HIV vaccine development at the turn of the 21st century

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Purpose of review
To review the status of HIV vaccine development

Recent findings
Since the discovery of HIV-1 in the early 1980s considerable effort has been exerted to develop a prophylactic vaccine, with relatively meagre results. The absence of natural immunity has proven to be a major stumbling block in identifying a mechanism of protection. However, many different animal models have contributed to our knowledge of the pathogenesis of infection and of the variety of antibody and cellular responses that are induced by the virus. The knowledge created by the studies in nonhuman primates, although important, has not necessarily been proven applicable in humans and thus an effective vaccine has been elusive. The combined lack of a fully predictive animal model ('mice lie and monkeys exaggerate') and lack of defined markers of immune protection against HIV-1 necessitate that HIV vaccines be tested directly for efficacy in phase IIb/III efficacy trials in human volunteers at risk. A trial conducted in Thailand showed moderate but significant protection against infection.

Summary
The process of HIV vaccine development is slow, costly and tedious. However, recent preclinical and clinical results have fortunately been a source of renewed optimism in the field.

Keywords
antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell-mediated virus inhibition, innate immunity, vaccines

INTRODUCTION

Thirty years after the AIDS epidemic first surfaced, just over 34 million people live today with HIV, according to the 2011 report from the Joint United Nations Programme on HIV/AIDS [1], and 2.6 million people become newly infected every year. Significant progress has been made over the past decade in the areas of basic virology, immunology, pathogenesis and treatment of HIV/AIDS, and even prevention of HIV infection appears to be achievable using antiretroviral drugs in a prophylactic manner [2], so that, for the first time in the history of HIV/AIDS, controlling and perhaps even ending the pandemic appear to be feasible [3]. Having a vaccine at hand would be a formidable asset in this endeavor.

However, the development of an HIV vaccine is still in its infancy, in spite of 25 years of research and of the multitude of candidate vaccine formulations that were developed and tested in nonhuman primate (NHP) models during that time (for review, see [4]). The difficulties met in the development of an HIV-1 vaccine stem from the fact that there is no spontaneous cure of the disease and no documented case of immune-mediated clearance of HIV from an infected individual, hence our inability to identify naturally protective immune responses, particularly in the mucosa, and to select the appropriate viral antigens to be made into a vaccine.

Furthermore, the virus is a terrible enemy: it rapidly establishes a reservoir of latently infected memory T cells early in infection [5], from which it can hardly be dislodged. Its incredible genetic variability readily allows it to escape the neutralizing antibody and cytotoxic T-cell lysis responses of the host during the course of infection [6]. In addition,

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KEY POINTS

- The nonhuman primate model tells us that antibodies can prevent acquisition of HIV and $CD8^+$ T cells can diminish viral replication.
- Prior clinical trials with poorly functional antibodies or with T-cell immunogenicity alone have failed to show efficacy.
- A recent trial that elicited antibodies with both neutralizing and nonneutralizing functions did show moderate efficacy and is being followed up.
- The definition of antibody correlates of protection will be crucial.

HIV infection triggers a high degree of systemic immune activation due to microbial translocation through the intestinal mucosa that gradually causes the collapse of protective immune mechanisms [7,8].

Studies in NHPs and the modest success of the RV144 phase III trial nevertheless suggest that, as in other diseases, antibodies of the right specificity and functionality can prevent infection [9,10], whereas cellular immunity controls virus replication and can even, in rare instances, lead to the elimination of the virus from the host [11,12,13▪▪]. The future path for HIV vaccine research seems, therefore, reasonably well outlined [14,15], but the challenge remains of translating this knowledge into the design of immunogens that could elicit a broadly protective immune response (for review, see [16]). Also, the current paradigm for an optimal HIV-1 vaccine to elicit effective neutralizing antibodies to act at sites of entry and effective cell-mediated immune responses to act postinfection has paradoxically been challenged by the result of the RV144 trial, in which neither of these responses were identified in spite of documented protection [17].

Attention is therefore turning to other immune responses as possible mechanisms of vaccine-induced protection, including nonneutralizing, HIV-binding antibodies, which may not be as effective as neutralizing antibodies but may play an important role in protection, as detailed below.

WHAT HAVE WE LEARNT FROM THE NONHUMAN PRIMATE MODEL?

The use of simian immunodeficiency virus (SIV) vaccines to protect macaque monkeys against experimental SIVmac infection provides the most reliable animal model for the testing of candidate vaccines against HIV-1 available today. The pathophysiology of SIV infection in monkeys closely mimics that of HIV-1 in humans, including preferential multiplication of the virus in the gut-associated lymphoid tissue and chronic immune activation in the host resulting in progressive impairment of T-cell responses, loss of Th17 cells and increase in the frequency of $CD4^+CD25^+$ $Foxp3^+$ Tregs [18–20].

T-cell-mediated protection

As in humans, some SIV-infected macaques maintain high viral loads and progress rapidly to AIDS, whereas others, the so called 'elite controllers', maintain barely detectable viral loads in the absence of antiviral therapy. Several MHC class I haplotypes (Mamu-A∗01, Mamu-B∗17 and especially Mamu-B∗08) have been identified that correlate with elite control in monkeys, underlying the importance of cell-mediated immune responses in the control of virus replication. Direct evidence that $CD8^+$ T-cell responses play a major role in controlling the level of virus replication and the rate of disease progression was obtained early on by showing that transient depletion of $CD8^+$ T cells in SIV-infected macaques resulted in a rapid and dramatic increase in viremia and accelerated the lethal outcome of the disease [21,22].

The conclusion that $CD8^+$ T cells can limit virus replication and control set point viremia also derives from multiple SIV vaccine experiments in the macaque model. Thus, rhesus macaques immunized with a peptide prime/modified vaccinia Ankara (MVA) boost vaccine regimen adjuvanted with Toll-like receptor agonists and interleukin 15 (IL-15) showed partial control of virus replication after high-dose intrarectal SIV challenge, with protection correlating both with innate immunity responses (the APOBEC3G cytidine deaminase) and with antigen-specific polyfunctional $CD8^+$ T cells [23▪▪]. Macaque monkeys vaccinated with prime-boost vaccine regimens involving two live recombinant vaccines (Ad26 followed by MVA, or Ad35 followed by Ad26) and repeatedly challenged with low-dose SIV by the rectal route showed decreased viral load set points by up to two logs that correlated with T-cell responses ([24], and D. Barouch, personal communication). In monkeys immunized with a SIVmac DNA-Ad5 vaccine prime-boost regimen and then challenged by repeated intrarectal infections with heterologous SIVsmE660, protective efficacy of the vaccine correlated with broad cellular immune responses directed to Gag and Vif [25] and Env [26].

The picture of the T-cell response that we entertain is, however, probably oversimplified, as measuring the number of circulating $CD8^+$ T cells that

secrete cytokines in response to synthetic peptides does not directly assess their antiviral function, and as circulating T cells may not be functionally equivalent to those present in mucosa-associated lymphoid tissues, wherein viral replication is concentrated. Indeed, the presence of virus-specific $CD8^+$ T-cells in colonic lamina propria, but not in blood, was correlated with delayed disease progression in vaccinated macaques challenged intrarectally with simian–human immunodeficiency virus (SHIV) [27]. Similarly, in humans, elite controllers definitely show more polyfunctional T-cell responses to HIV-1 in mucosa-associated lymphoid tissue than in blood [28].

A remarkable vaccine efficacy result in rhesus macaques was obtained with a replicating simian cytomegalovirus (CMV) vector expressing the SIV *gag*, *rev*, *tat*, *nef* and *env* genes: the vaccine efficiently induced effector memory $CD4^+$ and $CD8^+$ tissue-resident T cells, which did not protect the animals against infection following low-dose rectal challenge, but elicited early and profound control of virus replication, with 13 out of 24 monkeys showing viral loads below detection level [13▪▪]. Protection correlated with the magnitude of the peak SIV-specific $CD8^+$ T-cell response in the vaccine phase. The surprise was that, at 1 year after challenge, depleting either the $CD4^+$ or the $CD8^+$ T-cell populations in these monkeys had no effect on viral loads, in contrast to the control infected animals. Furthermore, a detailed search for SIV DNA or RNA in the spleen, liver, tonsils, bone marrow, intestine, lymph nodes and thymus of the protected macaques was unable to provide evidence of the presence of SIV in any of the tissues, suggesting that the vaccine-induced cell-mediated immune responses probably resulted in clearance of the virus over the long term. These outstanding results have prompted the search for a well tolerated human CMV vector that could carry HIV-1 genes and be used as a live, replicating recombinant vaccine against HIV-1 in humans.

Broadly neutralizing antibodies

Another important observation made with the help of the NHP model was that passive immunization with neutralizing antibodies, especially broadly neutralizing antibodies (bNAbs), such as b12, 2G12, 2F5 or 4E10, protected rhesus macaques against infection with a variety of SHIV isolates (see for example [29]). This situation will serve as a rationale for presently testing passive immunization with bNAbs such as VRC01 in high-risk adults and in babies born to and/or breast-fed by a HIV-positive mother (J. Mascola, personal communication). Protection against infection by bNAbs could also be achieved through 'genetic immunization', as demonstrated by immunizing rhesus macaques with an adeno-associated virus (AAV) vector expressing immunoadhesins derived from broadly neutralizing antibodies: the animals showed long-lasting neutralizing activity in their serum and were completely protected against the intravenous SIV challenge [30]. Broadly neutralizing antibodies, therefore, show definite protective efficacy against infection, although playing only minor role in the control of viremia in the host. The problem remains to design appropriate immunogens that could trigger a broadly neutralizing antibody response. Attempts at grafting well defined gp120 epitopes on virus-like particles (VLPs) such as chikungunya VLPs could be promising (G. Nabel, personal communication).

Nonneutralizing antibodies

Binding antibodies that attach to HIV Env antigens on the surface of an infected cell by their Fab fragment can recruit by their free Fc fragment innate immune cells that possess an Fc receptor, such as natural killer cells or monocyte/macrophages. This is eventually followed by antibody-dependent cell-mediated cytotoxicity (ADCC) and the killing of the infected cell or by antibody-dependent cell-mediated virus inhibition (ADCVI) and the arrest of virus replication in the targeted cell [31]. Both phenomena were shown to occur in rhesus macaques after passive antiviral antibody administration (as an example, see [32]).

Both ADCC and ADCVI were demonstrated to occur in rhesus macaques vaccinated with a replicating recombinant adenovirus and boosted with an Env subunit vaccine: the animals were partially protected against mucosal challenge with SIV or pathogenic SHIVs in the complete absence of a neutralizing antibody response. Reduced viral loads at both the acute and chronic stages of infection significantly correlated with both ADCC and ADCVI, and these in turn correlated with antibody-binding affinity [33,34▪]. Antibodies that mediate ADCC and ADCVI are a subset of the gp140env-binding antibodies, appear prior to neutralizing antibodies and, importantly, do not involve the same epitopes, so that neutralization-resistant virus strains remain susceptible to ADCVI [35,36].

Another function of nonneutralizing antibodies that can be of importance for protection against infection is the inhibition of virus transcytosis through the columnar epithelium of the endocervix, rectum or intestinal tract. Transcytosis-blocking antibodies are mostly IgAs that primarily target the

GalCer receptor-binding site in gp41. Intranasal and intramuscular immunization of female rhesus macaques with a gp41 virosomal vaccine elicited effective protection against repeated vaginal SHIV challenge that correlated with the induction of transcytosis-blocking IgAs and ADCC-associated IgGs in cervico-vaginal secretions, in the complete absence of a neutralizing antibody response [37▪].

The importance of innate immunity

Finally, the macaque/SIV model has been instrumental in outlining the importance of innate immune responses in protection against SIV/SHIV experimental infection. In the experiment of Sui *et al.* [23▪▪], the use of Toll-like receptor agonists and IL-15 cytokine as an adjuvant resulted by itself in significant decrease in the set point plasma and colonic tissue viral loads following rectal SIV challenge that correlated with induction of APOBEC3G (A3G) mRNA in dendritic cells, monocyte/macrophages and $CD4^+$ T cells. Host genetic factors such as tripartite motif 5 (TRIM5α) also play a critical role in mucosal transmission of SIV: some TRIM5α alleles have been shown to affect acquisition of SIV and can be a barrier to infection [38,39]. TRIM5 is responsible for the nonpermissivity of T cells from rhesus or cynomolgus monkeys to HIV-1 replication.

WHAT HAVE WE LEARNT FROM THE STUDY OF ELITE HIV-1 CONTROLLERS?

Elite controllers represent a unique group of HIV-1-infected persons with undetectable viral loads in the absence of antiretroviral therapy. They have been the object of multiple studies trying to identify correlates of immune protection against HIV-1 but the mechanisms responsible for their undetectable viremia appear to be multiple and complex. Most elite controllers show highly polyfunctional HIV-specific $CD8^+$ T-cell responses that can efficiently restrict HIV-1 replication *in vitro*. Certain HLA alleles such as HLA-B∗57, B∗27 and B∗14 are overrepresented in elite controller cohorts [11] and many show specific amino acid polymorphisms in the HLA-B-binding cleft [40].

However, these characteristics are not found in all elite controllers, suggesting that other mechanisms than T-cell activity play a role in the control of HIV-1 replication in these persons. $CD4^+$ T cells from elite controllers, which are less susceptible to HIV-1 infection than $CD4^+$ T cells from HIV-1 progressors and HIV-1-negative persons, have been shown to selective upregulate the cyclin-dependent kinase inhibitor p21 [41]. Other mechanisms also are probably in play, possibly involving several other factors of innate immunity.

WHAT HAVE WE LEARNT FROM THE STUDY OF CANDIDATE HIV-1 VACCINES?

The first efficacy trials, VAX003 and VAX004, were done with a mixture of gp120 HIV glycoproteins from two different clade B virus strains or from clades B and E virus strains, respectively. The approach was based on the idea that as is the case with many licensed viral vaccines, a neutralizing antibody would prevent acquisition of the pathogen [42]. However, the results were negative, because the breadth of antibody was inadequate to neutralize many different circulating HIV-1 strains [43], as was illustrated in chimpanzees with HIV-1 and in rhesus macaques with SHIV challenges [44].

The failure of the antibody-based vaccine approach led researchers to attempt protection by cellular immune responses, as observations both in simians and in humans had shown that $CD8^+$ T-cell responses were critical to control viral replication. Accordingly, the STEP phase IIb efficacy trial used a replication-defective Ad5 vector carrying the *gag*, *pol* and *nef* genes of HIV. The results of that trial not only failed to show efficacy, but also uncircumcised vaccinees appeared to have greater susceptibility to infection with HIV-1 if they had antibodies to the Ad5 vector [45]. Moreover, the T-cell responses elicited by the vector were not polyfunctional and were meagre compared with those elicited by an effective vaccine like that for yellow fever.

The tide may now have changed with the development of the prime-boost vaccine approach, which elicits broader and stronger cell-mediated immune responses by combining a DNA vaccine with a live recombinant vaccine or two live recombinant vaccines together. Ongoing (DNA-Ad5), or future (DNA-MVA and, eventually, Ad35-Ad26), phase IIb clinical trials in volunteers at risk will tell.

In the meantime, a different type of prime-boost vaccine regimen involving priming with a live recombinant vaccine followed by boosting with an Env subunit vaccine has opened a new approach to the field, as the protection it provides seems to be based on nonneutralizing antibodies and a $CD4^+$ T-cell response. The RV144 prime-boost phase III trial is the best illustration of this new paradigm [46]. This trial, which involved a canarypox vector (ALVAC) carrying HIV genes including env as a prime, accompanied by boosts with the same gp120 used in the VAX004 trial, resulted in a modest but significant 31% protection against infection in low-risk volunteers. Much effort is being devoted to a search for correlates of protection in that trial, and

although the conclusion is still tentative, it appears that a non-neutralizing antibody response involving V2 loop-binding antibody is responsible. ([47] and B Haynes, personal communication).

Future clinical trials building up on the results of the RV144 trial will help determine whether a better level of protection can be achieved in a sustained manner by using different, more immunogenic vaccine components, such as was recently achieved with success in the macaque/SHIV model using Venezuelan equine encephalitis virus replicons for priming and trimeric Env preparations with MF59 adjuvant for boosting [48▪].

CONCLUSION

It is urgent at present to improve on the RV144 trial results, as well as to further explore improved DNA-adenovirus or DNA-MVA prime–boosts regimens, novel adenovirus or poxvirus vectors, and, if feasible, a live replicating human CMV vector that would elicit effector, polyfunctional, high-avidity tissue-based T-cell responses [49]. The development of VLPs that could be engineered to present bNAb epitopes in the right conformation would doubtless constitute a major step forward in the quest for an effective HIV vaccine. The development of vaccines capable of inducing mucosal immunity, such as the gp41-based virosomal VLP vaccine of Bomsel *et al.* [37▪], could also be a critical asset.

Although it would be foolish to say that an HIV vaccine is around the corner, the prospects are certainly quite brighter now than in the past.

Acknowledgements

None.

Conflicts of interest

M.P.G. is a member of the board of Mymetics, which is developing a vaccine against HIV. S.A.P. is also a board member of Mymetics, as well as consultant to all of the major vaccine manufacturers, including Sanofi Pasteur.

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