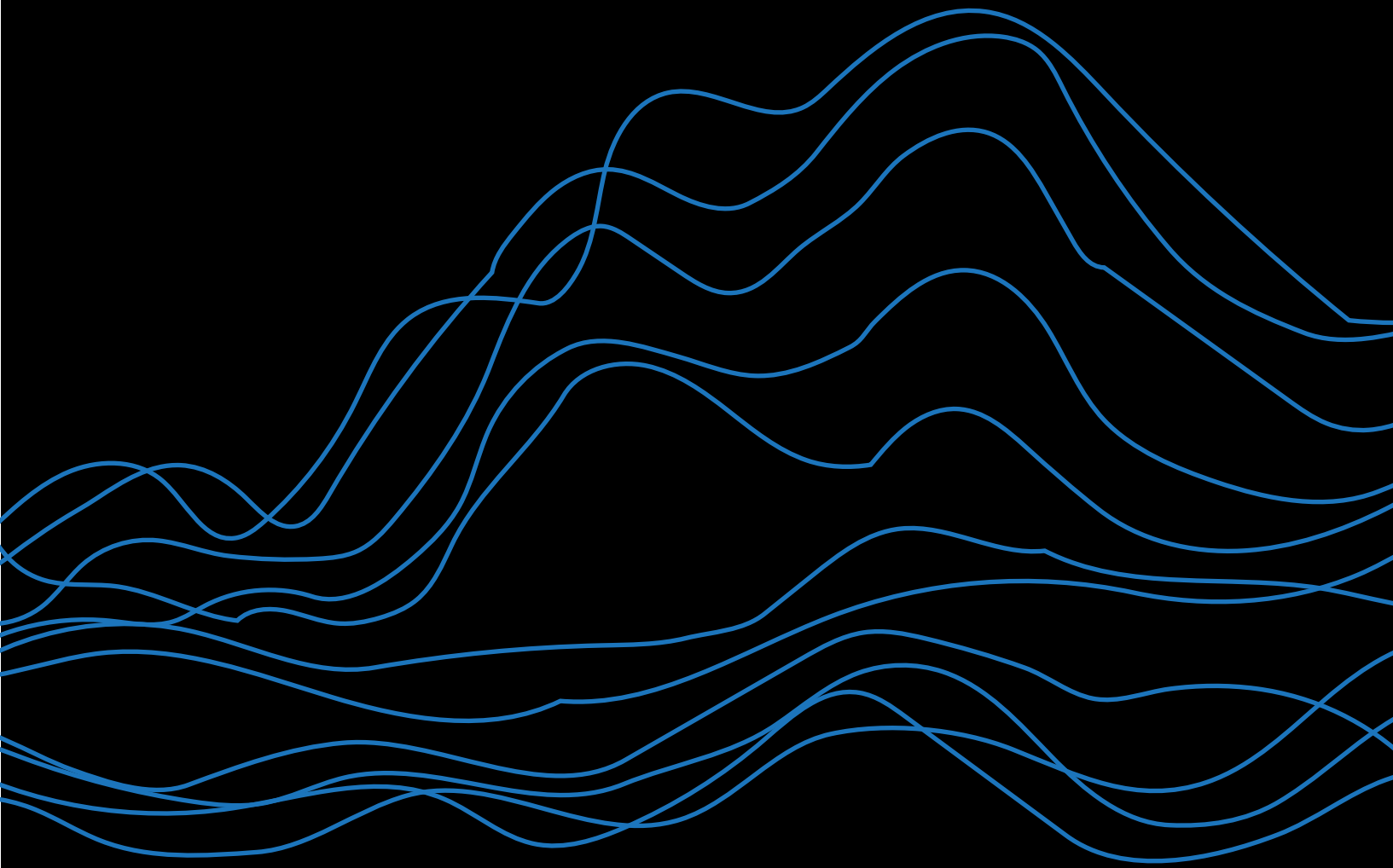
Pipeline Report » 2023

HIV Vaccines and Passive Immunization



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Treatment Action Group

The HIV Vaccines and Passive Immunization Pipeline Report 2023

By Richard Jefferys

The past few years have proven extremely consequential for the HIV vaccine field, with disappointing results from several efficacy trials necessitating a significant recalibration of the research agenda.

At the current time, there's only one type of immune response believed to be capable of achieving significant protection against acquisition of HIV, called a broadly neutralizing antibody (bNAb) response. The major challenge for vaccine development is that bNAbs are very rarely naturally induced in people living with HIV and no method has yet been developed for inducing them with vaccines (research is ongoing).

In the absence of an ability to create bNAbs with a vaccine, researchers were hoping that other types of immune responses—designated non-neutralizing responses—may be able to offer at least some level of efficacy for reducing the risk of acquiring HIV. The hope was bolstered by a large trial among people at relatively low risk of exposure to HIV in Thailand, RV144, which in 2009 reported an approximately one-third reduction in the incidence of HIV infection associated with receipt of a non-neutralizing vaccine regimen. However, the result was at the borderline of statistical significance, leaving residual uncertainty as to the robustness of the findings.

After the RV144 results, the best near-term prospect for an HIV vaccine was considered to be the development of regimens that could at least duplicate and preferably improve upon the slight degree of efficacy that was reported. But three large, post-RV144 efficacy trials of vaccines that induce non-neutralizing responses have since been conducted and none were able to demonstrate a significant protective effect against HIV acquisition:

- HIV Vaccine Trials Network (HVTN) 702 took place in South Africa with a prime-boost vaccine regimen closely modeled on the components used in RV144. Results, announced in February 2020, showed that the vaccines were ineffective at preventing HIV.
- Imbokodo was one of two efficacy trials jointly sponsored by HVTN and the vaccine manufacturer Janssen Vaccines & Prevention B.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. The study assessed a prime-boost regimen with an adenovirus serotype 26 vector and HIV envelope protein boosts in a population of 2,637 cisgender women at high risk of exposure to HIV in Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Initial results, disclosed on August 31, 2021, demonstrated no statistically significant efficacy but there was a slight, non-significant 25 percent lower HIV incidence among the vaccine recipients compared to the placebo (dummy vaccine) arm.

In a presentation at the International AIDS Conference in July 2022, the University of Washington statistician Avi Kenny revealed that there had been an error in the preliminary analysis and that the hint of a difference between the trial arms was essentially a mirage: in the revised analysis, HIV incidence was numerically around 14 percent lower in the vaccine arm, underscoring the absence of efficacy.

- The second and largest of the HVTN/Janssen HIV vaccine efficacy studies was Mosaico, which enrolled 3,887 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 United States. The vaccine regimen was very similar to that used in Imbokodo with just a small tweak in the design of the HIV envelope protein boost. On January 18 of this year, very disappointing news was released that the trial was being discontinued after an interim review by the Data Safety Monitoring Board (DSMB) found equivalent numbers of HIV acquisition events among vaccine and placebo recipients, precluding any possibility of efficacy. Details of the results were subsequently briefly presented by Dr. Susan Buchbinder at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI): the vaccines proved safe, but the HIV incidence was the same in the vaccine and placebo arms of the trial (113 cases of HIV acquisition in each group, which included 1,938 and 1,940 evaluable participants, respectively — this equated to an HIV incidence of 4.1 per 100 person-years in both arms of the trial).

Based on current scientific knowledge, Mosaico is likely to represent the last large scale efficacy evaluation of a non-neutralizing approach to HIV vaccination for the foreseeable future. Although the vaccines didn't work as hoped, the information collected in these trials may still provide important information to researchers. Mosaico remains in active follow up but has been removed from our pipeline table because the vaccine regimen will not be developed further.

One smaller phase IIb efficacy trial remains ongoing: PrEPVacc, which employs a novel design to assess whether non-neutralizing HIV vaccine regimens can add significantly to the protection obtained by oral pre-exposure prophylaxis (PrEP) with either Truvada or Descovy. The statistical parameters of the study are such that it can only detect vaccine efficacy of 70 percent or greater. The likelihood of success appears low, and results should become available within the next few years.

Dr. Lawrence Corey, head of the HVTN, spoke at CROI to outline the revised priorities of the HIV vaccine field after Mosaico. Work has been underway for several years to solve the daunting obstacles to inducing bNAbs with vaccines, and this research now takes center stage. Corey noted that vaccines that induce other types of non-neutralizing responses such as T-cell responses will continue to be investigated but will almost certainly need to be part of a combination approach that includes bNAbs.

Corey also highlighted several key obstacles HIV presents to traditional vaccination methods, with the virus having evolved multiple mechanisms for resisting antibody-mediated neutralization. The virus's outer envelope protein is enshrouded by glycan (sugar) molecules that most antibodies cannot penetrate. The HIV envelope is highly mutable, with few regions of the protein representing stable, conserved antibody targets. Lastly, envelope protein spikes are sparsely distributed on HIV's surface (in Corey's description, "a bald virus"), making them more difficult for antibodies to target.

Reflecting the new landscape, most new HIV vaccine trials added since the 2022 Pipeline Report aim to inform efforts to develop approaches capable of generating bNAb responses. In some cases, versions of the HIV envelope protein designed to mimic the natural three-pronged (trimeric) structure more closely are being evaluated.

Results from the first-in-human trial of an HIV envelope protein trimer, Trimer 4571, were published in the journal *eClinicalMedicine* in June 2022. Administration with alum proved safe, with transient injection site reactions the primary side effect. The researchers found that resulting antibody responses tended to be directed at a region at the base of the envelope that doesn't lead to virus neutralization, providing information to help refine candidate envelope trimers with the aim of inducing antibodies against better targets. For example, the recently launched HVTN 303 trial is investigating a fusion protein designed to steer immune responses away from the envelope trimer base (see table).

Another leading strategy, called germline targeting, involves administering specially engineered proteins intended to increase the number of B cells with the genetic properties believed to be necessary for ultimately producing bNAbs.

Results from a phase I study using a protein construct named eOD-GT8 (short for engineered outer domain germline targeting version 8), published in December 2022, documented the successful expansion of the desired type of B cell: at baseline, the cells were detected in only 5 of 36 study participants, but this increased to 35 of 36 (97 percent) after administration of eOD-GT8. A secondary analysis also showed the induction of CD4+ T-cell responses, which are needed to help support antibody production by B cells. However, it's important to appreciate that additional — yet to be designed — immunization strategies will be needed to guide the B cells further down the pathway to bNAb production. In this initial study, eOD-GT8 was delivered as a protein with an immune-stimulating adjuvant, but newer ongoing trials are assessing whether mRNA technology can be used to speed the evaluation of this and similar constructs.

A vaccine being developed by Vir Biotechnology that is based on a weakened version of cytomegalovirus (CMV) is considered a promising candidate for inducing T-cell responses against HIV, based on results in the macaque model of SIV infection. A phase I trial of a prototype version codenamed VIR-1111 has been completed and no safety signals emerged but, according to a financial report from the company in November 2022, sustained HIV-specific T-cell responses have not been observed in recipients of lower doses (analyses of responses to higher doses have yet to be presented). The company is now launching a trial of VIR-1388, an updated version of the vaccine, in collaboration with the Bill and Melinda Gates Foundation and HVTN (see table).

Investigations continue into whether passive immunization might represent an alternative means of achieving protection against HIV with bNAbs. Instead of vaccine-mediated induction, passive immunization directly administers bNAbs that have been isolated from people with HIV and manufactured at scale, either by intravenous infusion or subcutaneous injection. Almost all the bNAbs currently being studied have been modified into long-acting versions to allow for less frequent dosing (bNAbs with this modification have LS appended to their name).

The potential for bNAbs to protect against HIV acquisition has been demonstrated by the AMP trials, which found that intravenous infusion of VRC01 — one of the first bNAbs to be discovered — significantly lessened the risk of HIV acquisition among a subset of participants exposed to viral variants sensitive to neutralization by the antibody. The results have provided critical information on the levels of bNAb required to achieve protection against HIV while also emphasizing that the variability of circulating viruses will need to be addressed by using combinations of different bNAbs or antibody constructs engineered to inhibit multiple targets on the viral envelope (referred to as bispecific or trispecific bNAbs).

The largest current passive immunization study is CAPRISA 012C, the third in an iterative series of trials primarily focused on two long-acting bNAbs, CAP256V2LS and VRC07-523LS. The phase II trial will assess subcutaneous dosing of the combination either every four or every six months, compared to placebo, in over 900 cisgender women in South Africa aged 18–30.

Results from a smaller phase I trial, CAPRISA 012B, were published in *The Lancet* in April 2023. The study enrolled 42 cisgender women in South Africa and compared intravenous and subcutaneous administration of the bNAbs. Subcutaneous delivery was accomplished via a pump together with recombinant human hyaluronidase (trade name ENHANZE), which allows for administration of larger volumes of bNAb by temporarily alleviating a protein barrier present under the skin (see video animation of the mechanism). The time required for the subcutaneous pump was brief, with the maximum being 18 minutes.

The researchers report that the two bNAbs were generally well tolerated and showed favorable pharmacokinetic parameters, leading to the launch of CAPRISA 012C. The most serious side effect was a transient loss of white blood cells (lymphopenia), which recovered within days. The data relating to this adverse event was reviewed by specialists and adjudged not to be a health concern; the study authors note that it's unclear if other bNAbs may have similar effects because previous studies typically haven't assessed blood values the day after dosing.

Recombinant human hyaluronidase was also evaluated in a phase I study of the bNAb N6LS. Results were presented at CROI 2023, with the researchers concluding that the approach is safe and has potential to offer a viable alternative to intravenous infusion. The main side effect was erythema (reddening of the skin) around the injection site, which was of greater severity among recipients of the higher of the two bNAb doses that were assessed. Severe erythema wasn't associated with the use of recombinant

human hyaluronidase in the CAPRISA 012B trial, and this difference may deserve further analysis to understand if the absence was related to other factors such as the administration technique, the population, or the different bNAbs that were given.

Only one other new bNAb trial has been registered over the past year, a phase I investigation of VRC01.23LS delivered intravenously or subcutaneously. The bNAb is the product of a structure-based strategy for improving the potency of the parental antibody, VRC01. Preclinical laboratory studies of VRC01.23LS have demonstrated an approximately 10-fold greater potency (meaning superior inhibition of HIV at lower concentrations).

HVTN is now working toward an efficacy trial like the AMP studies but using a triple bNAb combination. While it's still unclear if passive immunization could become an effective, affordable, and practical HIV prevention option, the research also has the potential to shed additional light on the magnitude and diversity of bNAb responses that an HIV vaccine would need to induce to achieve efficacy.

Table: HIV Vaccines and Passive Immunization Pipeline 2023 (Active Clinical Trials)

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
HIV VACCINES				
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 (PrEPVacc)	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.				
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	NCT04927585 (WHV138)	NIAID	Phase I
■ Worcester HIV Vaccine (Press Release). The WHV138 trial reaches major milestone: the final dose of the investigational vaccine PDPHV has been administered. 2023 January 16. ■ Lu S, Ferrari G, et al. HVTN 124 – antibody & cellular. Paper presented at: HVTN Full Group Meeting; 2021 May 6; Virtual (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.				
BG505 SOSIP.664 gp140/ASO1B	Native-like HIV-1 Env trimer + AS01B adjuvant	NCT03699241 (IAVI W001)	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.				

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
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
■ Day S, Kaur C, Cheeseman HM, et al. Comparison of blood and lymph node cells after intramuscular injection with HIV envelope immunogens. *Front Immunol.* 2022 Oct 5;13:991509. ■ Day S, Groot E, Cheeseman HM, et al. Towards a prophylactic HIV vaccine: fine needle aspiration reveals cellular features of human lymph nodes compared with blood in the EAVI2020_01 study (Abstract P027). *HIV Medicine*. 2022;23(Suppl. 2):23–95. ■ 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.				
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).				
BG505 SOSIP.GT1.1 gp140 vaccine	Soluble, cleavage-competent, trimeric HIV-1 Env glycoprotein gp140 + adjuvant	NCT04224701 (IAVI C101)	IAVI	Phase I
■ De Bree G, et al. Germline-targeting by native-like envelope trimers. SY07.05. Paper presented at: R4P; 2021 February 3; Virtual.				
ChAdOx1.tHIVconsv1 MVA.tHIVconsv3 MVA.tHIVconsv4	Chimpanzee adenovirus and MVA vectors encoding conserved HIV antigens	NCT04553016	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 (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
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 (RV460)	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 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
BG505 MD39.3 BG505 MD39.3 gp151 BG505 MD39.3 gp151 CD4KO HIV trimer mRNA vaccines	Messenger RNA (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.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
eOD-GT8 60mer mRNA Vaccine (mRNA-1644) Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core)	Messenger RNA (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)	Messenger RNA (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.				
VIR-1388	CMV vector	NCT05854381	Vir Biotechnology, Inc.	Phase I
■ 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.				

Agent	Class/Type	Trial Registry Identifier(s)	Manufacturer/Sponsor	Status
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.				
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	IAVI	Phase I
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
PASSIVE IMMUNIZATION				
CAP256V2LS VRC07-523LS	LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PACTR202112683307570	CAPRISA	Phase II
3BNC117-LS-J 10-1074-LS-J	LA monoclonal bNAbs administered subcutaneously or intravenously	NCT04173819 (IAVI C100)	IAVI	Phase I/II
PGDM1400LS VRC07-523LS PGT121.414.LS	LA monoclonal bNAbs administered subcutaneously or intravenously, with a comparison of fixed or weight-based dosing	NCT05184452 (HVTN 140/HPTN 101)	NIAID	Phase I
CAP256V2LS VRC07-523LS PGT121	LA and non-LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PACTR202003767867253 (CAPRISA 012B)	CAPRISA	Phase I
■ 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.				

Shaded entries represent additions since the 2022 Pipeline Report.

Abbreviations

Ad4: adenovirus serotype 4

bNAb: broadly neutralizing antibody

CMDR: Chiang Mai double recombinant

CROI: Conference on Retroviruses and Opportunistic Infections

DREP: alphavirus DNA-launched replicon

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

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

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

TLR: toll-like receptor

UFO: uncleaved pre-fusion optimized

UVRI: Uganda Virus Research Institute

VRC: The Dale and Betty Bumpers Vaccine Research Center