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Current views on the potential for development of a HIV vaccine

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Abstract

Introduction—Despite many recent advances in the HIV prevention landscape, an effective vaccine remains the most promising tool to end the HIV-1 pandemic.

Areas covered—This review summarizes past HIV vaccine efficacy trials and current vaccine strategies as well as new approaches about to move into first-in-human trials.

Expert opinion—Despite many setbacks in early HIV vaccine efficacy trials, the success of RV144 has provided the glimmer of hope necessary to invigorate the vaccine field, and has led to the development of a large number of vaccine strategies aiming at inducing an array of different immune responses. The follow-up pox-protein trials, developed to replicate and enhance the polyfunctional antibody responses induced by the RV144 regimen, are already reaching efficacy trials, while a large body of work providing a more complete understanding of the development of broadly neutralizing antibodies is now being translated into immunogen design using several different strategies. T-cell based vaccines, fallen out of favor after Ad5-based trials showed increased infection rates in Ad5 seropositive vaccine recipients, are experiencing a comeback based in part on the promising results from non-human primate challenge studies using rhCMV-based immunogens. This diverse array of vaccine candidates may finally allow us to identify a broadly effective HIV vaccine able to contain the epidemic.

1. Introduction

The last ten years have seen an extraordinary acceleration in the development of at least partially effective HIV prevention modalities. Twenty years into the use of antiretroviral therapy, the first randomized trial to test treatment as prevention showed a 96% reduction of HIV acquisition in the group receiving immediate treatment¹, confirming the assumption that treatment not only benefits the HIV-infected subject but also dramatically reduces the risk of transmission. Male circumcision was demonstrated to reduce HIV-1 acquisition in three large randomized clinical trials^{2–4}. A vaginal microbicide based on the reverse transcriptase inhibitor Tenofovir disoproxil fumarate (TDF) showed efficacy in the CAPRISA trial⁵, although the VOICE trial failed to replicate CAPRISA's success, likely

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Declaration of Interest:

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due to reduced adherence to study product use⁶. Similarly, oral Pre-Exposure Prophylaxis (PrEP) reduced HIV acquisition in men who have sex with men (MSM) in the iPrEx study⁷ and in serodiscordant heterosexual couples in the Partners PrEP Study⁸, though PrEP failed to provide protection in the FEM-PrEP⁹ and VOICE studies⁶.

Despite all these advances, an effective vaccine remains the holy grail of HIV prevention due to its ease of delivery, relatively low cost, independence on adherence, and lack of associated stigma. This review will present an overview of past HIV vaccine efficacy trials, current proof-of-concept trials as well as provide an outlook on promising new vaccine strategies about to move into phase 1 clinical trials.

2. Past HIV vaccine efficacy trials

The first HIV vaccines to advance to efficacy testing were based on the notion that – similarly to other vaccines preventing viral diseases – antibodies were most likely necessary for protection from infection. Two vaccines, each consisting of VaxGen's bivalent recombinant HIV Env proteins (AIDSVAX B/B and AIDSVAX B/E), were tested concurrently in two trials in ~2500 injection drug users in Thailand (VAX003) and ~5400 MSM and high-risk women in the US and the Netherlands (VAX004). While high antibody titers were achieved in vaccine recipients, infection rates were similar between vaccine and placebo recipients in both trials; vaccine efficacy (VE) was estimated at 0.1% (95% Confidence Interval [CI], –30.8% to 23.8%) for VAX003¹⁰ and 6% (95% CI –17% to 24%) for VAX004¹¹.

The inability of the induced antibodies to prevent infection was attributed to their narrow specificity and thereby mismatch to most circulating HIV strains; since Env is one of the most variable proteins in HIV, the focus of HIV vaccine research switched to the induction of T-cell responses because the cellular arm of the immune system can target the more conserved, internal proteins of the virus. The Step Study (enrolling MSM and high-risk women in the Americas) and its sister trial Phambili (studying heterosexual men and women in South Africa) tested the concept of whether a pure T-cell based vaccine could prevent infection or, if not, at least reduce viremia in breakthrough cases. The immunogen was based on an adenoviral vector developed by Merck that encoded for HIV Gag, Nef and Pol (MRKAd5 HIV), and therefore had no potential for inducing Env-specific neutralizing antibodies. The vaccine had shown promising immunogenicity in early-phase trials¹², but shortly after enrollment of the ~3000 participants in the Step Study was complete, the study was stopped because it met the pre-specified futility boundaries¹³, which in turn halted enrollment at ~800 participants in the Phambili trial¹⁴. In a great setback to the field, instead of reducing the incidence of HIV in vaccine recipients, the MRKAd5 HIV vaccine was associated with an increased number of infections in vaccine compared to placebo recipients, although this increase was not overall statistically significant in either study. Post hoc subgroup analyses of the Step Study results showed that the increased susceptibility seemed to be more pronounced in the first 18 months of follow up, being higher in male vaccinees who were both uncircumcised and Ad5 seropositive at baseline (Hazard Ratio [HR] 4.2, 95% CI 1.4 – 12.7, $P=0.02$), while increased risk was not observed in those men who were circumcised and Ad5 seronegative at baseline (HR 0.38, 95% CI 0.2 – 0.9, $P=$

0.06)¹⁵. Longer term follow up interestingly led to an inversion of the hazard ratios across these groups, although these were no longer significant¹⁵. Of note, while risk was concentrated during early follow up (up to 18 months) in the Step Study, it seemed to be higher during late follow up in Phambili (beyond 30 months)¹⁶.

A large number of follow up studies aimed at determining the underlying biology of the observed risk, with the favored hypothesis being that the vaccine activated pre-existing Ad5-specific CD4⁺ T cells, thereby providing increased target cells for HIV and facilitating infection. This hypothesis was refuted by the demonstration that seropositivity for Ad5 (determined as the presence of neutralizing antibody (nAb) titers >18) did not predict the presence or absence of Ad5-specific T cells. Ad-specific T-cell responses are highly cross-reactive across many adenovirus serotypes¹⁷, and more than half of Ad5 seronegative subjects have detectable Ad-specific CD4⁺ T-cell responses, likely induced by infection with other common adenoviruses such as Ad1 and Ad2. Interestingly, post hoc analyses revealed that even though there was no difference in the viral load of breakthrough infections between the vaccine and placebo arms in the Step Study, vaccine-induced targeting of a higher number of epitopes in Gag was associated with a decrease in viral load¹⁸. Similarly, increased targeting of Gag post-infection in the vaccine arm of the Phambili trial was associated with reduced viral loads and slower CD4⁺ T-cell count decline in HLA-B*58:02-positive participants¹⁹; subjects expressing this HLA allele tend to be more susceptible to disease progression in natural infection. These data may suggest some benefit of vaccine-induced cellular immunity post infection, although this advantage is muted in the larger context of increased risk of infection in both of these trials.

Considering the lack of efficacy in the trials aiming at solely inducing HIV-specific T-cell responses, the next concept to move into a phase 2b trial intended to generate both cellular and humoral immunity. The HIV Vaccine Trials Network (HVTN) 505 trial was the first to test a heterologous prime/boost approach consisting of three DNA primes followed by an Ad5 boost developed by the NIAID Vaccine Research Center. Enrollment in HVTN 505 was restricted to MSM and transgender women who were Ad5 seronegative and circumcised, the subgroup that did not show increased risk of infection in the Step Study. This vaccine induced antibodies in all vaccinees as well as a balanced CD4⁺ and CD8⁺ T-cell response, yet again the number of infections was higher in the vaccine than the placebo group²⁰, leading to early discontinuation of vaccinations. In a follow-up meta-analysis of all three trials testing Ad5 vaccines, inclusion of additional follow-up data suggested lack of increased risk in circumcised, Ad5 seronegative men in HVTN 505 (HR 0.88, 95% CI 0.61 – 1.26, $P=0.48$), though it did confirm higher risk in recipients of MRKAd5 HIV over all follow up time (HR 1.41, 95% CI 1.11 – 1.78, $P=0.005$), again concentrated in Ad5 seropositive and/or uncircumcised men (circumcised Ad5 seronegative men: HR 0.97, 95% CI 0.58 – 1.63, $P=0.91$)²¹.

Around the time early results from the VaxGen trials were becoming available, the RV144 efficacy trial combining the AIDSVAX B/E protein with a canarypox vector prime started enrolling ~16,000 participants in Thailand. Based on the lack of efficacy in VAX003 and the inability of the ALVAC vector to induce nAbs targeting more than one primary isolate²², there was significant controversy in the field on whether it was prudent to move forward

with a vaccine that was predicted to fail²³. Yet, as if to make a point that a certain level of empiricism is required for HIV vaccine development, RV144 remains the only HIV vaccine trial to date to show positive efficacy for preventing HIV acquisition²⁴. Vaccine efficacy at 31.2% in the MITT cohort was determined to be too low for licensure, but the pox vector prime/protein boost strategy applied in this trial forms the basis for a whole suite of studies aiming at (at least incrementally) improving on the results in RV144. The Pox Protein Public Private Partnership (P5) brought together vaccine developers, funders and scientists to advance vaccine strategies that build on the ALVAC/protein combination by including more potent adjuvants for the protein vaccine (alum in RV144, MF59 and AS01B for the P5 studies), DNA prime to increase cellular immunity²⁵, and additional late boosts to increase the longevity of vaccine-induced immune responses since early efficacy in RV144, estimated at 60.5% (95% CI 22%–80%) at 12 months, waned quickly²⁶. Immune responses in these upcoming trials will be measured up against the correlates of risk identified in RV144²⁷, especially whether the new immunogens can induce comparable (or higher) levels of antibodies to the V2 region of the HIV Env that were most strongly associated with reduced risk of infection in RV144, as well as polyfunctional CD4⁺ T-cell responses²⁸.

3. Current and planned HIV vaccine efficacy trials

The first of the P5 concepts to advance to a Phase 2b/3 trial is HVTN 702, testing a vaccine that is analogous to the RV144 regimen in a South African population. The vaccine was adapted to viruses circulating in that region by replacing the gp120 insert in the ALVAC vector: RV144 used a CRF01 *env*, 92TH023, whereas HVTN 702 uses a South African clade C isolate *env*, 96ZM651. In addition, AIDSVAX B/E is replaced by a bivalent clade C protein combination, 1086.C and TV1.C, in MF59 rather than alum. HVTN 702 is the culmination of a series of studies that were designed to translate the results from RV144 into an African population at high general risk of infection: the first trial, HVTN 097 (ClinicalTrials.gov Identifier: NCT02109354), tested the exact RV144 products and regimen in South Africa, and found that both antibody and T-cell responses were similar to or greater than those reported for RV144²⁹. The second trial, HVTN 100 (ClinicalTrials.gov Identifier: NCT02404311), tested the safety and immunogenicity of the new clade C constructs, and determined that immunogenicity was of sufficient magnitude to move forward with HVTN 702, which began enrollment at the end of 2016.

Another vaccine candidate with a high likelihood to move into an efficacy trial within the next two years is the concept developed by Janssen, including an Ad26 vector with mosaic HIV inserts that showed promising results in the preclinical challenge model³⁰. The HIV-V-A004/APPROACH first in human study is comparing different combinations of Ad26, MVA and protein to select the most promising regimen for further testing³¹.

Two phase 2b studies, conducted in collaboration between the HVTN and the HIV Prevention Trials Network (HPTN), are currently enrolling participants to evaluate whether passive administration of a broadly neutralizing monoclonal antibody, VRC01, can reduce acquisition of HIV in women in Southern Africa (HVTN 703/HPTN 081, ClinicalTrials.gov Identifier: NCT02568215) and in MSM and transgender persons in the Americas (HVTN 704/HPTN 085, ClinicalTrials.gov Identifier: NCT02716675). Participants in these

antibody-mediated protection (AMP) trials will receive one of two doses of the antibody (10 mg/kg or 30 mg/kg) or placebo by intravenous infusion every 8 weeks for a total of 10 infusions (72 weeks). This concept will address whether broadly neutralizing antibodies (bnAbs), which are inherently difficult to induce by vaccination (see below), can prevent HIV infection as shown in animal models^{32–34}. In addition, the different pharmacokinetics of the two doses, coupled with frequent HIV testing in trial participants, will allow for the determination of the level of antibody necessary to provide at least partial protection. While operational constraints make the regimen used in these studies unsustainable as a general approach for HIV prevention, the information on the antibody levels needed for prevention of infection gathered in these trials will be critical to inform both the development of alternative delivery strategies for longer-acting antibodies, as well as of vaccines aiming at inducing bnAbs by active immunization strategies. Of note, a phase 1 clinical trial testing the safety and immunogenicity of delivering another bnAb, PG9, using recombinant AAV is currently ongoing (ClinicalTrials.gov NCT01937455). This strategy had previously been shown to be effective at protecting humanized mice from mucosal HIV transmission³⁵.

4. Immunogens for the induction of broadly neutralizing antibodies

Broad neutralizing activity has been detected in up to 50% of sera from chronic HIV-1-infected subjects^{36–43}. From a subset of these HIV-1-infected subjects, potent broadly neutralizing monoclonal antibodies (bnAbs) have been isolated (summarized elsewhere including in⁴⁴). Passive infusion of bnAbs has been shown to prevent SHIV and HIV infection in animal models^{45–55}, postpone the rebound of viral loads in HIV-1 infected persons not currently receiving anti-retroviral therapy^{32, 56–58}, and is currently being evaluated for prevention of HIV-1 infection in humans (see above).

While bnAbs have not been induced by active immunization in HIV-1 clinical vaccine trials thus far, several hurdles to the elicitation of bnAbs by vaccination have been identified. First, the bnAbs isolated during chronic HIV-1 infection tend to have one or more extraordinary characteristics such as increased auto/poly-reactivity, long CDR3 regions and a high proportion of somatic mutations, suggesting a prolonged affinity maturation process (reviewed in⁴⁴). Although not all of the mutations are required for binding and neutralization of diverse HIV-1 virions, some amount of antibody affinity maturation will likely be necessary in order for a vaccine-elicited response to develop broad neutralizing activity. Additionally, previous attempts at reverse engineering Env immunogens for eliciting bnAbs were inherently flawed, as the reverted unmutated ancestor, or germline, versions of the bnAb B-cell receptors (BCR) lacked the ability to recognize the recombinant forms of HIV-1 Env proteins^{59–62}. Therefore, the initiation of the bnAb B-cell lineages was biologically not feasible with previous generations of HIV-1 Env immunogens, and as a result there has been a shift in the field toward structure-based design of Env-derived immunogens to specifically bind to the naïve B cells of interest. While antigenicity in itself does not necessarily predict immunogenicity, increases in antigenicity are likely essential in developing immunogens with improved immunogenicity, as has been elegantly shown for a human respiratory syncytial virus (RSV) vaccine^{63, 64}. However, there remains some controversy as to the likely success of structure-based reverse vaccinology for HIV⁶⁵, as it is based on the concept that engineering of an immunogen with increased binding affinity to

the desired germline nAb will recapitulate the evolution of bnAbs observed in HIV-infected subjects; while the immunogen will in fact elicit a polyclonal response and any modification of the Env trimer will likely generate novel epitopes for competing undesirable B cell responses. Yet, understanding the basis of previous failures in structure-based reverse vaccinology for HIV, in the context of the success story of reverse vaccinology in RSV, has led to significant progress in the field.

Multiple recent novel approaches to immunogen design have confronted the lack of germline binding to recombinant Env proteins with some *in vitro* and preclinical success. Convergent strategies have been employed to iteratively improve recombinant Env proteins to preferentially bind germline-reverted bnAbs and discourage recognition by non-neutralizing antibodies. For instance, next generation Env immunogens have been empirically or computationally designed to optimally activate the germline predecessors of specific bnAbs such as the CD4-binding site (CD4-BS) targeting VRC01-class of bnAbs^{61, 66, 67}. Many of the VRC01-family of bnAbs evolved independently in multiple HIV-infected subjects by convergent mechanisms and utilizing the same variable heavy chain allele (VH1-2*02) and same angle of approach, which has made this family of bnAbs a particularly desirable target for vaccine strategies⁶⁸. Currently, two main VRC01-class germline-binding Env immunogens have been described, the 426c gp140 TM4 V1-3 and the eOD-GT8 60mer, which are hypothesized to be able to activate naïve B cells of the VRC01-like class of bnAb lineages. Thus far, both immunogens have demonstrated the ability to activate B cells expressing inferred germline VRC01-class bnAb BCRs in the context of BCR-transduced cell lines^{61, 66, 67} and knock-in mice^{69–75}. Another aspect to the design of the VRC01-germline binding immunogens is that the variable loops have been truncated in order for the immunogens to preferentially bind the VRC01-germline BCR and not bind to non-neutralizing or autologous neutralizing BCR lineages, which tend to dominate natural infection and vaccination with previous recombinant Env immunogens. Multimerization of these immunogens, and others, into multivalent nanoparticles is also being used to increase the avidity of the binding of these proteins to germline BCRs in order to improve their immunogenicity^{70, 73}. However, even if these germline-targeting immunogens are successful at initiating the process, induction of highly mutated broadly reactive antibodies by vaccination will likely require successive immunization, boosting with additional immunogens to drive the affinity maturation of the B cells to become broadly neutralizing.

An alternative strategy has been employed in the case of the broadly neutralizing antibodies CH103-CH106, which were derived from an HIV-1-infected subject (CH505). Multiple viral *env* sequences have been isolated in parallel to reconstruct the coevolution of the bnAb lineages^{76, 77}. Using longitudinal sequencing data, the putative initial and intermediate bnAb lineage BCRs have been derived in combination with an array of *env* variant sequences over the course of infection. The different stage bnAb BCRs have been reconstructed as recombinant antibodies and tested against the contemporaneous Env variants for binding. The Env variants with the highest affinities of binding to the initial or intermediate BCRs have been hypothesized to have the ability to activate those BCR-expressing B cells *in vivo*. By thoroughly charting the evolution of bnAb lineages and *env* variants in CH505, a set of Env proteins with the potential to drive bnAb development has been identified and is being

developed as a combinatorial vaccine regimen within the HVTN. Initial immunization is designed to activate the germline lineage predecessor, and then sequential immunization with Env variants is intended to broaden the response⁷⁸.

Lastly, a major issue in Env immunogen design has been that the structure of recombinant uncleaved Env proteins has not accurately reflected the conformation of the Env trimer as expressed on the surface of the HIV-1 virion, which likely has also contributed to the lack of significant neutralizing activity induced by previous Env immunogens. Recent advances in bioengineering have improved the generation of cleaved soluble trimers with a structure more closely resembling the native spike. The first native-like Env trimers relied on cleavage of the Env gp160 protomer into the native subunits (gp120 and the gp41 ectodomain), stabilization by the introduction of a disulfide bond between the two subunits, and an isoleucine to proline substitution in the gp41 region to stabilize trimerization, referred to as SOSIP⁷⁹. Recently generated SOSIP native-like Env immunogens include the BG505 SOSIP.664 gp140 trimer. BG505 SOSIP.664 has been used for a wide range of structural as well as antigenicity and immunogenicity studies, and has been shown to preferentially bind neutralizing in contrast to non-neutralizing antibodies^{80–82} and to elicit autologous tier 2 neutralizing antibodies in rabbits, and to a lesser extent in macaques^{83, 84}. Alternatively, the addition of flexible GLY-SER linkers of variable lengths in the place of the proteolytic cleavage site have demonstrated similar ability to reconstruct soluble native-like Env spikes which are not dependent on cleavage^{85, 86}. Further advances in SOSIP design involve restricting the accessibility of non-neutralizing epitope exposure by further constraining the conformation of the trimer through additional targeted disulfide bonds across gp120 subunits, termed SOSIP version 4 (SOSIP.v4), which succeeded in reducing the prevalence of undesirable antibody responses in murine and rabbit immunizations⁸⁷. Because of the preference of most V2 binding bnAbs for the native structure, it is not surprising that a SOSIP (CRF02_AG) has been engineered to bind the germline versions of many of the V2 apex-binding bnAbs⁸⁸. V2 binding bnAbs are an attractive vaccine target because they are relatively common in the context of HIV-1 infection and they tend to be less mutated, suggesting that they may be easier to induce by immunization.

The vaccination strategies outlined are not necessarily mutually exclusive and may indeed be most successful when implemented in combination. For example, one could predict a vaccine regimen combining a vector-based prime for induction of CD4⁺ T helper responses and a germline-engaging Env protein to initiate a bnAb lineage, followed by a native-like trimer or series of immunogens to mature or broaden the neutralizing antibody response. In fact, additional evidence that this strategy may be effective has been recently demonstrated in multiple humanized mice models expressing the knock-in VRC01 germline (gIVRC01) heavy chain⁷², or human VH1-2*02 allele⁷³. Parallel immunization strategies by different groups have demonstrated that the germline-engaging immunogens are necessary, but not sufficient for inducing cross-reactive serum neutralization of tier II viruses in these models. Indeed, successive boosting with immunogens, which progressively increased in likeness toward native Env structure and glycosylation with time, is also obligatory to drive neutralizing activity^{72–74}. This premise was simultaneously confirmed for another bnAb lineage, PGT121, which targets a patch of glycans at the base of the V3 loop. A knock-in mouse expressing the germline-inferred PGT121 BCR was similarly immunized with a

germline-targeting immunogen followed by progressive iterations of increasingly native-like Env immunogens, and many of the mice likewise developed significant neutralizing activity. In contrast, the mice immunized repeatedly with only the germline-targeting immunogen did not⁷⁴. While HIV-1 vaccine design remains a formidable challenge, many technical advances have occurred to provide some optimism, including the design of modified germline bnAb-engaging Env immunogens and establishment of new assays to evaluate them, such as measuring activation of BCR-expressing B cell lines⁶⁰, and multiple humanized mouse models, which allow for evaluation of these candidate immunogens under various combinations and conditions. Overall, recent advances in rational vaccine design offer new promise in the pursuit of an effective HIV vaccine.

5. T-cell based vaccine concepts

Based on the history of previous HIV vaccine efficacy trials, most current vaccine concepts aim at inducing antibody responses in the context of appropriate CD4⁺ T-cell help, while pure CD8⁺ T-cell approaches have mostly fallen out of favor. Nevertheless, a couple of promising T-cell focused approaches have been developed over the last years, and are scheduled to move into phase 1 trials in the near future.

One immunogen, based on a CMV vector, has consistently led to complete control of virus replication in 50–60% of animals in non-human primate challenge studies^{89, 90}.

Interestingly, this vaccine does not prevent HIV acquisition entirely as viral blips can be detected after exposure; rather, infections seem to be aborted and virus is cleared over time⁹⁰. While no formal correlates of protection have been identified, control may be associated with CD8⁺ T-cell responses that defy immunological dogma: rather than recognizing antigens in the context of MHC class I alleles, vaccine-induced CD8⁺ T cells are restricted by MHC class II⁹¹ or by MHC E alleles⁹². The vector used in these studies was based on attenuated Rhesus CMV; whether these interesting immunological features will translate to clinical trials using a human CMV vector remains to be determined.

Another T-cell immunogen is based on the rationale that variable regions in HIV serve as immunodominant decoys, while protective responses should target conserved parts of the virus⁹³. The extensive sequence variability in HIV is one of the major stumbling blocks in the development of a protective vaccine, since most immunogens are not able to induce responses that cross-react with circulating virus strains (mosaic vaccines, such as the one developed by Janssen [see above] and another one tested in HVTN 106 [ClinicalTrials.gov Identifier: NCT02296541], are the exception that embrace sequence variation and aim at maximizing immunologic breadth^{94–96}). Focusing the immune response on “Conserved Elements” (CE) ensures a match of the vaccine strain to circulating viruses, and these regions are enriched for protective epitopes in HIV-infected subjects⁹⁷. Preclinical data shows that a Gag p24 CE vaccine directs T-cell and antibody responses to these critical regions in all animals, while T-cell responses to CE were only elicited in 5/11 NHP receiving a full Gag construct^{98, 99}. Since these studies were done using HIV rather than SIV constructs, no challenge data are available at this point; nevertheless, these products are scheduled to move into clinical testing within the next year.

6. Conclusion

The success of the RV144 trial has re-energized the field of HIV vaccine research, and led to a flurry of concepts building on the pox-protein strategy used in the Thai trial. The analogous vaccine, adapted for the viruses circulating in Southern Africa and including a new adjuvant and an additional boost, is about to be tested in an efficacy trial, which will confirm whether or not the correlates of risk identified in RV144 translate into protection in a population at much higher general risk than the communities in Thailand. At the same time, the burst of newly identified bnAbs and a better understanding of the biology underlying their development in HIV-infected subjects is translating into new concepts for immunogens that are able to replicate that process by vaccination. While antibodies – polyfunctional¹⁰⁰ or neutralizing – take center stage, induction of T-cell responses remains an important goal, whether focused on CD4⁺ helper (and potentially follicular helper) T cells to aid in the development of affinity-matured long-lived B-cell responses, or CD8⁺ T cells able to destroy virus-infected cells. The past few years have seen an explosion in the depth of knowledge and number of new potential approaches to generating an effective HIV vaccine, and each new idea has promising concepts in the pipeline aimed at achieving its goals. Alone or in combination, these approaches may finally result in a highly effective vaccine to end the epidemic.

7. Expert Opinion

For many years, HIV vaccine efficacy trials were riddled with disappointments, and the positive results of the RV144 trial, albeit barely significant and doubted at that time by many researchers in the field, brought much-needed hope that an effective vaccine may not be completely elusive. Since those results were announced in 2009, a broad pipeline of new products and strategies, not limited to those discussed in this review, have been developed. In addition to the currently ongoing AMP trials, one P5 efficacy trial's start is imminent, while another efficacy trial, testing a different viral vector concept including Ad26, is soon to follow. Meanwhile, a number of novel recombinant HIV Env immunogens show great promise for inducing tier 2 neutralizing antibodies, and several are in or entering GMP manufacturing and will be entering phase 1 clinical trials in the near future.

One of the major hurdles for the HIV vaccine field has been the lack of a fully predictive animal model. New humanized mouse models may provide a unique preclinical framework for testing the induction of bnAb lineages. However, it is unknown how effective they will be at predicting the immunogenicity in vaccinated humans, as well as their effectiveness at inducing protection. One of the anticipated outcomes of the AMP trials is a better understanding of the breadth and potency of a cross-reactive neutralizing antibody response that would be necessary to provide protection from HIV acquisition.

Some of the greatest challenges moving forward are due to the breadth of the approaches moving into clinical vaccine trials, and include determining the appropriate endpoints for bnAb-inducing immunogens. Current data suggest that induction of bnAbs will be an iterative process, and that the 1st generation of bnAb immunogens will, if successful, start the process by activating naïve B cells expressing germline bnAb BCRs, but are unlikely

induce mature bnAbs unless paired with the correct successive boosting strategies. Therefore, it will be key to use sophisticated sequencing methods to appropriately evaluate the success of these immunogens in initiating and expanding the desired B-cell lineage in phase 1 trials. Even if these immunogens are moderately successful, other significant obstacles with this strategy will be identifying the appropriate immunogens and adjuvants to further drive the affinity maturation, neutralizing activity, and breadth of this response.

As multiple approaches move forward covering diverse immunological space, there will be hurdles to assess how best to combine approaches, and in determining the best strategies to invest in as they will almost all likely require iterative improvements if even partially effective in order to be viable for widespread distribution. Concurrently pursuing multiple vaccine strategies may be challenging in terms of appropriately allocating resources. Unfortunately, much remains unknown about the immune responses necessary to prevent HIV acquisition or disease progression, and therefore determining the logical next steps will remain a challenge.

Within the past seven years, several key findings came to light: the potential of non-neutralizing but otherwise polyfunctional antibodies to protect from HIV infection^{27, 100, 101}; a dramatically improved understanding of the determinants of bnAb induction in HIV infection (reviewed in⁴⁴); and the appreciation that vaccine-induced T-cell responses may prevent systemic infection^{89, 90}. Nevertheless, important questions remain in each of these areas before they can be fully exploited to result in a highly effective vaccine: is the specificity towards Env V1V2 critical for non-neutralizing antibodies to mediate protection? What are the best combinations of germline-engaging and fully native trimer immunogens for driving truly broad vaccine-induced nAbs? Furthermore, what are the correlates of protection necessary to achieve clearance in just over half of the CMV-vaccinated animals, and once identified, will they translate to humans? The next seven years may yield the answers to all of these questions, with HVTN 702 providing additional clues as to the importance of V2-targeting antibodies, and many upcoming phase 1 trials addressing the latter two questions. The diversity of concepts already in or reaching the clinic provides a solid basis from which to choose the most effective vaccine candidates to be included in the growing toolbox of prevention strategies that will provide protection from HIV acquisition for generations to come.

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Article Highlights

- The identification of immune correlates of risk in RV144 precipitated a flurry of new vaccine trial development within the framework of the P5 (Pox-Protein Public Private Partnership)
- Several P5 Phase 1 trials have shown promising results, and a new efficacy trial testing the ALVAC/protein combination optimized for Southern Africa is set to start this year
- Heterologous prime-boost concepts that have shown promise in NHP models are also moving into efficacy testing
- Characterization of a vast array of new broad and potent neutralizing antibodies and their maturation pathways in HIV-infected subjects has informed the design of novel immunogens to engage the naïve B-cell repertoire in vaccines for the induction of bnAbs
- Several complementary concepts aimed at inducing cellular immune responses are in, or about to enter, clinical trials