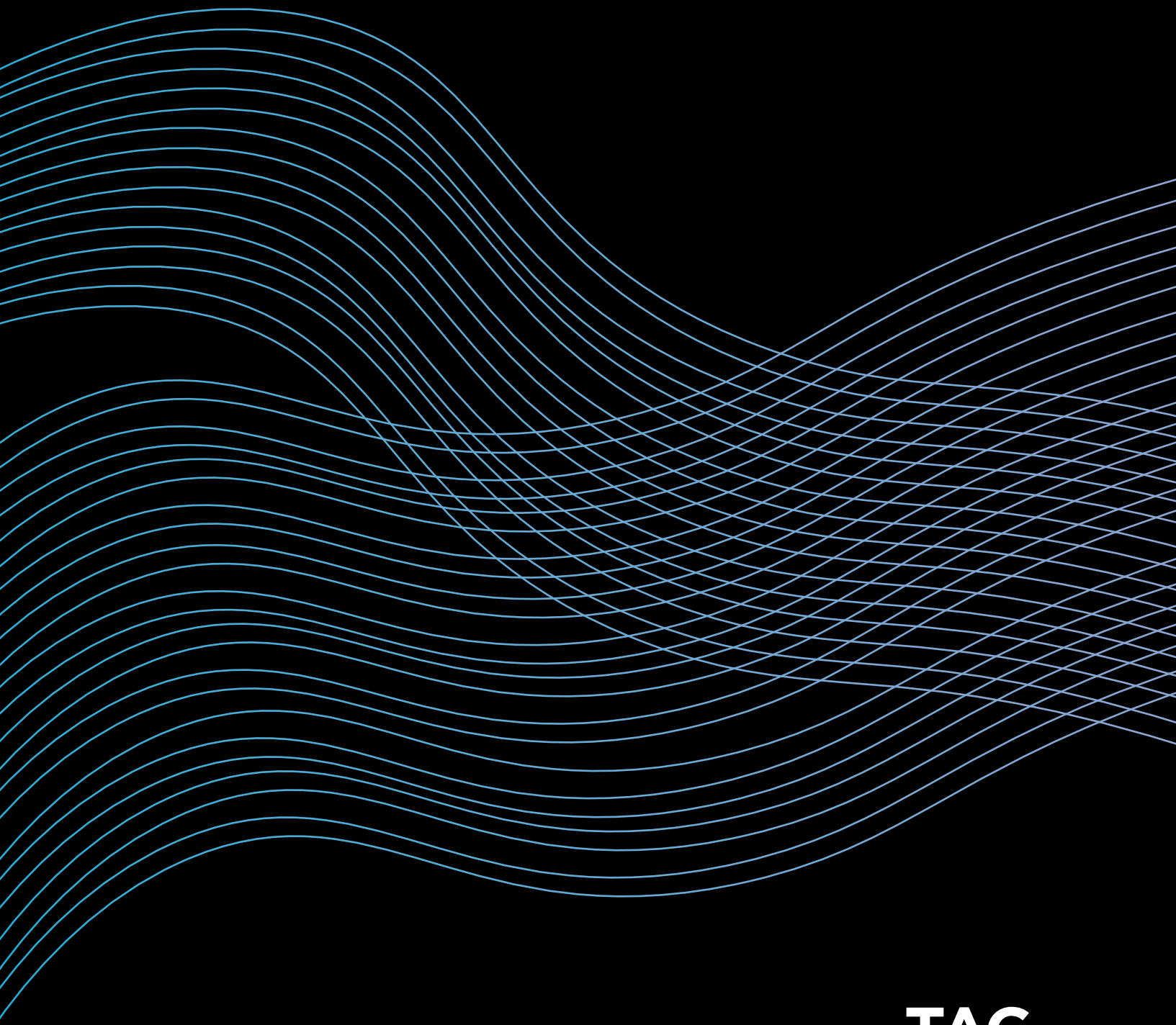
Pipeline Report » 2024

HIV Vaccines and Passive Immunization



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Treatment Action Group

The HIV Vaccines and Passive Immunization Pipeline Report 2024

By Richard Jefferys

HIV vaccine research is now primarily focused on solving the extremely challenging conundrum of designing vaccines capable of inducing broadly neutralizing antibodies (bNAbs). These are rare, unusually shaped antibodies identified in blood samples from people living with HIV that show strong activity against diverse global viral variants. In most cases, they aren't present in large enough amounts to effectively suppress HIV in the person they were sampled from, but they can be isolated and manufactured for administration by infusion or subcutaneous injection.

Results from the Antibody-Mediated Prevention (AMP) trials have provided evidence that a single bNAb (VRC01) can protect against HIV acquisition under the right circumstances: if the bNAbs are present in high enough concentrations and circulating HIV variants are susceptible to inhibition by the specific bNAb. VRC01 was one of the earliest bNAbs to be identified, and researchers are now planning a follow up to the AMP trial that will test the efficacy of a combination of three newer and more potent candidates.

Delivering bNAbs directly is an established approach called passive immunization. A recent example in another setting is the limited use of neutralizing antibodies against SARS-CoV-2 for prevention and treatment of COVID-19. But there are drawbacks compared to active vaccination, particularly the requirement for repeated dosing of large amounts of bNAb to maintain protection.

The HIV vaccine field's shift away from T-cell-based, non-neutralizing approaches was underscored in December 2023 with the announcement that PrEPVacc, the last remaining efficacy to include this type of HIV vaccine candidate, was discontinuing immunizations. The decision was based on the recommendation of the trial's independent data monitoring committee, who reviewed interim results and concluded there was an insufficient prospect of efficacy. A component of the trial administering pre-exposure prophylaxis (PrEP) will continue to completion, with full results anticipated in the second half of 2024.

The current research landscape can be mapped into three broad areas:

- Work toward designing vaccines capable of inducing bNAb responses.
- Research on T-cell-based vaccines that could potentially be used in combination with bNAb-inducing vaccines to bolster protection.
- Passive immunization studies directly administering bNAbs, with the dual goal of identifying efficacious combinations that could be licensed for HIV prevention and establishing parameters of bNAb protection to set a benchmark for vaccine candidates.

When bNAbs arise in people with HIV, it tends to be after prolonged interactions between the virus and the antibody-producing B cells of the immune system. Scientists are studying this process in detail and attempting to mimic and accelerate it in a step-by-step process using experimental vaccine candidates.

The approach is called "germline targeting" because it seeks to identify the B cells that represent the starting point for bNAb production and then stimulate a process called somatic hypermutation in which the cell's original genetic code (referred to as the germline) is shuffled repeatedly to produce the final bNAb shape. A recent study has shown that B cells with the potential to undergo this process and generate bNAbs can be detected to a similar extent in people with and without HIV.

The past year has seen reports of progress using vaccine constructs in preclinical animal models to boost the numbers of precursor B cells that represent the first step toward production of several different bNAbs. This follows the published first-in-human trial demonstrating the boosting of precursor B cells for producing VRC01-type bNAbs targeting the CD4 binding site on HIV's outer envelope.

There are now several vaccine constructs in clinical trials containing proteins engineered to accomplish the first step of the germline targeting approach for bNAbs that recognize HIV's CD4 binding site:

- The eOD-GT8-60mer nanoparticle antigen, developed by William Schief and colleagues at IAVI and Scripps Research, is the first candidate reported to increase levels of the desired precursor B cells for VRC01 production. Delivery via Moderna's mRNA vaccine platform is also being tested, although an unexpected occurrence of adverse skin reactions among some recipients has been noted and is under investigation (see Jon Cohen's article in Science and related IAVI statement).
- BG505 SOSIP.664.v4.1-GT1.1, designed by Roger Sanders and John Moore at Weill Medical College of Cornell University.
- 426c.Mod.Core-C4b, a self-assembling nanoparticle developed by Leo Stamatatos and colleagues at the Fred Hutch Cancer Center.
- A Stabilized CH505 TF chTrimer being developed by a group led by Bart Haynes at Duke University.

Additionally, studies are getting underway with proteins designed to begin the process of inducing bNAbs recognizing other potentially vulnerable regions of HIV, such as N332-GT5 gp140 (which is among those that showed promise in recent preclinical work) and V3G CH848. The goal of these approaches is to generate bNAbs targeting the V3 glycan region on HIV's outer envelope. Targeting multiple vulnerable sites on HIV is believed to be key for a bNAb-based vaccine.

In another sign of progress, trials are also starting for vaccines designed to further stimulate the B-cell precursors along the pathway to bNAb production, a process researchers call "shaping" and "polishing" the B cell response:

- NCT05001373 (IAVI G002), which is evaluating a boosting strategy in recipients of the eOD-GT8-60mer protein.
- NCT05863585 (IAVI C107) and NCT05983874 (IAVI C110), both testing a BG505 SOSIP.664 gp140 vaccine in recipients of the BG505 SOSIP.664.v4.1-GT1.1 protein. Encouraging preliminary findings from IAVI C107 were presented at CROI 2024 by Karlijn van der Straten from the Academic Medical Center in Amsterdam (see webcast).

As can be seen from the table, the primary sponsors of this bNAb vaccine clinical research portfolio are the nonprofit organization IAVI and the HIV Vaccine Trials Network (HVTN) with funding from the National Institute of Allergy and Infectious Diseases (NIAID).

In a first for the field, both HVTN and IAVI are also sponsoring trials in people with HIV where the primary goal is to generate information to assist in the design of bNAb-inducing preventive vaccines. The idea is to assess how natural pre-existing immune responses against HIV influence B cell and antibody responses generated by the vaccines. HVTN 807 is taking place at multiple sites in the US and involves an optional analytical treatment interruption (ATI), while IAVI C112 is planning to enroll participants in Uganda and Zambia on stable antiretroviral therapy and will not include an ATI.

The only commercially sponsored trial of a bNAb-based vaccine involves a candidate developed by Jiang Zhu and colleagues at Scripps Research in La Jolla, California. Scripps has spun off a company, UVAX Bio, which is now sponsoring a clinical trial in Australia. Administration of the first doses was announced on January 30, 2024. The two constructs being tested, UVAX-1107 and UVAX-1197, utilize a proprietary technology to deplete the HIV envelope protein trimer of some of the decoy components known to impede bNAb generation.

Investigations of T-cell-based vaccine candidates continue to a limited extent, with a trial of Vir Biotechnology's revised CMV delivery vector VIR-1388 having started enrollment in the US and South Africa last year. Researchers at Oxford University announced results in July 2023 showing successful induction of T cell responses with their chimpanzee adenovirus (ChAd) and modified vaccinia Ankara strain (MVA) vectors, but the manuscript preprint suggests that they're focusing on studies in people with HIV for the time being: "Much more data addressing the T-cell vaccines' contribution to clinical efficacy is expected through HIV cure studies with analytical treatment interruption in the coming years."

The only remaining trials that appear to be pursuing induction of T cells and non-neutralizing antibody responses (based on the marginal efficacy reported in the RV144 trial in Thailand) are two sponsored by the ANRS in France — see ANRS VRI06 and VRI08 in the table.

On the passive immunization front, the major priority involves work toward a second version of the AMP trials that will test a combination of three bNAbs instead of one. The aim is to initiate an efficacy trial before the end of 2026. The leading candidates for inclusion — PGT121, PGDM1400, and VRC07-523 — showed impressive anti-HIV activity in a therapeutic trial reported at CROI 2024 by Boris Juelg from the Ragon Institute of Mass General, MIT, and Harvard.

A trial of long-acting versions of these three bNAbs in HIV-negative participants has been completed by the HVTN, with results pending. There's hope that this combination could be licensed for HIV prevention if sufficient efficacy is obtained, but some concerns remain about costs, practicality, accessibility, and who might sponsor commercial development. The trial may also have potential to provide guidance for the development of bNAb-inducing vaccines.

Only one new clinical trial of passive immunization was identified in clinical trial registries over the past year: an assessment of long-acting versions of the bNAbs VRC01.23, PGDM1400, and PGT121.414 cosponsored by HVTN and HPTN (the HIV Prevention Trials Network). The registry entry notes that it's currently suspended while a "mild adverse event related to VRC01.23LS administration" is investigated.

Last year's Pipeline Report mentioned a concern regarding transient lymphocytopenia that occurred immediately after receipt of bNAbs in the CAPRISA 012B trial. The details of these findings have now been published in the open access journal *Scientific Reports*, showing associations with baseline lymphocyte counts and several biomarkers that might

help predict which participants are most at risk. While there were no health consequences, the authors note that further studies are needed to better understand the phenomenon and inform monitoring of passive immunization trials with bNAbs. The portion of CAPRISA 012B that enrolled HIV-negative participants is now complete, but a therapeutic component involving an analytical treatment interruption in participants with HIV is ongoing.

In summary, it's likely to be at least two years before another efficacy trial occurs involving candidates from this pipeline, and it will almost certainly involve a passive immunization approach with a combination of bNAbs. Predicting the timeline for a bNAb-inducing HIV vaccine is difficult given the challenges involved, but the encouraging signs of progress give hope that efficacy testing might become possible during the next decade.

Table: HIV Vaccines and Passive Immunization Pipeline 2024 (Active Clinical Trials)

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
HIV VACCINES				
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
▪ Houser KV, Gaudinski MR, Happe M, et al. Safety and immunogenicity of an HIV-1 prefusion-stabilized envelope trimer (Trimer 4571) vaccine in healthy adults: A first-in-human open-label, randomized, dose-escalation, phase 1 clinical trial. *EClinicalMedicine*. 2022 Jun 1;48:101477.				
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; Virtual (see video starting at 1:14:13). ▪ Kasturi SP, Rasheed MAU, Havenar-Daughton C, et al. 3M-052, a synthetic TLR-7/8 agonist, induces durable HIV-1 envelope-specific plasma cells and humoral immunity in nonhuman primates. *Sci Immunol*. 2020 Jun 19;5(48):eabb1025.				
BG505 SOSIP.GT1.1 gp140 vaccine	Soluble, cleavage-competent, trimeric HIV-1 Env glycoprotein gp140 + adjuvant	NCT04224701 (IAVI C101)	IAVI	Phase I
▪ van der Straten K, Caniels T, Reiss E, et al. Safety profile and immunogenicity of a phase I clinical trial using germline-targeting trimer GT1.1. Paper presented at: CROI; 2024 March 3-6, Denver, CO. ▪ De Bree G, et al. Germline-targeting by native-like envelope trimers. SY07.05. Paper presented at: R4P; 2021 February 3; Virtual.				
CH505TF gp120 GLA-SE adjuvant	HIV-1 CH505 transmitted/founder gp120 + GLA-SE adjuvant	NCT04607408 (HVTN 135)	HVTN	Phase I
▪ Haynes BF, Wiehe K, Alam SM, Weissman D, Saunders KO. Progress with induction of HIV broadly neutralizing antibodies in the Duke Consortia for HIV/AIDS Vaccine Development. *Curr Opin HIV AIDS*. 2023 Nov 1;18(6):300-308. ▪ Saunders KO, Edwards RJ, Tilahun K, et al. Stabilized HIV-1 envelope immunization induces neutralizing antibodies to the CD4bs and protects macaques against mucosal infection. *Sci Transl Med*. 2022 Sep 7;14(661):eabo5598.				
IHV01 A244/AHFG ALFQ adjuvant	IHV01 (FLSC) protein and A244/AHFG protein ± ALFQ adjuvant	NCT04658667 (RV 546)	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.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
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 VRI06)	ANRS	Phase I
■ Lelièvre JD, Moog C, Wiedemann A, et al. CD40.HIVRI.Env vaccine induces strong and durable immune responses: ANRS VRI06 Trial (Abstract 324). Paper presented at: CROI; 2023 February 19–22, Seattle, WA. ■ LinKinVax (Press Release). LinKinVax welcomes interim results of the ANRS VRI06 phase i trial evaluating a novel HIV vaccine candidate. 2023 February 22.				
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 (EHVA P01/ANRS VRI08)	ANRS	Phase I
AdC6-HIVgp140 AdC7-HIVgp140 CH505TF gp120 GLA-SE adjuvant	Chimpanzee adenovirus vectors encoding clade C gp140 ± CH505TF gp120 protein boost in GLA-SE adjuvant	NCT05182125 (HVTN 139)	HVTN	Phase I
Stabilized CH505 TF chTrimer 3M-052-AF/alum adjuvants	Stabilized CH505 TF chTrimer protein 3M-052-AF (imidazoquinoline) + alum adjuvants	NCT04915768 (HVTN 300)	NIAID	Phase I
■ Haynes BF, Wiehe K, Alam SM, Weissman D, Saunders KO. Progress with induction of HIV broadly neutralizing antibodies in the Duke Consortia for HIV/AIDS Vaccine Development. *Curr Opin HIV AIDS*. 2023 Nov 1;18(6):300-308. ■ Saunders KO, Edwards RJ, Tilahun K, et al. Stabilized HIV-1 envelope immunization induces neutralizing antibodies to the CD4bs and protects macaques against mucosal infection. *Sci Transl Med*. 2022 Sep 7;14(661):eabo5598.				
BG505 MD39.3 BG505 MD39.3 gp151 BG505 MD39.3 gp151 CD4KO HIV trimer mRNA vaccines	mRNA vaccines encoding one of three HIV trimer proteins: BG505 MD39.3, BG505 MD39.3 gp151 or BG505 MD39.3 gp151 CD4KO	NCT05217641 (HVTN 302)	NIAID	Phase I
■ National Institutes of Health (Press Release). NIH launches clinical trial of three mRNA HIV vaccines. 2022 March 14. ■ Steichen JM, Kulp DW, Tokatlian T, et al. HIV vaccine design to target germline precursors of glycan-dependent broadly neutralizing antibodies. *Immunity*. 2016 Sep 20;45(3):483-96.				
eOD-GT8 60mer mRNA Vaccine (mRNA-1644) Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core)	mRNA vaccines encoding engineered priming immunogens designed to sequentially activate B-cell precursors as steps toward induction of bNAbs	NCT05001373 (IAVI G002)	IAVI	Phase I
eOD-GT8 60mer mRNA Vaccine (mRNA-1644)	mRNA vaccine encoding an engineered priming immunogen designed to activate B-cell precursors as a step toward induction of bNAbs	NCT05414786 (IAVI G003)	IAVI	Phase I
■ IAVI (Press Release). IAVI and Moderna launch trial of HIV vaccine antigens delivered through mRNA technology. 2022 January 17.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
VIR-1388	CMV vector	NCT05854381	Vir Biotechnology, Inc.	Phase I
■ NIAID (Press Release). Clinical trial of HIV vaccine begins in United States and South Africa. 2023 September 20. ■ Vir Biotechnology (Press Release). Vir Biotechnology receives expanded support to develop its novel T cell vaccine platform with new $10 million grant for HIV prevention. 2023 May 2.				
426c.Mod.Core-C4b 3M-052-AF + alum adjuvant	Priming Env protein immunogens designed to sequentially activate B-cell precursors as steps toward induction of bNAbs + adjuvants	NCT05471076 (HVTN 301)	NIAID	Phase I
■ Knudsen ML, Agrawal P, MacCamy A, et al. Adjuvants influence the maturation of VRC01-like antibodies during immunization. *iScience*. 2022 Nov 2;25(11):105473.				
HIV-1 fusion peptide conjugate vaccine +/- Env trimer 4571 and 6931 vaccines Adjuplex adjuvant	HIV-1 fusion peptide conjugated to recombinant tetanus toxoid heavy chain fragment C via sulfo-SIAB chemical linker +/- Env trimer 4571 derived from HIV-1 clade A variant BG505 and Env trimer 6931 derived from HIV-1 clade C consensus sequence	NCT05470400 (HVTN 303)	NIAID	Phase I
■ Corrigan AR, Duan H, Cheng C, et al. Fusion peptide priming reduces immune responses to HIV-1 envelope trimer base. *Cell Rep*. 2021 Apr 6;35(1):108937. ■ Ou L, Kong WP, Chuang GY, et al. Preclinical development of a fusion peptide conjugate as an HIV vaccine immunogen. *Sci Rep*. 2020 Feb 20;10(1):3032.				
A244/B.63521 HIV-1 protein vaccines ALFQ adjuvant	HIV clade E and B Env proteins + ALFQ adjuvant	NCT05423418 (RV575)	U.S. Army Medical Research and Development Command	Phase I
■ U.S. MHRP (Press Release). MHRP launches new HIV vaccine trial to optimize ALFQ adjuvant dosage. 2022 October 12.				
INO-6160 +/- HIV Env Trimer 4571 with 3M-052-AF + alum adjuvants	DNA vaccine encoding a native-like HIV Env Trimer and the cytokine interleukin-12 (IL-12) Env trimer 4571 derived from HIV-1 clade A variant BG505 + TLR 7/8 agonist 3M-052-AF + alum adjuvants	NCT05828095 (HVTN 304)	NIAID	Phase I
INO-6172 +/- HIV Env Trimer 4571 with 3M-052-AF + alum adjuvants	DNA vaccine encoding nanoparticle (NP) GT8 and IL-12 +/- TLR 7/8 agonist 3M-052-AF + alum adjuvants	NCT05781542 (HVTN 305)	NIAID	Phase I
■ Xu Z, Wise MC, Chokkalingam N, et al. In vivo assembly of nanoparticles achieved through synergy of structure-based protein engineering and synthetic DNA generates enhanced adaptive immunity. *Adv Sci (Weinh).* 2020 Feb 27;7(8):1902802.				
SOSIP v8.2 763 vaccine + MPLA liposomes adjuvant	Recombinant HIV-1 Env protein + MPLA liposomes adjuvant	NCT05772286	Fundacion Clinic per a la Recerca Biomédica	Phase I
■ Beltran-Pavez C, Bontjer I, Gonzalez N, et al. Potent induction of envelope-specific antibody responses by virus-like particle immunogens based on HIV-1 envelopes from patients with early broadly neutralizing responses. *J Virol.* 2022 Jan 12;96(1):e0134321.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
BG505 SOSIP.664 gp140 vaccine with 3M-052 AF + alum adjuvant	Native-like HIV-1 Env trimer + TLR 7/8 agonist 3M-052 AF + alum adjuvants	NCT05863585 (C107)	IAVI	Phase I
■ van der Straten K, Caniels T, Reiss E, et al. Safety Profile and Immunogenicity of a Phase I Clinical Trial Using Germline-Targeting Trimer GT1.1. Paper presented at: CROI; 2024 March 3-6, Denver, CO.				
V3G CH848 Pr-NP1 + V3G CH848 mRNA-Tr2 lipid nanoparticle with 3M-052 AF + alum adjuvant	Ferritin nanoparticles expressing eight copies of an Env trimer + mRNA lipid nanoparticle encoding a soluble Env trimer + TLR 7/8 agonist 3M-052 AF + alum adjuvants	NCT05903339 (HVTN 307)	NIAID	Phase I
■ Haynes BF, Wiehe K, Alam SM, Weissman D, Saunders KO. Progress with induction of HIV broadly neutralizing antibodies in the Duke Consortia for HIV/AIDS Vaccine Development. *Curr Opin HIV AIDS*. 2023 Nov 1;18(6):300-308.				
BG505 SOSIP.664 gp140 Vaccine	Native-like HIV-1 Env trimer	NCT05983874 (IAVI C110)	IAVI	Phase I
HIV Env Trimer, N332-GT5 gp140 + SMNP adjuvant	Native-like HIV-1 Env trimer + saponin/MPLA nanoparticle (SMNP) adjuvant	NCT06033209 (HVTN 144)	NIAID	Phase I
■ Steichen JM, Phung I, Salcedo E, et al. Vaccine priming of rare HIV broadly neutralizing antibody precursors in nonhuman primates. *Science*. 2024 May 17;384(6697):eadj8321. ■ Xie Z, Lin YC, Steichen JM, et al. mRNA-LNP HIV-1 trimer boosters elicit precursors to broad neutralizing antibodies. *Science*. 2024 May 17;384(6697):eadk0582. ■ Silva M, Kato Y, Melo MB, et al. A particulate saponin/TLR agonist vaccine adjuvant alters lymph flow and modulates adaptive immunity. *Sci Immunol*. 2021 Dec 3;6(66):eabf1152.				
Ad26.Mos4.HIV + CH505 TF chTrimer	Adenovirus vector + stabilized CH505 TF chTrimer protein	NCT06205056 (RV 591)	U.S. Army Medical Research and Development Command	Phase I
UVAX-1107 + UVAX-1107 or UVAX-1197 with CpG 1018/alum adjuvant	Glycan trimmed HIV-1 vaccine (UVAX-1107), wildtype non-glycan trimmed HIV-1 vaccine (UVAX-1197), CpG 1018/alum adjuvant	ACTRN12624000064505	UVAX Bio LLC	Phase I
■ Uvax Bio (Press Release). Uvax Bio announces dosing of first participant in phase 1 clinical trial evaluating two vaccines to prevent HIV-1 infection. 2024 January 30. ■ Zhang YN, Paynter J, Antanasijevic A, et al. Single-component multilayered self-assembling protein nanoparticles presenting glycan-trimmed uncleaved prefusion optimized envelope trimmers as HIV-1 vaccine candidates. *Nat Commun*. 2023 Apr 8;14(1):1985.				
CD4BS CH505M5 Pr-NP1 + CH505 TF chTrimer + lipid nanoparticles or 3M-052-AF + alum adjuvant	CH505 Env trimers + + lipid nanoparticles or 3M-052-AF + alum adjuvants	NCT06267872 (HVTN 309)	NIAID	Phase I
16055 NFL Delta Gly4 Env Trimer + Trimer 4571 + 3M-052-AF + alum adjuvant + Ad4-Env145N-FL viral particles	Env protein trimers + 3M-052-AF + alum adjuvant + replication-competent Ad4 HIV vaccines encoding Env protein	NCT06332339 (HVTN 313)	NIAID	Phase I

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
PASSIVE IMMUNIZATION				
CAP256V2LS VRC07-523LS	LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PACTR202112683307570 (CAPRISA 012C)	CAPRISA	Phase II
■ Mahomed S, Garrett N, Potloane D, et al. Extended safety and tolerability of subcutaneous CAP256V2LS and VRC07-523LS in HIV-negative women: study protocol for the randomised, placebo-controlled double-blinded, phase 2 CAPRISA 012C trial. *BMJ Open*. 2023 Aug 28;13(8):e076843.				
3BNC117-LS-J 10-1074-LS-J	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT04173819 (IAVI C100)	IAVI	Phase I/II
CAP256V2LS VRC07-523LS PGT121	LA and non-LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PACTR202003767867253 (CAPRISA 012B)	CAPRISA	Phase I
■ Sobia P, Mahomed S, Sivro A, et al. Circulating immunoglobulins and transient lymphocytopenia in a sub-study of CAPRISA 012B, testing HIV monoclonal antibodies in a phase 1 trial. *Sci Rep*. 2024 Jun 12;14(1):13499. ■ Mahomed S, Garrett N, Capparelli EV, et al. Safety and pharmacokinetics of escalating doses of neutralising monoclonal antibody CAP256V2LS administered with and without VRC07-523LS in HIV-negative women in South Africa (CAPRISA 012B): a phase 1, dose-escalation, randomised controlled trial. *Lancet HIV*. 2023 Apr;10(4):e230–e243. ■ Mahomed S, Garrett N, Karim QA, et al. Assessing the safety and pharmacokinetics of the anti-HIV monoclonal antibody CAP256V2LS alone and in combination with VRC07-523LS and PGT121 in South African women: study protocol for the first-in-human CAPRISA 012B phase I clinical trial. *BMJ Open*. 2020 Nov 26;10(11):e042247.				
VRC01.23LS	LA bNAb administered subcutaneously or intravenously	NCT05627258	NIAID	Phase I
■ Kwon YD, Asokan M, Gorman J, et al. A matrix of structure-based designs yields improved VRC01-class antibodies for HIV-1 therapy and prevention. *MAbs*. 2021 Jan-Dec;13(1):1946918.				
VRC01.23LS PGDM1400LS PGT121.414.LS	LA bNAbs administered intravenously	NCT05959707 (HVTN 143/HPTN 109)	NIAID	Phase I

Shaded entries represent additions since the 2023 Pipeline Report.

ABBREVIATIONS

Ad4: adenovirus serotype 4

AHFG: aluminum hydroxide fluid gel

ALFQ: army liposome formulation containing QS21 saponin

bNAb: broadly neutralizing antibody

CMV: Cytomegalovirus

CROI: Conference on Retroviruses and Opportunistic Infections

DREP: alphavirus DNA-launched replicon

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

HPTN: HIV Prevention Trials Network

HVTN: HIV Vaccine Trials Network

IAVI: International AIDS Vaccine Initiative

LA: long-acting

mAb: monoclonal antibody

MHRP: U.S. Military HIV Research Program

MPLA: monophosphoryl lipid A

mRNA: messenger RNA

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

SMNP: saponin/MPLA nanoparticles

TLR: toll-like receptor

UFO: uncleaved pre-fusion optimized

VRC: The Dale and Betty Bumpers Vaccine Research Center