Pipeline Report » 2021

HIV Vaccines & Passive Immunization

The HIV Vaccines and Passive Immunization Pipeline 2021

By Richard Jefferys

The most highly anticipated results to emerge over the past year came from the Antibody-Mediated Prevention (AMP) studies, which assessed the efficacy of passive immunization with intravenous infusions of the broadly neutralizing antibody (bNAb) VRC01 given every eight weeks.

The AMP studies comprised two separate trials: HVTN 704/HPTN 085 recruited 2,699 men and transgender people who have sex with men in Brazil, Peru, Switzerland, and the U.S., while HVTN 703/HPTN 081 recruited 1,924 cisgender women in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.

The results were announced by press release on January 26, 2021, and presented a day later at the virtual HIVR4P conference. A manuscript was subsequently published in the *New England Journal of Medicine*. Overall, outcomes were disappointing: VRC01 did not demonstrate protective efficacy in either trial. Combining the results of the two trials, there were 67 HIV infections in placebo recipients (4.3% of this group), 60 among those given a 10mg dose of VRC01 (3.9%) and 47 in recipients of a 30mg dose (3%). The slightly lower numbers in the VRC01 groups were not statistically significant. The explanation for the lack of efficacy was that the majority of circulating HIV variants showed greater resistance to VRC01 than the researchers had predicted when the studies were planned.

There was, however, evidence from a subset of participants that protection was achieved against HIV variants that were highly sensitive to VRC01 (these variants were estimated to represent about 30% of the viruses circulating in the communities where the trials were conducted). This analysis was preplanned in the study protocols, and it found that the incidence of infection with VRC01-sensitive HIV isolates was 0.2 per 100 person-years among VRC01 recipients compared with 0.86 per 100 person-years among placebo recipients (representing a total of nine HIV infections in the VRC01 groups and 19 in the placebo group). The results of this subset analysis indicated an estimated 75.4% efficacy of VRC01 against HIV that was highly sensitive to the bNAb.

The researchers leading the AMP studies conclude that these data offer “proof of concept” that a bNAb can prevent HIV infection. Information from the trials may also help define threshold levels that bNAbs need to achieve to protect against HIV. The completion of the large and logistically complex trials should be considered a success and a testament to the commitment of the participants and many collaborators involved.

The major challenge highlighted by the results is that the concentration of VRC01 required to prevent HIV was higher than predicted (by approximately tenfold). Lawrence Corey, the head of HVTN and presenter of the AMP results at HIVR4P, has since written in a commentary that the findings indicate that "large doses of combination monoclonal antibodies to cover the broad spectrum of HIV isolates would be required to advance this concept further."

As reflected in the passive immunization pipeline table below, multiple bNAb candidates are being evaluated both individually and in combinations, including constructs designed to be long-acting to allow less frequent administration. Single antibodies capable of targeting more than one site on HIV—referred to as bispecific or trispecific antibodies—are also under investigation. Most of these bNAbs were discovered more recently than VRC01 and display stronger inhibitory activity against HIV in laboratory testing.

The robust bNAb pipeline offers some hope for the future of passive immunization, but questions remain about prospects for practical application. The parts of HIV targeted by bNAbs are typically more prone to mutation and the generation of resistance than those targeted by antiretroviral drugs, a potential issue highlighted by initial results from a study of a triple bNAb combination in HIV-positive people that demonstrated relatively transient viral load suppression (see this video presentation by Dan Barouch at the 2021 HVTN Full Group Meeting, starting at 1:36:35).

Additionally, bNAb delivery can currently be accomplished only via intravenous infusion or subcutaneous injection. The extremely high efficacy observed with both oral and injectable pre-exposure prophylaxis (PrEP) using antiretroviral drugs sets a very lofty bar that passive immunization will need to reach to be considered for implementation (see TAG's PrEP and Microbicides Pipeline Report for additional information).

On the HIV vaccine front, results are expected very soon from HVTN 705/HPX2008 (Imbokodo), one of two ongoing efficacy trials testing a prime-boost regimen developed by Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Imbokodo has enrolled 2,637 cisgender women in Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. The Data Safety Monitoring Board (DSMB) for the trial allowed the study to progress to completion, and the primary analysis of the results is planned for July 2021.

The second efficacy trial, Mosaico, is recruiting cisgender men and transgender people who have sex with cisgender men and/or transgender people at sites in Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, and the U.S. Mosaico is the first vaccine efficacy trial to specifically focus on people at risk for HIV infection who choose not to use PrEP (although the design allows for enrollees to change their mind during the trial without being withdrawn). As of May 2021, the trial had enrolled about half the target of 3,800 participants.

The vaccine regimens under evaluation comprise priming immunizations with adenovirus serotype 26 (Ad26) vectors encoding four different HIV "mosaic"antigens that combine elements from multiple virus clades, followed by a boost containing the HIV gp140 envelope protein in alum adjuvant. In Imbokodo, the gp140 boost is derived from a clade C virus, while Mosaico employs a bivalent clade C and mosaic gp140 protein construct. The trials represent a key test of whether vaccine strategies that induce non-neutralizing antibody responses can protect against HIV infection.

The Ad26 vector technology is the same technology used for Johnson & Johnson's single-dose COVID-19 vaccine, which has been given emergency authorization in Europe and the U.S. and is listed as safe and effective by the World Health Organization. An unexpected concern that has arisen in this context is the rare occurrence of potentially serious blood clotting disorders. This has not been reported in any of the trials of Ad26 vectors for HIV, and it's not yet clear if it relates to the Ad26 vector or a combined effect of the vector and the SARS-CoV-2 antigen contained in the COVID-19 vaccine. Certainly, data from the HIV trials will be closely evaluated for any evidence of this adverse event.

The majority of other vaccines in the pipeline are part of the expanding effort to design candidates capable of inducing bNAbs against HIV. The endeavor represents a monumental challenge because HIV has evolved a shape-shifting outer envelope that excels at repelling antibodies. Notably, this capacity stands in stark contrast to the susceptibility of SARS-CoV-2 to antibody neutralization, which explains why vaccines could be developed rapidly for COVID-19 but remain elusive for HIV.

Only over the past decade or so have technologies allowed researchers to identify rare bNAbs capable of strongly inhibiting a broad spectrum of HIV variants, a feat typically accomplished by an unusual antibody structure that allows for penetration of the virus's shield. Studies have found that the generation of these bNAbs usually results from multiple rounds of gene rearrangements in B cells, a process called somatic hypermutation. The goal now is to figure out how to design vaccine regimens capable of guiding B cells down the gene-shuffling pathway that would lead to the production of similar bNAbs.

In January 2021, encouraging results from a phase I trial of a vaccine strategy intended to take a first small step toward bNAb generation were presented at HIVR4P by William Schief (the webcast is no longer available, but see the table below for a link to a video of Schief's talk at the more recent HVTN Full Group Meeting). The study involved a specially designed protein named eOD-GT8 60mer administered with an adjuvant (AS01B). The aim was to increase the proportion of participants with detectable levels of B cells with a certain genetic signature known to represent a potential starting point for the pathway to bNAb production.

The trial succeeded in its aim: 35 of 36 (97%) of the recipients displayed the desired type of B cell after immunization, whereas only five had detectable levels before immunization. The researchers are now working to design what they call "shepherding" and "polishing"

vaccines, to guide the B cells down the remaining steps of the path to bNAb production. To facilitate this research, a collaboration has been initiated with the vaccine manufacturer Moderna. The hope is that the use of mRNA technology—which Moderna employed to create its efficacious COVID-19 vaccine—can accelerate the identification of promising shepherding and polishing vaccines.

Regrettably, the news of Schief's presentation became garbled on social media, leading to wildly erroneous claims that an effective HIV vaccine is imminent. In reality, the results are a potentially promising first step, but a long road remains.

The AMP trial results have implications for bNAb-related vaccine strategies as well as for passive immunization efforts. If bNAbs can one day be successfully induced by vaccination, it appears likely that the antibody titers will need to be high, and more than one vulnerable site on HIV will need to be targeted.

Outside of the realm of bNAbs, the past year witnessed a milestone with the launch of the first human trial of an HIV vaccine vector derived from cytomegalovirus (CMV). The research group of Louis Picker at Oregon Health Sciences University has been developing the candidate for more than a decade after obtaining impressive results in an SIV/macaque model. The vaccine has reliably protected about half of the animals exposed to a highly pathogenic SIV challenge, and the efficacy is associated with induction of unusual CD8 T cell responses. The potential for CMV to cause complications in certain settings has necessitated a cautious approach to human testing, but a phase Ia study is now underway at multiple U.S. sites.

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 D. HVTN 705-706 Imbokodo & Mosaico updates, plans for correlates and sieve analyses. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 1:00). ■ Baden LR, Stieh DJ, Sarnecki M, et al. Safety and immunogenicity of two heterologous HIV vaccine regimens in healthy, HIV-uninfected adults (TRAVERSE): a randomised, parallel-group, placebo-controlled, double-blind, phase 1/2a study. *Lancet HIV*. 2020 Oct;7(10):e688–98.				
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.C gp120 and 1086.C gp120)	NCT02968849 (HVTN 702)	NIAID/HVTN/Bill & Melinda Gates Foundation/South African Medical Research Council/ Sanofi Pasteur/ GlaxoSmithKline	Phase IIb/III
■ Gray GE, Bekker L-G, Laher F, et al. Vaccine efficacy of ALVAC-HIV and bivalent subtype C gp120-MF59 in adults. *N Engl J Med*. 2021 Mar 25;384(12):1089–1100. ■ 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 and LSHTM Uganda Research Unit	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.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
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
■ Stieh D. HVTN 705-706 Imbokodo & Mosaico updates, plans for correlates and sieve analyses. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 1:00). ■ NIH (Press Release). NIH and partners launch HIV vaccine efficacy study. 2017 November 30.				
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 AIDS/STD Control and Prevention of China CDC/Beijing Institute of Biological Products Co., 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.				
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 Development Command	Phase II
■ Pitisuttithum P, Nitayaphan S, Chariyalertsak S, et al. Late boosting of the RV144 regimen with AIDSVAX B/E and ALVAC-HIV in HIV-uninfected Thai volunteers: a randomised controlled trial. *Lancet HIV*. 2020 Apr;7(4):e238–48. ■ Easterhoff D, Pollara J, Luo K, et al. HIV vaccine delayed boosting increases Env variable region 2-specific antibody effector functions. *JCI Insight*. 2020 Jan 30;5(2):e131437. ■ Easterhoff D, Pollara J, Luo K, et al. Boosting with AIDSVAX B/E enhances Env constant region 1 and 2 antibody-dependent cellular cytotoxicity breadth and potency. *J Virol. 2020* Jan 31;94(4):e01120-19. ■ 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. ■ Rerks-Ngarm S, Pitisuttithum P, Excler J-L, 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. ■ 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			

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
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/IIa
▪ 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.				
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). *Lancet*. 2018 Jul 21;392(10143):232-243.				
ChAdOx1.HTI MVA.HTI	Chimpanzee adenovirus and MVA vectors encoding HIVACAT T cell immunogen (HTI)	NCT04563377	University of Oxford	Phase I/IIa
VIR-1111	Prototype CMV vector	NCT04725877	Vir Biotechnology, Inc.	Phase Ia
▪ Vir Biotechnology (Press Release). Vir Biotechnology announces initiation of phase 1 clinical trial to evaluate a novel vaccine platform. 2021 January 6.				
EnvSeq-1 Envs adjuvanted with GLA-SE	Four individual EnvSeq-1 Env proteins (CH505TF, CH505w53, CH505w78, CH505 M5), GLA-SE adjuvant	NCT03220724 (HVTN 115)	NIAID	Phase I
▪ Williams W et al. Repertoire analysis and function of B cell lineages expanded by HIV-1 vaccines HVTN 115-Part A and HVTN 133. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 26:10).				
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
▪ Kalams S, et al. HVTN 119: a phase 1 clinical trial to evaluate the safety and immunogenicity of pDNA vaccines expressing HIV M group P24Gag conserved elements (CE) and/or P55Gag, administered with IL-12 pDNA by intramuscular electroporation, in healthy, HIV-uninfected adult participants. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 55:31).				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
Env/Gag DNA vaccine gp120 protein vaccine/ GLA-SE adjuvant (PDPHV-201401)	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
■ Lu S, Ferrari G, et al. HVTN 124 – antibody & cellular. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 36:33). ■ Worcester HIV Vaccine (Press Release). HVTN 124 study conclusion supports advancement to WHV 138 clinical trial. 2021 March 3.				
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
■ Schief W. Review of eOD studies and what is next. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 0:47). ■ IAVI (Press Release). First-in-human clinical trial confirms novel HIV vaccine approach developed by IAVI and Scripps Research. 2021 February 3. ■ 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.				
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. ■ IAVI (Press Release). IAVI announces first-in-human clinical trial of native-like HIV envelope vaccine candidate. 2019 March 27.				
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
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
■ De Bree G, et al. Germline-targeting by native-like envelope trimers. SY07.05. Paper presented at: R4P; 2021 February 3.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
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. ▪ 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
▪ Saunders 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.				
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
▪ Williams W, et al. Repertoire analysis and function of B cell lineages expanded by HIV-1 vaccines HVTN 115-Part A and HVTN 133. Paper presented at: HVTN Full Group Meeting; May 6, 2021 (see video starting at 26:10).				
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
▪ McElrath J, et al. HVTN 137 - antibody & cellular. Paper presented at: HVTN Full Group Meeting; 2021 May 6 (see video starting at 1:14:13).				
BG505 SOSIP.GT1.1 gp140 vaccine	Soluble, cleavage-competent, trimeric HIV-1 Env glycoprotein gp140 + adjuvant	NCT04224701	IAVI	Phase I
▪ De Bree G, et al. Germline-targeting by native-like envelope trimers. SY07.05. Paper presented at: R4P; 2021 February 3.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
ChAdOx1.tHIVconsv1 MVA.tHIVconsv3 MVA. tHIVconsv4	Chimpanzee adenovirus and MVA vectors encoding conserved HIV antigens	NCT04553016	University of Oxford	Phase I
ChAdOx1.tHIVconsv1 MVA.tHIVconsv3 MVA. tHIVconsv4	Chimpanzee adenovirus and MVA vectors encoding conserved HIV antigens	NCT04586673	University of Oxford	Phase I
CH505TF gp120 GLA-SE adjuvant	HIV-1 CH505 transmitted/ founder gp120 + GLA-SE adjuvant	NCT04607408 (HVTN 135)	HVTN	Phase I
IHV01 A244/AHFG ALFQ adjuvant	IHV01 (FLSC) protein and A244/AHFG protein ± ALFQ adjuvant	NCT04658667	U.S. Army Medical Research and Development Command	Phase I
▪ Chua JV, Davis C, Husson JS, et al. Safety and immunogenicity of an HIV-1 gp120-CD4 chimeric subunit vaccine in a phase 1a randomized controlled trial. *Vaccine*. 2021 Jun 4:S0264-410X(21)00685-X.				
Env-C DNA HIV Env gp145 C.6980 protein Rehydragel/ALF43/ dmLT adjuvants	DNA vaccine encoding clade C Env ± HIV Env gp145 C.6980 protein ± adjuvant (Rehydragel, ALF43 or dmLT)	NCT04826094	NIAID	Phase I
CD40.HIVRI.Env DNA-HIV-PT123	Adjuvanted anti-CD40 mAb fused to Env gp140 HIV clade C ZM-96 ± DNA vaccines encoding clade C ZM96 Gag, clade C ZM96 Env, and CN54 Pol-Nef	NCT04842682	ANRS	Phase I
DREP-HIV-PT1 DNA-HIV-PT123 CN54gp140/MPLA-L	Clade C DNA-launched replicon (DREP) DNA vaccines encoding clade C ZM96 Gag, clade C ZM96 Env, and CN54 Pol-Nef recombinant CN54gp140 Env protein from the clade C 97/CN/54 isolate in MPLA-L adjuvant	NCT04844775	ANRS	Phase I

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
PASSIVE IMMUNIZATION				
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
VRC01 VRC01LS VRC07-523LS	Monoclonal bNAbs administered subcutaneously to infants	NCT02256631	NIAID	Phase I
■ McFarland EJ, Cunningham CK, Muresan P, et al. Safety, tolerability, and pharmacokinetics of a long-acting broadly neutralizing HIV-1 monoclonal antibody VRC01LS in HIV-1-exposed newborn infants. *J Infect Dis*. 2021 May 2:jiab229. ■ Cunningham CK, Capparelli EV, McFarland EJ, et al. Safety and PK of potent anti-HIV monoclonal AB VRC07-523LS in HIV-exposed infants (Abstract OA03.02). Paper presented at: R4P; 2021 January 27. ■ Cunningham CK, McFarland EJ, Morrison RL, et al. Safety, tolerability, and pharmacokinetics of the broadly neutralizing human immunodeficiency virus (HIV)-1 monoclonal antibody VRC01 in HIV-exposed newborn infants. *J Infect Dis*. 2020 Aug 15;222(4):628–36.				
VRC07-523LS	LA monoclonal bNAb administered intravenously	NCT03387150 HVTN 127/ HPTN 087	NIAID	Phase I
■ Walsh S, Gay C, Karuna S, et al. Safety and single-dose pharmacokinetics of VRC07-523LS administered via different routes and doses. Paper presented at: R4P; 2021 January 27. ■ 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):e667–79.				
10-1074-LS 3BNC117-LS	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT03554408	Rockefeller University	Phase I
N6LS	LA monoclonal bNAb administered subcutaneously or intravenously	NCT03538626	NIAID	Phase I
■ Widge AT, Houser KV, Gaudinski MR, et al. A phase I dose-escalation trial of human monoclonal antibody N6LS in healthy adults (Abstract 508). Paper presented at: CROI; 2020 March 8–11, Boston, MA.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Status
PGT121 PGDM1400 10-1074 VRC07-523LS	Monoclonal bNAbs administered intravenously	NCT03928821 (HVTN 130/ HPTN 089)	NIAID	Phase I
■ Paez C, Huang Y, et al. HVTN 130/HPTN 089 (triple combo) neutralization and PK data. Paper presented at: HVTN Full Group Meeting; 2021 May 5 (see video starting at 18:22).				
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. ■ 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.				
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.				
PGT121.414.LS VRC07-523LS	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT04212091 (HVTN 136/ HPTN 092)	NIAID	Phase I
VRC-HIVMAB0102-00-AB (CAP256V2LS)	LA monoclonal bNAb administered subcutaneously or intravenously	NCT04408963	NIAID	Phase I

Shaded entries represent additions since the 2020 Pipeline Report.

ABBREVIATIONS

Ad4: adenovirus serotype 4

Ad26: adenovirus serotype 26

NAb: broadly neutralizing antibody

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

mAb: monoclonal antibody

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