Prophylactic HIV-1 vaccine trials: past, present, and future

Joseph P Nkolola, Dan H Barouch

An effective HIV-1 vaccine is a global health priority but has remained elusive for more than 40 years. Key scientific hurdles that have hampered vaccine development are the unprecedented genetic variability of the virus, the rapid establishment of persistent viral latency, and the challenges associated with induction of broadly neutralising antibodies. Clinical trials have been instrumental in evaluating scientific concepts and testing vaccine strategies. This Review discusses lessons learned from clinical trials of HIV-1 vaccines, current technologies that are being explored, and future considerations in the development of a safe and effective HIV-1 vaccine.

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See Comment page e70

Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA, USA (J P Nkolola PhD, Prof D H Barouch MD)

Correspondence to: Prof Dan H Barouch, Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA 02139, USA **dbarouch@bidmc.harvard.edu**

Introduction

HIV-1 is the causative agent of AIDS.[1,2] Infection with HIV-1 results in the progressive depletion of CD4⁺ T cells, which leads to failure of the immune system and life-threatening opportunistic infections and cancers if untreated. Since the first cases of HIV-1 were reported 40 years ago, approximately 84·2 million people have been infected and 40·1 million have died from AIDS-related illnesses.[3] The UNAIDS (2022) estimates that globally 38·4 million people were living with HIV-1, with 1·5 million new infections and 650 000 deaths occurring in 2021 alone.[3] Antiretroviral drugs have proven highly effective in protecting against HIV-1 infection,[4,5] but it is generally recognised that an effective HIV-1 vaccine will be critical for ending the HIV-1 pandemic.

Multiple groups developed safe and effective SARS-CoV-2 vaccines in an unprecedented timeframe of 1 year,[6–8] leading to the question: why has development of an HIV-1 vaccine taken more than 40 years? Development of SARS-CoV-2 vaccines benefited from previous research in related viruses causing severe acute respiratory syndrome and Middle East respiratory syndrome, as well as vaccine technologies developed and refined over several decades. Moreover, HIV-1 vaccine development faces major scientific challenges not faced by SARS-CoV-2 vaccine development (table 1).[9] Of these challenges, viral sequence diversity in the surface envelope (Env) glycoprotein is a key obstacle, with circulating strains differing from one another in Env by up to 35%.[10,11] In addition, HIV-1 leads to viral integration shortly following exposure and establishes lifelong persistence.[12,13] Moreover, there are no known immunological correlates of protection for HIV-1 infection and no methods that reliably induce broadly neutralising antibodies (bNAbs).[14] Nevertheless, there are a wide array of concepts currently being tested as vaccine strategies for HIV-1.[15,16] Clinical efficacy trials have shed light on the features and limitations of various vaccine approaches. The major HIV-1 clinical efficacy trials are summarised below.

Major vaccine efficacy trials

Over several decades of HIV-1 vaccine research, HIV-1 vaccine efficacy trials have tested five distinct vaccine concepts, but none have resulted in robust efficacy (table 2). In early efficacy trials, VAX003 and VAX004 tested bivalent HIV-1 Env Gp120 proteins formulated with aluminium (alum)-containing adjuvant but failed to show efficacy, potentially because the antibody response failed to neutralise clinical isolates. These vaccines also had no significant effect on viral load, CD4⁺ T-cell count, or disease progression.[17–19] Due to these early disappointing results and the increasing recognition of the importance of CD8⁺ T cells in control of HIV-1 replication, the HIV-1 vaccine field shifted focus towards concepts aimed at inducing cellular immune responses.

Using an adenovirus serotype 5 (Ad5) viral vector to express HIV-1 Gag, Pol, and Nef internal proteins, the Step Study (HVTN 502) was the first efficacy trial that focused on cell-mediated immunity in men and women at high risk of HIV-1 infection in North America, the Caribbean, South America, and Australia.[20] Both this trial and the Phambili study (HVTN 503), conducted in participants in South Africa, were unsuccessful in conferring protection against HIV-1 infection.[20–22] Potential limitations of this approach included the limited breadth of T-cell responses and pre-existing immunity to the Ad5 vector.

The next major efficacy trial, RV144, used a pox-protein prime-boost strategy in which a recombinant canarypox

	HIV-1 vaccine	SARS-CoV-2 vaccine
Viral diversity	Extensive viral clade and sequence diversity	Sequence diversity limited
Viral latency	Early establishment of latent viral reservoirs	No establishment of a viral reservoir
Neutralising antibody induction via vaccination	No method to elicit broadly reactive neutralising antibodies via vaccination	Cross-reactive neutralising antibodies can be elicited via vaccination
Glycan shielding	Highly dense oligomannose glycan shielding of HIV Env	Less extensive glycan shielding of spike protein

Env=surface envelope.

Table 1: **Comparison of the scientific hurdles in the development of HIV-1 and SARS-CoV-2 vaccines**

	Phase	Vaccine description	Clinical trial number	Year of results	Efficacy (primary outcome)
VAX 003	3	AIDSVAX B/E (subtype B MN and CRF01_AE CM244) Gp120 protein subunits in alum	NCT00006327	2003	No efficacy
VAX 004	3	AIDSVAX B/B (MN and GNE8 subtype B) Gp120 protein subunits in alum	NCT00002441	2003	No efficacy
HVTN 502	2b	Adenovirus type 5 expressing Clade B *gag*, *pol*, and *nef*	NCT00095576	2007	No efficacy
HVTN 503	2Ib	Adenovirus type 5 expressing Clade B *gag*, *pol*, and *nef*	NCT00413725	2007	No efficacy
RV 144	3	ALVAC-HIV (recombinant canarypox vector) vCP1521 expressing subtype E *gp120* linked to the transmembrane anchoring portion of Gp41 and *gag* and *protease* plus AIDSVAX B/E Gp120 in alum	NCT00223080	2009	31·2%*
HVTN 505	2	DNA expressing HIV-1 subtype B *gag*, *pol*, and *nef*, and *env* from subtypes A, B, and C plus adenovirus type 5 expressing subtype B *gag*, *pol*, and *env* A, B, and C	NCT00865566	2013	No efficacy
HVTN 702	2b/3	Canarypox vector expressing clade C *env*, *gag*, and *pro* plus bivalent clade C Gp120 protein subunit with MF59 adjuvant	NCT02968849	2020	No efficacy
HVTN 705	2b	Tetravalent adenovirus type 26 vector expressing mosaic *env*, *gag*, and *pol* plus clade C Gp140 subunit protein with alum	NCT03060629	2021	No efficacy
HVTN 706	3	Tetravalent adenovirus type 26 vector expressing mosaic *env*, *gag*, and *pol* plus bivalent mosaic or clade C Gp140 subunit proteins with alum adjuvant	NCT03964415	2023	No efficacy

Alum=aluminium. *Post-hoc analysis result p=0·04.

Table 2: **Completed HIV-1 clinical efficacy trials 1998–2023**

vector ALVAC-HIV (vCP1521) was boosted with alum adjuvanted bivalent protein AIDSVAX B/E used in VAX003 and aimed to elicit both cellular and humoral responses. RV144 enrolled over 16 000 participants at low heterosexual risk for HIV-1 infection in Thailand.[23] The RV144 trial failed to show significant efficacy in prespecified outcomes, but a post-hoc modified intention-to-treat analysis showed 31·2% efficacy,[23] which reinvigorated enthusiasm for the possibility of an HIV vaccine.

The next major efficacy trial was HVTN 505, which tested a multiclade DNA prime with a recombinant Ad5 boost targeting Env, Gag, Pol, and Nef proteins in men or transgender women who have sex with men in the USA, and aimed to generate both humoral and cellular responses.[24] Although the vaccine regimens raised the desired immune responses, they were not associated with protection, and the trial was halted due to lack of efficacy.[25]

The HVTN 702 phase 2b/3 (Uhambo) study in South Africa was a follow-up of the RV144 study and used a pox-protein regimen directed at HIV-1 subtype C in which ALVAC-HIV (vCP2438) expressed HIV subtype C *gp120*, subtype B *gp41*, *gag*, and *pro*, followed by a bivalent subtype C (TV1/1086) Gp120 boost in MF59 oil-in-water adjuvant.[26,27] This trial showed no efficacy, demonstrating the difficulty in generalising the observations from RV144 in Thailand to South Africa.[27]

The most recent efficacy trials involved combining adenovirus serotype 26 (Ad26) vectors expressing bioinformatically optimised mosaic immunogens designed to address global HIV-1 diversity followed by Env Gp140 protein boosts in HVTN 705 (Imbokodo) and HVTN 706 (Mosaico).[28–31] HVTN 705 assessed the efficacy of a heterologous prime-boost regimen of tetravalent Ad26.Mos4.HIV and alum adjuvanted Clade C Gp140 in women in sub-Saharan Africa, whereas HVTN 706 was conducted in the Americas and Europe with Ad26.Mos4.HIV and a combined Clade C and Mosaic M Gp140 boost in cisgender men and transgender individuals who have sex with cisgender men or transgender individuals. No safety concerns were observed in HVTN 705 or HVTN 706, but these vaccine regimens did not provide significant protection against HIV-1 infection.[32,33]

Non-vaccine HIV-1 prevention strategies

HIV-1 vaccine strategies are currently being developed in the context of an increasingly effective portfolio of other HIV-1 prevention strategies. Highly effective strategies for HIV-1 prevention include male circumcision, use of condoms, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis with antiretroviral drugs, and treatment as prevention, which reduce the virus inoculum or limit available target cells. Antiretroviral treatment of HIV-1 infection has been shown to effectively prevent HIV-1 transmission (ie, undetectable is untransmissible, or U=U).

In addition, passive immunisation with HIV-1 bNAbs has recently shown promise. The HVTN 703 phase 2b study among women in South Africa and the HVTN 704 phase 2b study among men and transgender individuals who have sex with men (AMP Study) showed that although the CD4 binding site-specific bNAb VRC01 did not achieve the primary outcome of prevention of HIV-1 acquisition in the overall population, VRC01 provided substantial protection against acquisition of highly susceptible HIV-1 viruses.[34] These findings suggest that bNAb cocktails with increased coverage of global isolates will probably achieve broad protection.[34]

Long-active antiretroviral drugs are currently being developed for PrEP and have the potential to transform the HIV-1 prevention field. In a non-human primate

proof-of-concept study, a long-acting capsid inhibitor was shown to provide protection against simian-HIV challenges for 6 months.[35] An extended-release injectable formulation of the integrase inhibitor cabotegravir has been approved[36] and the capsid inhibitor lenacapavir is currently in clinical efficacy trials.[37]

Preclinical development of vaccines aimed at inducing bNAbs

The HIV-1 vaccine field is at a crossroads, currently with no vaccine candidates in efficacy trials. Given the lack of efficacy observed in HVTN 702, HVTN 705, and HVTN 706, as well as in the ongoing PrEPVacc study, the field is now focused on the development of new vaccine strategies that induce bNAbs, which is a major scientific challenge. Native-like Env trimers designed to present multiple bNAb epitopes, such as BG505 SOSIP.664, are currently being evaluated, but alone do not appear to induce bNAbs.[38] Although several clinical trials are ongoing to evaluate the BG505 SOSIP.664 SOSIP trimer and other stabilised trimers (table 3), additional HIV-1 bNAb vaccine concepts are also being explored.

To this end, bNAbs that target relatively conserved epitopes on the viral Env glycoprotein have provided critical insights on how vaccine design can be improved through reverse vaccinology.[39,40] bNAbs typically attain their affinity-enhancing mutations when B cells mutate and mature from their germline sequences. Germline-targeting vaccine designs are therefore derived to induce bNAbs by first priming rare bNAb-precursor B cells and subsequently guiding B-cell affinity maturation with a series of rationally designed boosting immunogens. As germline precursors of bNAbs typically have no detectable affinity for Env glycoproteins, a vaccine to initiate bNAb induction might require a dedicated germline-targeted priming immunogen with appreciable affinity for such precursors.[41] Several variations of this vaccination strategy are currently being pursued (see below), including B-cell lineage vaccines, germline-targeting vaccines, and epitope-targeted vaccines.

Lineage and germline vaccine strategies

The B-cell lineage vaccine design strategy involves a series of immunisations using Env immunogens developed from longitudinal analyses of bNAb development in infected individuals such that the priming immunogen has affinity for the unmutated common ancestor for the bNAb lineage.[41] This is followed by vaccination with Envs specifically selected to stimulate somatic mutation pathways that give rise to bNAbs. This strategy was highlighted by the report of the isolation, evolution, and structure of bNAbs from an HIV-1-infected African donor followed-up from time of infection to when the mature antibody (CH103) neutralised about 55% of HIV-1 isolates.[42] In this study, virus and antibody gene sequencing revealed concomitant virus evolution and antibody maturation. A follow-up study established the feasibility of this approach in human bNAb-precursor knock-in mice and non-human primates in which Env immunogens that bound precursor B cells of either a CD4 binding site or V3-glycan bNAb lineage were capable of initiating bNAb B-cell lineages and selecting for key mutations required for bNAb development.[43] In another study, macaques that were primed with a transmitted-founder clade-B Env capable of engaging germline bNAb precursors followed by multiple booster immunisations with glycan-repaired

	Clinical trial number	Vaccine concept	Platform	Vaccine description
IAVI W001	NCT03699241	Multiple bNAb epitope targeting	Subunit protein	Adjuvanted recombinant HIV-1 BG505 SOSIP.664 Gp140 vaccine
IAVI C101	NCT04224701	Multiple bNAb epitope targeting	Subunit protein	Adjuvanted recombinant HIV-1 BG505 SOSIP.GT1.1 Gp140 vaccine
NL69161.000.19	NCT03961438	Multiple bNAb epitope targeting	Subunit protein	ConM SOSIP.v7 Gp140, adjuvanted with MPLA liposomes
HVTN 300	NCT04915768	B-cell lineage	Subunit protein	CH505 TF chTrimer plus adjuvants 3M-052-AF (imidazoquinoline) and alum
HVTN 303	NCT05470400	Fusion-peptide epitope targeted	Subunit protein	Adjuvanted HIV-1 fusion-peptide conjugate vaccine alone or in prime-boost regimens with adjuvanted HIV-1 Env trimer 4571 and HIV-1 trimer 6931 vaccines
WHV138	NCT04927585	Multiple epitope targeting	Subunit protein and DNA	Polyvalent *env* (A, B, C, A/E) and *gag* (C) DNA and Gp120 (A, B, C, A/E) protein vaccines (PDPHV201401) co-administered together with or without adjuvant
HVTN 302	NCT05217641	Germline targeted	mRNA	BG505 MD39.3 gp151, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV trimer mRNA vaccines
IAVI G003	NCT05414786	Germline targeted	mRNA	eOD-GT8 60mer mRNA vaccine (mRNA-1644)
IAVI G002	NCT05001373	Germline targeted	mRNA	eOD-GT8 60mer mRNA vaccine (mRNA-1644) and core-g28v2 60mer mRNA vaccine (mRNA-1644v2-Core)
VIR-1111-2001	NCT04725877	Multiple epitope targeting	Viral vector	Human CMV-based vaccine (VIR-1111) for HIV
HIV-CORE 006	NCT04553016	Multiple epitope targeting	Viral vector	Non-replicating Chimpanzee adenovirus (ChAdOx.1) expressing mosaic immunogen tHIVconsv1 and non-replicating poxvirus (MVA) expressing mosaic immunogens tHIVconsv3 and tHIVconsv4
HVTN 139	NCT05182125	Multiple epitope targeting	Viral vector and subunit protein	Chimpanzee adenovirus vectors AdC6-HIVgp140 and AdC7-HIVgp140 expressing Clade C *gp140* plus CH505TF Gp120 protein boost

Alum=aluminium. bNAb=broadly neutralising antibody. CMV=cytomegalovirus. Env=surface envelope. MPLA=monophosphoryl lipid A.

Table 3: **Select HIV-1 vaccine concepts in phase 1 clinical testing**

autologous and subsequently bivalent heterologous Envs (clades A and C) elicited neutralising antibodies to select HIV-1 strains.[44] The B-cell lineage vaccine design concept is currently in phase 1 clinical testing, with the hypothesis that an Env trimer vaccine derived from a transmitted or founder virus can expand B-cell precursor lineages and might be capable of producing autologous and heterologous bNAbs (table 3). However, a clinically relevant proof of concept of this hypothesis has not yet been achieved.

Germline-targeting vaccine design involves priming with an Env immunogen that is engineered to bind diverse precursors within a particular bNAb class and is typically followed by successive boosts with lineage immunogens or Env trimers with native conformations, or both.[45,46] Initial exploration of this concept used computation-guided, in vitro screening to engineer a germline-targeting engineered HIV-1 outer domain Gp120 (eOD gp120) Env immunogen that was able to bind multiple classes of VRC-01 bNAbs and their germline precursors (figure).[45,46] Iterative design resulted in the development of a 60mer self-assembling nanoparticle presenting 60 copies of eOD Gp120 (eOD-GT8) genetically fused to and arrayed externally on an interior lumazine synthase nanoparticle.[47] Although eOD-GT8 was shown to prime VRC01-class B-cell responses in mice,[48] boost immunogens to guide the B-cell lineage to VRC01-class antibody responses have not been defined.[49] In recent phase 1 clinical testing, adjuvanted eOD-GT8 60mer had a favourable safety profile and induced VRC01-class bNAb precursors in most vaccine recipients, with median frequencies reaching 0·1% among B cells in blood (table 2).[50] Although bNAb precursors shared multiple properties with notable gains in somatic hypermutation and affinity with the boost,[50] additional investigation is required to develop the boosting modalities and regimens to lead to induction of bNAbs. Therefore, it remains unclear if this strategy will lead to bNAbs with the consistency, magnitude, and breadth needed to be clinically relevant.

Epitope-focused vaccine design

Epitope-focused HIV-1 vaccine design is a strategy that involves immunogens that focus immune responses on one or more neutralising epitopes on the HIV-1 Env trimer. Despite the identification of several well characterised, structurally defined bNAb epitopes on the HIV-1 Env glycoprotein that include the CD4-binding site,[51] a quaternary site at the V2 trimer apex,[52] a V3-glycan supersite,[53] and membrane-proximal external region,[54] induction of bNAbs to these sites has proven difficult due to the need for extensive somatic hypermutation,[55] unusual recombination,[56] recognition of N-linked glycan,[53] or co-recognition of membrane.[57] In early efforts of epitope-focused vaccine design targeting the glycan-polypeptide located at the base of the HIV-1 Env variable loop 3 (V3), a homogeneous minimal immunogen with high-mannose glycans, reflective of a native Env V3-glycan bNAb epitope (Man9-V3) bound V3-glycan bNAbs with similar affinities to native-like gp140 Env trimers.[58]Although it was not a potent immunogen, immunisation with Man9-V3 monomer in non-human primates primed precursors of V3-glycan B-cell lineages to clonally expand.[58]

A critical component of the HIV-gp41 virus-cell entry machinery, the fusion peptide comprising

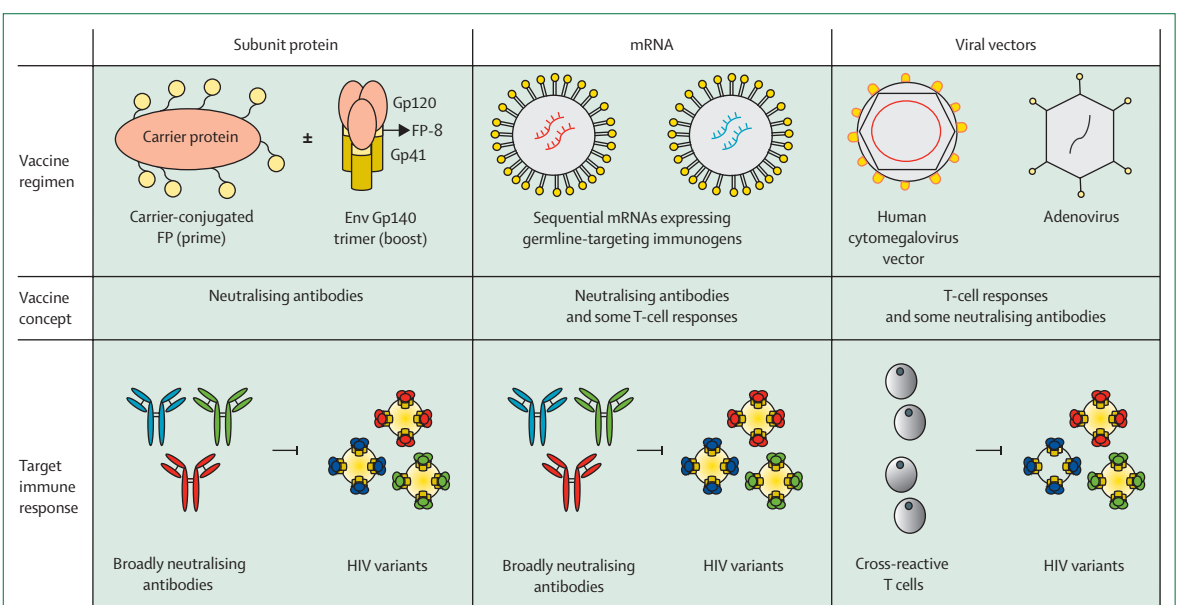

Figure: **Emerging HIV-1 vaccine concepts in early phase clinical testing**
Env=surface envelope. FP=fusion peptide.

15–20 hydrophobic residues at the N terminus of the Env-Gp41 subunit has been identified to be an attractive site of neutralisation vulnerability.[59] In particular, neutralising antibody VRC34.01 was shown to direct the majority of its binding to the eight linear, N-terminal residues of FP-8, and the ability of VRC34.01 to neutralise through recognition of this conserved FP-8 linear peptide exposed in the prefusion-closed conformation of Env, suggested that the epitope would be amenable to epitope-based approaches of vaccine design.[59] Preclinical studies with fusion peptide immunogens showed that mice were able to elicit monoclonal antibodies capable of neutralising up to 31% of a cross-clade panel of 208 tier 2 HIV-1 strains, with immunisation of guinea pigs and rhesus macaques inducing similarly broad fusion peptide-directed neutralising antibody responses, showing the potential translatability of the approach.[60,61] In a subsequent study, five neutralising antibody lineages targeting the HIV-1 fusion peptide in vaccinated non-human primates were identified, characterised, and tracked over time, and genetic and structural analyses revealed two of five of these lineages belonged to a reproducible class capable of neutralising up to 59% of 208 diverse tier 2 viral strains.[62] B-cell analysis showed that all five lineages were initiated and expanded by fusion peptide priming, with Env trimer boosts inducing cross-reactive neutralisation. On the basis of these preclinical data, early phase clinical testing of fusion peptide in combination Env trimers is now under way (figure; table 2).

In an alternative epitope-focused vaccine strategy, Env variable loop 2 (V2) apex epitope bNAb signatures were used to inform immunogen design of signature-based epitope targeted (SET) Env trimers.[63] In this strategy, data from large tier 2 neutralisation panels were used for comprehensive mapping of viral signatures associated with bNAb sensitivity, and signature sites were identified using a strategy that incorporated phylogenetic correction for amino acids potential N-linked glycosylation sites, as well as the effects of hypervariable region characteristics and clades.[63] V2 bNAb signature-guided mutations were introduced into the acute Env 459C, a strain previously shown to elicit modest neutralisation of some tier 2 primary isolate strains in guinea pigs.[64] V2-SET Env immunogens were engineered to be a trivalent combination of 459C wild-type plus two additional proteins designed by modifying 459C to include V2 bNAb signatures intended to both enhance V2 epitope exposure and include relevant variation. In guinea pig studies, V2-SET cocktail vaccines expressing stabilised Gp140 Env immunogens elicited increased neutralising antibody breadth compared with 459C, providing the proof-of-concept of this epitope-focused vaccine design.[63] A combination of the V2-SET and fusion peptide concepts is currently under evaluation in non-human primates.

Preclinical development of vaccines aimed at inducing T-cell responses

It is generally accepted that HIV-1 vaccine efficacy will require vaccine-induced immune responses that either prevent detectable HIV-1 infection by the induction of bNAbs or halt early viral replication and spread by cellular immune responses. For halting early viral replication, HVTN 502 and HVTN 503 efficacy trials were unsuccessful (table 1), but newer vaccine concepts for HIV-1 cellular immunity have emerged. Among these, the cytomegalovirus viral vector is being explored as a potential HIV-1 vaccine delivery platform due to its ability to maintain high-frequency effector memory $CD8^+$ T cells,[65] including unconventional MHC-E-restricted $CD8^+$ T-cell responses that mediate arrest and clearance of simian immunodeficiency virus (SIV), presumably before establishment of long-lived reservoirs.[65] If vaccine-induced MHC-E-restricted $CD8^+$ T-cell responses can be recapitulated in humans, this might provide a new approach to HIV-1 vaccine development. To this end, a phase 1a, first-in-human study in healthy adult participants is currently under way using a prototype human cytomegalovirus-based vaccine (VIR-1111) for HIV-1 (figure; table 2).

An extension of viral vector-based vaccines is heterologous viral vector (HVV) vaccination. In this scenario, multiple viral vectors are administered via sequential immunisation to induce high frequencies of $CD8^+$ T cells in mucosal tissues at the portals of HIV-1 entry, with the aim of offering enhanced protection in the presence of neutralising antibodies. Preclinically, macaques sequentially immunised with three HVVs expressing SIVmac239 Gag (vesicular stomatitis virus [VSV])-Gag, vaccinia virus [VV]-Gag and Ad5-Gag) induced a high magnitude of Gag-specific T-cell responses in blood-resident and tissue-resident $CD8^+$ memory T cells in vaginal mucosa.[66] In regimens where HVVs were combined with a clade C HIV-1 Env Gp140 protein adjuvanted with nanoparticles containing a TLR7/TLR8 agonist (3M-052), enhanced protection was observed in a subset of animals against intravaginal infection with a heterologous simian-HIV, providing an early proof-of-concept that vaccination strategies that induce both $CD8^+$ T-cell and antibody responses can confer enhanced protection against infection.[66] In a subsequent study, non-human primates immunised with an HVV regimen and an HIV Env trimer were protected after vaginal challenges with autologous virus, with the observed cellular immune responses able to reduce the threshold of neutralising antibodies required to confer protection compared with the HIV Env alone.[67] The protection in this particular study was durable, as the animals resisted additional challenges 5 months later and antigen stimulation of T cells in ex vivo vaginal tissue cultures triggered antiviral responses in myeloid and $CD4^+$ T cells.[64]

T-cell vaccine candidates will probably not block infection but might lead to control of viral replication.

Conventional central memory T-cell responses might be kinetically too slow for protection, and effector memory T-cell responses might prove more effective. In contrast, bNAb vaccine candidates could theoretically provide high-level protection against infection if antibodies of sufficient magnitude, breadth, and durability could be induced. A combination approach might prove most effective.

mRNA as a delivery platform for HIV-1 vaccines

mRNA has recently become an attractive vaccine delivery platform as a result of the rapid and successful deployment of mRNA vaccines for SARS-CoV-2.[68,69] Untranslated region sequences, a 5□ cap, a 3□ poly(A) tail flank the coding region, and nucleosides within the mRNA are modified to delay degradation in the cytoplasm, decrease immunogenicity, and enhance translation.[68,69] Key attributes of the mRNA platform include its synthetic nature and straightforward manufacturing, allowing for fast and flexible vaccine production,[68,69] making it attractive for use in HIV-1 vaccine development.[70,71] However, the durability of mRNA vaccines appears to be limited and, more importantly, they will not solve the key scientific challenges of HIV-1 immunogen design, but they will probably accelerate iterative testing of HIV-1 vaccine concepts.

Several preclinical data using the mRNA platform for HIV-1 vaccine delivery have encouraging preliminary results. In mouse studies, BALB-c and outbred mice administered self-amplifying RNA vaccines expressing functionally conserved regions of HIV-1 proteins induced broadly specific, plurifunctional $CD8^+$ and $CD4^+$ T cells at high frequencies over several months post administration.[72] In more recent macaque studies, animals immunised with an mRNA vaccine co-expressing membrane-anchored HIV-1 Env and SIV Gag proteins to generate virus-like particles, had a 79% per-exposure risk reduction upon repeated low-dose mucosal challenges with heterologous tier-2 SHIV-AD8.[44] Several phase 1 clinical trials are now under way to evaluate the safety and immunogenicity of different HIV-1 mRNA vaccines, primarily of the germline-targeting vaccine design previously covered in this Review. In the HVTN 302 trial, sequential immunisation with BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV-1 trimer mRNA vaccines is being evaluated (figure 1; table 2). In a separate study, the eOD-GT8 60mer mRNA vaccine (mRNA-1644) and Core-g28v2 60mer mRNA vaccine (mRNA-1644v2-Core) are being evaluated (figure 1; table 2). Data from these trials will provide early data on the safety and immunogenicity of coupling germline-targeting vaccine design to the mRNA platform.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "HIV interventions", "HIV vaccine", "HIV vaccine clinical trial", "HIV vaccine design", and "HIV efficacy", from Jan 1, 1983 to April 13, 2023. Articles were also identified through searches of the authors' own files and publications. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Conclusion

The HIV-1 vaccine field is now at a crossroads. Five vaccine concepts have been tested over the course of 40 years in nine clinical efficacy trials, none of which showed high efficacy. Currently there are no HIV-1 vaccine candidates in advanced phase clinical trials and no HIV-1 vaccine products that will enter large-scale efficacy trials in the immediate future.[73] Promising early concepts are being explored, but it will probably be years before we have an HIV-1 vaccine. Although the mRNA platform will increase the speed of iterative testing of vaccine concepts, this technology itself does not solve the key antigen design challenges for an HIV-1 vaccine.

Nevertheless, an HIV-1 vaccine remains a global health priority and will be critical for control of the global HIV-1 pandemic. Therefore, it is time to redouble efforts to develop an HIV-1 vaccine. As the next generation of HIV-1 vaccine concepts are evaluated, HIV-1 prevention strategies with long-acting monoclonal antibodies and long-acting PrEP will continue to improve. Future HIV-1 vaccine efficacy trials will therefore be conducted in the context of increasingly effective non-vaccine prevention strategies.

Contributors

JPN and DHB reviewed the literature and wrote the Review.

Declaration of interests

DHB is a co-inventor on HIV-1 vaccine patents that have been licensed. JPN declares no competing interests.

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