infect Dis. 2017 Apr 15;215(8):1255–63. doi: 10.1093/infdis/jix099. ■ Easterhoff D, Moody MA, Fera D, et al. Boosting of HIV envelope CD4 binding site antibodies with long variable heavy third complementarity determining region in the randomized double blind RV305 HIV-1 vaccine trial. PLoS Pathog. 2017 Feb 24;13(2):e1006182. doi: 10.1371/journal.ppat.1006182.				
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	NCT02315703	Janssen Vaccines & Prevention B.V./NIAID/ MHRP/IAVI/Beth Israel Deaconess Medical Center	Phase I/IIa
■ Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). 2018 Jul 6. Lancet. doi: 10.1016/S0140-6736(18)31364-3. [Epub ahead of print]				
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	NCT02296541 (HVTN 106)	NIAID/CHAVI/IPPOX/ MHRP/HVTN	Phase I
■ Frahm N, Fiore-Gartland A, Harman Malhi H, et al. Increased breadth of T-cell responses after mosaic HIV vaccination in humans (HVTN 106) (Abstract OA07.01). Paper presented at: R4P; 2018 October 21–25; Madrid, Spain.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
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	NCT02771730 (HVTN 110)	PaxVax, Inc./NIAID	Phase I
▪ Alexander J, Mendy J, Vang L, et al. Pre-clinical development of a recombinant, replication-competent adenovirus serotype 4 vector vaccine expressing HIV-1 envelope 1086 clade C. PLoS One. 2013 Dec 3;8(12):e82380. doi: 10.1371/journal.pone.0082380.				
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	NCT02935686	Janssen Vaccines & Prevention B.V.	Phase I
▪ Stieh DJ, Tomaka F, Comeaux CA, et al. ASCENT: Phase 2a, randomized, double-blind, placebo controlled study evaluating safety and immunogenicity of two HIV-1 prophylactic vaccine regimens comprising Ad26.Mos4.HIV and either clade C gp140 or bivalent gp140 (Abstract TUAC0402LB). Presented at: 10th IAS Conference on HIV Science (IAS 2019); 2019 July 21–24; Mexico City, Mexico.				
EnvSeq-1 Envs adjuvanted with GLA-SE DNA Mosaic-Tre Env	Four individual EnvSeq-1 Env proteins (CH505TF, CH505w53,CH505w78, CH505w100), DNA vaccine encoding mosaic Env antigen	NCT03220724 (HVTN 115)	NIAID	Phase I
p24CE1/2 DNA vaccine p55^gag DNA vaccine/ IL-12 DNA adjuvant	DNA vaccines encoding Gag p24 conserved elements and/or Gag p55 + DNA vector encoding IL-12 adjuvant, delivered via intramuscular electroporation	NCT03181789 (HVTN 119)	NIAID	Phase I
Env/gag DNA vaccine gp120 protein vaccine/ GLA-SE adjuvant	Polyvalent DNA vaccine encoding Envs from HIV-1 clades A, B, C, and A/E and clade C Gag + polyvalent gp120 protein vaccine + GLA-SE adjuvant	NCT03409276 (HVTN 124)	NIAID	Phase I
eOD-GT8 60mer/ AS01B/ DPBS sucrose	Engineered priming immunogen designed to activate B-cell precursors as a step toward induction of bNAbs + AS01B adjuvant	NCT03547245	IAVI	Phase I
▪ Jardine JG, Ota T, Sok D, et al. Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen. Science. 2015 Jul 10;349(6244):156-61. doi: 10.1126/science.aac5894.				
BG505 SOSIP.664 gp140/ASO1B	Native-like HIV-1 Env trimer + AS01B adjuvant	NCT03699241	IAVI	Phase I
▪ Dey AK, Cupo A, Ozorowski G, et al. cGMP production and analysis of BG505 SOSIP.664, an extensively glycosylated, trimeric HIV-1 envelope glycoprotein vaccine candidate. Biotechnol Bioeng. 2018 Apr;115(4):885–99. doi: 10.1002/bit.26498. ▪ IAVI (Press Release). IAVI announces first-in-human clinical trial of native-like HIV envelope vaccine candidate. 2019 March 27.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
Ad4-Env145NFL Ad4-Env150KN VRC-HIVRGP096-00-VP (Trimer 4571) /alum	Replication-competent Ad4 HIV vaccines encoding Env proteins + native-like HIV-1 Env trimer with alum adjuvant	NCT03878121	NIAID	Phase I
VRC-HIVRGP096-00-VP (Trimer 4571) /alum	Native-like HIV-1 Env trimer with alum adjuvant	NCT03783130	NIAID	Phase I
▪ Caringal RT, Fleischman M, Chaudhuri R, et al. Development of a stable formulation for stabilized HIV-1 Env trimer vaccine candidate (HIV-1 trimer 4571) (Abstract W1030-12-094). Paper presented at: AAPS PharmSci 360; 2018 November 4–7; Washington, D.C.				
ConM SOSIP.v7 gp140/ MPLA liposomes	Native-like HIV-1 envelope vaccine adjuvanted with MPLA liposomes	NCT03961438	Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	Phase I
ConM SOSIP EDC ConM SOSIP ConS UFO EDC ConS UFO Mosaic SOSIPs/MPLA	Prime-boost combinations of model immunogens based on HIV-1 envelope proteins with MPLA adjuvant	NCT03816137	Imperial College London	Phase I
▪ Sliepen K, Han BW, Bontjer I, et al. Structure and immunogenicity of a stabilized HIV-1 envelope trimer based on a group-M consensus sequence. Nat Commun. 2019 May 29;10(1):2355. doi: 10.1038/s41467-019-10262-5. ▪ Markus S. EAVI2020 announces start of new HIV vaccine trial. Imperial College London. 2019 April 2.				
Stable CH505TF gp120 Transient CH505TF gp120/GLA-SE	CH505TF gp120 produced from stably transfected cells or CH505TF gp120 produced from transiently transfected cells, with GLA-SE adjuvant	NCT03856996 (HVTN 123)	NIAID	Phase I
▪ KO, Verkoczy LK, Jiang C, et al. Vaccine induction of heterologous tier 2 HIV-1 neutralizing antibodies in animal models. Cell Rep. 2017 Dec 26;21(13):3681–90. doi: 10.1016/j.celrep.2017.12.028.				
HIV-1 gp41 MPER-656 liposome vaccine/alum	Priming immunogen designed to activate B-cell precursors as a step toward induction of bNAbs + alum adjuvant	NCT03934541 (HVTN 133)	NIAID	Phase I
HIV-1 BG505 SOSIP.664 gp140/TLR agonist/alum adjuvants	Native-like HIV-1 Env trimer + TLR 7/8 agonists ± alum adjuvants	NCT04177355 (HVTN 137)	NIAID	Phase I
BG505 SOSIP.GT1.1 gp140 vaccine	Soluble, cleavage-competent, trimeric HIV-1 Env glycoprotein gp140 + adjuvant	NCT04224701	IAVI	Phase I

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
PASSIVE IMMUNIZATION				
VRC01	Monoclonal bNAb administered intravenously	NCT02716675 (HVTN 704/HPTN 085) NCT02568215 (HVTN 703/HPTN 081)	NIAID/HVTN/HPTN	Phase IIb
▪ NIAID (Press Release). NIH launches large clinical trials of antibody-based HIV prevention. 2016 April 7.				
PGT121 VRC07-523LS PGDM1400	Monoclonal bNAbs administered intravenously	NCT03721510	IAVI	Phase I/IIa
3BNC117-LS-J 10-1074-LS-J	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT04173819	IAVI	Phase I/II
P2G12	Monoclonal neutralizing antibody administered intravenously	NCT02923999	St George's, University of London	Phase I
VRC01 VRC01LS VRC07-523LS	Monoclonal bNAbs administered subcutaneously to infants	NCT02256631	NIAID	Phase I
VRC07-523LS	LA monoclonal bNAb administered intravenously	NCT03387150 NCT03735849	NIAID	Phase I
▪ Gaudinski MR, Houser KV, Doria-Rose NA, et al. Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial. Lancet HIV. 2019 Oct;6(10):e667-e679. doi: 10.1016/S2352-3018(19)30181-X.				
3BNC117-LS	A monoclonal bNAb administered intravenously	NCT03254277	Rockefeller University	Phase I
10-1074-LS 3BNC117-LS	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT03554408	Rockefeller University	Phase I
PGDM1400 PGT121	Monoclonal bNAbs administered intravenously	NCT03205917	IAVI	Phase I
N6LS	LA monoclonal bNAb administered subcutaneously or intravenously	NCT03538626	NIAID	Phase I
▪ Huang J, Kang BH, Ishida E, et al. Identification of a CD4-binding-site antibody to HIV that evolved near-pan neutralization breadth. Immunity. 2016 Nov 15;45(5):1108–21. doi: 10.1016/j.immuni.2016.10.027.				
PGT121 PGDM1400 10-1074 VRC07-523LS	Monoclonal bNAbs administered intravenously	NCT03928821	NIAID	Phase I

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
10E8.4/iMab	Bispecific monoclonal antibody administered subcutaneously or intravenously	NCT03875209	David Ho	Phase I
■ Padte NN, Yu J, Huang Y, Ho DD. Engineering multi-specific antibodies against HIV-1. Retrovirology. 2018 Aug 29;15(1):60. doi: 10.1186/s12977-018-0439-9. ■ Huang Y, Yu J, Lanzi A, et al. Engineered bispecific antibodies with exquisite HIV-1-neutralizing activity. Cell. 2016 Jun 16;165(7):1621-31. doi: 10.1016/j.cell.2016.05.024.				
VRC07-523LS PGT121	Monoclonal bNAbs administered subcutaneously	PACTR201808919297244 (CAPRISA 012A)	Centre for the AIDS Programme of Research in South Africa	Phase I
■ Mahomed S, Garrett N, Capparelli E, et al. Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: study protocol for the CAPRISA 012A randomised controlled phase I trial. BMJ Open. 2019 Jul 3;9(7):e030283. doi: 10.1136/bmjopen-2019-030283.				
PGT121.414.LS VRC07-523LS	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT04212091	NIAID	Phase I

Shaded entries represent additions since the 2019 Pipeline Report.

TABLE ABBREVIATIONS

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

CMDR: Chiang Mai double recombinant

CROI: Conference on Retroviruses and Opportunistic Infections

DPBS: Dulbecco's phosphate-buffered saline

GLA-AF: glucopyranosyl lipid adjuvant (aqueous formulation)

GLA-SE: glucopyranosyl lipid adjuvant formulated in a stable emulsion

HVTN: HIV Vaccine Trials Network

IAVI: International AIDS Vaccine Initiative

IL: interleukin

LA: long-acting

MHRP: U.S. Military HIV Research Program

MPER: membrane-proximal external region

MPLA: monophosphoryl lipid A

MVA: modified vaccinia Ankara strain

NIAID: U.S. National Institute of Allergy and Infectious Diseases

NIH: U.S. National Institutes of Health

PrEP: pre-exposure prophylaxis

R4P: HIV Research for Prevention Conference

STD: sexually transmitted disease

TLR: toll-like receptor

UFO: uncleaved pre-fusion optimized

UVRI: Uganda Virus Research Institute

VLP: virus-like particle

VRC: The Dale and Betty Bumpers Vaccine Research Center