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The HIV Vaccines and Passive Immunization Pipeline Report 2025

By Richard Jefferys

The development of an effective HIV vaccine <u>remains vital for ending the epidemic</u>. The <u>recent advent</u> of twice yearly injectable pre-exposure prophylaxis (PrEP) with the HIV capsid inhibitor lenacapavir is a major advance, but there are notable limitations including side effects, drug interactions, and a prerequisite to recognize the need for PrEP. A major and unique advantage of vaccines is the potential to offer broad population coverage regardless of self-assessment of HIV exposure risk.

The challenges that have so far precluded development of an effective HIV vaccine are manyfold:

- Unlike most pathogens, HIV preferentially infects a key cell responsible for orchestrating the immune response (the CD4 T cell), meaning that vaccination must equip the immune system with the ability to fend off an infection of itself (not an infection of the liver or the lung, as is the case for hepatitis B or SARS-CoV-2, for example).
- HIV integrates its DNA into the genetic code of infected CD4 T cells, making elimination of the virus extremely difficult once established.
- HIV has evolved to resist neutralization by antibodies typically a key contributor to immune protection with the virus' outer envelope being highly mutable (and therefore a moving target) and cloaked in decoy sugar molecules called glycans. The surface of HIV is also sparsely populated with the viral spikes that antibodies must bind to achieve neutralization, leading scientists to refer to it as a "bald" virus.
- The mutability of HIV also facilitates evasion of other types of immune responses, including CD4 and CD8 T cells.

These obstacles have conspired to stymie HIV vaccine development despite efficacy testing of multiple candidates over the years. Only the RV144 trial in Thailand was able to demonstrate a slight and borderline statistically significant reduction in risk of HIV acquisition associated with a non-neutralizing HIV vaccine regimen, and this result couldn't be confirmed in other populations.

These apparent failures are sometimes cited to cast the field in a poor light, but the scientific work hasn't been for naught — technological advances and trial infrastructure made possible by HIV vaccine research funding have contributed to the licensing of other vaccines, including those for COVID-19. Despite the avalanche of politically motivated misinformation that has surrounded them, COVID-19 vaccines have saved vast numbers of lives.

The work has also guided scientists to focus on solving the stubborn problem of inducing broadly neutralizing antibody (bNAb) responses against HIV. Many bNAbs capable of inhibiting diverse global HIV variants have now been identified and isolated from blood samples of people living with the virus. They tend to be unusually shaped antibodies that 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 (passive immunization).

The B cells that produce bNAbs can also be analyzed in exquisite detail thanks to technological advances largely made possible by research funded by the US National Institutes of Health (NIH). These investigations have allowed scientists to develop guideposts for vaccination protocols designed to coax B cells step by step along the complex pathway toward bNAb generation. The methodology is called germline targeting and involves boosting the numbers of the right type of B cell and then stimulating repeated shuffling of the cell's antibody-producing genetic code (a process called somatic hypermutation).

There has been significant progress in this work in recent years, but the administration that took over the executive branch in the US in January 2025 has launched an ideological slash-and-burn assault on science that has included the termination of the NIH-supported research consortia that was largely responsible for this progress. The fate of the HIV Vaccine Trials Network (HVTN), which is conducting clinical evaluations of potential bNAb-inducing vaccines developed by the consortia (and others), also appears concerningly uncertain. The newly appointed secretary for the Department of Health and Human Services (HHS), Robert F. Kennedy Jr., is both a vaccine denialist and AIDS denialist (the false belief that HIV does not cause AIDS).

The upshot of these alarming developments is that the HIV vaccine and passive immunization research pipeline is under graver threat than at any time since TAG began publishing our reports.

Of the twelve newly registered clinical trials identified since last year (see shaded entries in table), ten are funded by the National Institutes of Allergy and Infectious Diseases (NIAID) at NIH. Nine of the ten are being conducted by HVTN, including two collaborations with the NIH-funded HIV Prevention Trials Network (HPTN). The other is led by the NIH-funded International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network. The two remaining trials are sponsored by International AIDS Vaccine Initiative (IAVI) and ViiV Healthcare, respectively. IAVI has lost considerable funding due to the egregious and unconscionable destruction of the United States Agency for International Development (USAID) by the new administration.

Eight of the additions are assessing HIV vaccine constructs, with the majority addressing aspects of the germline targeting approach to inducing bNAbs. IAVI plans to investigate the capacity of an adenovirus vector derived from gorillas to induce T cell responses against HIV, and a dendritic cell-based approach to delivering the HIV Env protein developed by researchers in France named VRIPRO will be tested in people who previously participated in the completed MOSAICO efficacy trial (if the new HVTN-sponsored study is able to proceed).

Three trials involve delivery of HIV proteins via messenger RNA (mRNA), a technology that has reportedly <u>fallen foul</u> of the anti-science conspiracy mongering political preferences of current administration officials. The mRNA approach is ideal for the iterative evaluation of different protein variants, and it's unclear the extent to which progress might be impeded.

Recently published studies have <u>shown great promise</u> toward bNAb induction using mRNA delivery, but an unexpected side effect of persistent (and in one case transiently severe) <u>urticaria in a subset of</u> recipients is ill-timed and will need to be addressed. Immune reactions to the HIV Env protein <u>are considered the likely</u> cause rather than the mRNA.

Additionally, two of the new trials were due to take place entirely in South Africa, which could cloud their future. The racist ethos of the US president quickly led to termination of NIH funding to the country, leading to a scramble to avoid abandoning participants in ongoing research in violation of US public health law and international ethical rules. Recent reports indicate some relenting of this heinous policy, but the extent is unclear.

Four new passive immunization studies are investigating direct delivery of bNAbs either intravenously or subcutaneously. Among them is a phase II trial conducted by HVTN assessing a triple combination that could potentially be a candidate for an efficacy trial, although NIAID has expressed reluctance to fund such a trial in the absence of a commercial manufacturer for the bNAbs (see Dr. Carl Dieffenbach's comments during a webinar held in May 2024).

Two protocols are testing bispecific bNAbs, which are single antibodies capable of recognizing two different neutralization targets on HIV's envelope. The IMPAACT network is testing subcutaneous injection of single or dual bNAbs in infants with a view to developing an additional intervention capable of preventing HIV transmission via breastfeeding.

The lack of clarity about the future of HIV vaccine and passive immunization research is deeply troubling and we call on all people in the US who care about science to contact their Congressional representatives to advocate for maintaining support for this essential work, including the capacity to continue studies internationally.

Table: HIV Vaccines and Passive Immunization Pipeline 2025 (Active Clinical Trials)

Agent	Class/Type	Trial Registry Identi- fier(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
	Happe M, et al. Safety and immunog ults: a first-in-human open-label, rar			
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
Dhitavat J, Nitayaphan S, Pitisuttithum P, et al. RV546: impact of late boost with IHV01 and A244 gp120 proteins with fractional dosing and/or ALFQ on immune responses in previously vaccinated volunteers (Abstract WEPE056). Paper presented at: R4P 2024 2024 October 6-10; Lima, Peru. 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.				
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

Agent	Class/Type	Trial Registry Identi- fier(s)	Manufacturer/ Sponsor	Status
Stabilized CH505 TF chTrimer	Stabilized CH505 TF chTrimer protein	NCT04915768 (HVTN 300)	NIAID	Phase I
3M-052-AF/alum adjuvants	3M-052-AF (imidazoquinoline) + alum adjuvants			

Walsh S, Hahn W, Williams W, et al. A CH505TF envelope trimer targeting CD4 binding site neutralizing antibody precursors and adjuvanted with 3M-052-AF + Alum is safe, generally well-tolerated, and immunogenic (HVTN 300) (Abstract WEPE052). Paper presented at: R4P 2024; 2024 October 6-10; Lima, Peru.

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	mRNA vaccines encoding one of	NCT05217641	NIAID	Phase I
MD39.3 gp151	three HIV trimer proteins: BG505	(HVTN 302)		
BG505 MD39.3 gp151	MD39.3, BG505 MD39.3 gp151,			
CD4KO HIV trimer mRNA	or			
vaccines	BG505 MD39.3 gp151 CD4KO			

Parks KR, Moodie Z, Allen MA, et al. Vaccination with mRNA-encoded membrane-anchored HIV envelope trimers elicited tier 2 neutralizing antibodies in a phase 1 clinical trial. Sci Transl Med. 2025 Jul 30;17(809):eady6831.

National Institutes of Health (Press Release). NIH launches clinical trial of three mRNA HIV vaccines. 2022 Mar 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):483-496.

eOD-GT8 60mer mRNA Vaccine (mRNA-1644) Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-	mRNA vaccines encoding en- gineered priming immunogens designed to sequentially activate B-cell precursors as steps toward	NCT05001373 (IAVI G002)	IAVI	Phase I
Core)	induction of bNAbs			

Willis JR, Prabhakaran M, Muthui M, et al. Vaccination with mRNA-encoded nanoparticles drives early maturation of HIV bnAb precursors in humans. Science. 2025 May 15:eadr8382. doi: 10.1126/science.adr8382.

VIR-1388	CMV vector	NCT05854381	Vir Biotechnology, Inc.	Phase I
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NIAID (Press Release). Clinical trial of HIV vaccine begins in United States and South Africa. 2023 Sep 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	Priming Env protein immunogens designed to sequentially activate	NCT05471076 (HVTN 301)	NIAID	Phase I
adjuvant	B-cell precursors as steps toward induction of bNAbs + adjuvants			

Hahn W, Parks KR, De Rosa S, et al. Vaccination with a novel fractional escalating dose strategy improves early humoral responses with a novel germline targeting HIV vaccine (426.mod.core-C4b): preliminary results from HVTN 301 (Abstract OA1204). Paper presented at: R4P 2024; 2024 October 6-10; Lima, Peru.

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.

Agent	Class/Type	Trial Registry Identi- fier(s)	Manufacturer/ Sponsor	Status
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
	: al. RV 575 study: a phase 1 double g A244 and B.63521 results of a bl Lima, Peru.			
J.S. MHRP (Press Release).	MHRP launches new HIV vaccine tr	ial to optimize ALFQ adjuva	ant dosage. 2022 Oct 12.	
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
	Gonzalez N, et al. Potent induction o relopes from patients with early broa			
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 encod- ing a soluble Env trimer + TLR 7/8 agonist 3M-052 AF + alum adjuvants	NCT05903339 (HVTN 307)	NIAID	Phase I
	SM, Weissman D, Saunders KO. Prog OS Vaccine Development. Curr Opin			es in the
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, Salce Science. 2024 May 17;384(do E, et al. <u>Vaccine priming of rare H</u> 6697):eadj8321.	IV broadly neutralizing ant	ibody precursors in nonhuma	n primates.
Xie Z, Lin YC, Steichen JM, May 17;384(6697):eadk058	et al. mRNA-LNP <u>HIV-1 trimer boos</u> 32.	ters elicit precursors to bro	ad neutralizing antibodies. Sc	ience. 202
Silva M, Kato Y, Melo MB, e immunity. Sci Immunol. 202	et al. <u>A particulate saponin/TLR agon</u> 21 Dec 3;6(66):eabf1152.	ist vaccine adjuvant alters l	lymph flow and modulates ad	aptive
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), wild-type non- glycan-trimmed HIV-1 vaccine (UVAX-1197), CpG 1018/alum adjuvant	AC- TRN12624000064505	UVAX Bio LLC	Phase I

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Zhang YN, Paynter J, Antanasijevic A, et al. Single-component multilayered self-assembling protein nanoparticles presenting gly-can-trimmed uncleaved prefusion optimized envelope trimmers as HIV-1 vaccine candidates. Nat Commun. 2023 Apr 8;14(1):1985.

Agent	Class/Type	Trial Registry Identi- fier(s)	Manufacturer/ Sponsor	Status
16055 NFL Delta Gly4 Env Trimer + Trimer 4571 + 3M-052-AF + alum ad- juvant + Ad4-Env145NFL viral particles	Env protein trimers + 3M-052- AF + alum adjuvant + replica- tion-competent Ad4 HIV vaccines encoding Env protein	NCT06332339 (HVTN 313)	NIAID	Phase I
CH505M5 N197D mR- NA-gp160 + CH505 TF mRNA-gp160	mRNA vaccines encoding Env protein trimers	NCT06557785 (HVTN 312)	NIAID	Phase I
426c.Mod.Core-C4b vaccine + 3M-052-AF + Alum in infants	Engineered protein priming immunogens designed to sequentially activate B-cell precursors as steps toward induction of bNAbs + Alum adjuvant	NCT06613789 (HVTN 316)	NIAID	Phase I
with a novel germline targe	a S, et al. Vaccination with a novel fra ting HIV vaccine (426.mod.core-C4b 024 October 6-10; Lima, Peru.			
Gorilla adenovirus vectored networked epitopes vaccine	Gorilla adenovirus vector encoding networked HIV T cell epitopes	NCT06617091 (IAVI C114)	IAVI	Phase I
CD40.HIVRI.Env (VRI- PRO) + Hiltonol adjuvant	HIV Env protein + Poly-ICLC adjuvant	NCT06665646 (HVTN 318)	NIAID	Phase I
	un A, et al. <u>Safety and immunogenicit</u> st-in-human randomized, placebo-co			
eOD-GT8 60mer, core- g28v2 60mer, N332-GT5 gp151	mRNA vaccines encoding engineered priming immunogens designed to sequentially activate B-cell precursors as steps toward induction of bNAbs	NCT06694753 (HVTN 317)	NIAID	Phase I
Leggat DJ, Cohen KW, Willi Dec 2;378(6623):eadd6502	is JR, et al. <u>Vaccination induces HIV b</u> 2	proadly neutralizing antibod	y precursors in humans. Scien	ce. 2022
426c.Mod.Core-C4b + HxB2.WT.Core-C4b with 3M-052 AF + Alum adjuvant	Engineered protein priming immunogens designed to sequentially activate B-cell precursors as steps toward induction of bNAbs + Alum adjuvant	NCT06796686 (HVTN 320)	NIAID	Phase I
with a novel germline targe	a S, et al. Vaccination with a novel fra ting HIV vaccine (426.mod.core-C4b 024 October 6-10; Lima, Peru.			
UVAX-1107 + UVAX- 1197 with 3M-052-AF + Alum adjuvant	Glycan-trimmed HIV-1 nanopar- ticle + homologous or wild-type HIV-1 nanoparticle vaccines	NCT06905275 (HVTN 319)	NIAID	Phase I
Tatoud R, Brander C, Hwan, Dec;13(1):2384460.	g C, et al. Biotech's role in advancing	HIV vaccine development.	Emerg Microbes Infect. 2024	
	asijevic A, et al. Single-component m fusion optimized envelope trimmers			
DV700P-RNA + DV701B1.1-RNA	mRNA-encoded HIV Env V3 region-directed immunogens	NCT06919016 (HVTN 321)	NIAID	Phase I

Agent	Class/Type	Trial Registry Identi- fier(s)	Manufacturer/ Sponsor	Status
PASSIVE IMMUNIZATION				
VRC07-523LS, PGT121.414.LS, PGDM- 1400LS	LA bNAbs administered intrave- nously	NCT06812494 (HVTN 206/HPTN 114)	NIAID	Phase II
	om H, et al. <u>Fixed dosing versus weig</u> otocol pharmacokinetics modelling s			odies in
monoclonal antibody PGT1	ohenson KE, et al. Safety, tolerability 21.414.LS administered alone and in first-in-human, open-l. Lancet HIV. 2	combination with VRC07-		
CAP256V2LS VRC07-523LS	LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PAC- TR202112683307570 (CAPRISA 012C)	CAPRISA	Phase II
	loane D, et al. <u>Extended safety and to</u> protocol for the randomised, placelo 076843.			
CAP256V2LS VRC07-523LS PGT121	LA and non-LA bNAbs administered subcutaneously ± recombinant human hyaluronidase PH20 (rHuPH20)	PAC- TR202003767867253 (CAPRISA 012B)	CAPRISA	Phase I
	A, et al. Circulating immunoglobulins ibodies in a phase 1 trial. Sci Rep. 20		penia in a sub-study of CAPRIS	SA 012B,
Mahomed S, Garrett N, Cap CAP256V2LS administered	oparelli EV, et al. <u>Safety and pharmac</u> with and without VRC07-523LS in I d controlled trial. Lancet HIV. 2023 A	okinetics of escalating dose		
CAP256V2LS alone and in	im QA, et al. Assessing the safety an combination with VRC07-523LS and se I clinical trial. BMJ Open. 2020 No	PGT121 in South African v	·	-
PGT121.414.LS +/- VRC07-523LS in infants	LA bNAbs administered subcutaneously	NCT06517693 (IMPAACT 2037)	NIAID	Phase I
	d EJ, Muresan P, et al. Safety, tolerab 7-523LS in newborn infants exposed			
Vrc-Hivmab0121-00-Ab (CAP256.J3LS)	LA bispecific bNAb administered intravenously	NCT06585891	NIAID	Phase I
Zhang B, Gorman J, Kwon Y potency. MAbs. 2023 Jan-D	//D, et al. <u>Bispecific antibody CAP256</u> Dec;15(1):2165390.	5.J3LS targets V2-apex and	CD4-binding sites with high b	readth and
VH4527079	Bispecific bNAb administered intravenously or subcutaneously	NCT06652958	ViiV Healthcare	Phase I

Shaded entries represent additions since the 2024 Pipeline Report.

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

HPTN: HIV Prevention Trials Network

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 $\textbf{HVTN:} \ \mathsf{HIV} \ \mathsf{Vaccine} \ \mathsf{Trials} \ \mathsf{Network}$

IAVI: International AIDS Vaccine Initiative

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network

LA: long-acting

mAb: monoclonal antibody

MHRP: U.S. Military HIV Research Program

MPLA: monophosphoryl lipid A

mRNA: messenger RNA

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

VRC: The Dale and Betty Bumpers Vaccine Research Center