Prospect of a prophylactic vaccine for HIV

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Human immunodeficiency virus (HIV) continues to infect about 15,000 people every day, 90% of whom live in non-industrialised countries. So far, education programmes have only managed to slow, but not cease, the HIV spread, while powerful drug combinations are too costly and complex for the majority of HIV-infected people and in any case fail to clear HIV from the body. Under these circumstances, the best hope for controlling the HIV pandemic is the development of an effective prophylactic vaccine. With a series of new technologies and increased political and financial commitments, a growing momentum in the field of HIV-vaccine development promises exciting years ahead.

Without going into the details of the devastation that human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) cause around the world, particularly in some non-industrialised countries, it is generally agreed that the best hope for halting the spread of HIV is the development of a safe, effective, accessible prophylactic vaccine. Indeed, vaccination remains the most effective method for prevention of infectious diseases since the sanitation of water and milk. Its success has been well illustrated by the world-wide eradication of smallpox and a control of a number of other infectious diseases in industrialised countries.

Despite a considerable effort, no effective vaccine against HIV is yet available. Isolation of HIV in 1983 triggered a phase of optimism and a belief that a vaccine would be available within the next 10 years. Without a real understanding of which immune responses are important for containing the HIV replication, researchers applied the ‘good old’ strategies. A period of frustration followed when it was realized that traditional immunization approaches of live attenuated or whole inactivated virus vaccines cannot be easily applied for HIV and that antibodies neutralizing primary HIV isolates were nearly impossible to induce. It is only recently that advances in molecular biology and basic HIV research have led to the development of novel promising strategies and renewed optimism among scientists that an effective vaccine against HIV is possible. These together with an increased awareness and commitment of the politicians, drive from organizations such as the International AIDS Vaccine Initiative and major financial injections from national
governments, charities, foundations and generous individuals have created a feeling that the prospects for a development of a successful HIV vaccine have never been greater than now.

The HIV challenge

Scientifically, HIV is a fascinating virus. Unfortunately for the prevention, all the fascinating features of HIV put together make the development of vaccines extremely difficult. First, a successful HIV vaccine may have to induce both neutralizing antibody (nAb) and cell-mediated immunity, which is sometimes expressed more mysteriously as ‘a barrier created by the sum of several immune defences’. This is because no clear single immunological correlate of protection has yet been identified. Second, HIV has a tropism for many cell types in the body including the very cells that play essential roles in eliciting and maintaining the immune responses such as CD4+ T-cells, macrophages and dendritic cells. Third, HIV integrates into the host chromosome and can make at least some of the HIV-carrying cells invisible to the immune system. Fourth, HIV has multiple ways of transmission. The most common route is through a heterosexual contact, but it can be also passed from mother-to-child or reach the blood stream directly, thus bypassing all natural protective barriers against environmental microorganisms. Moreover, HIV can be transmitted as both a cell-free virus and virus-infected cells. Fifth, even if an effective vaccine becomes available, total eradication of HIV will be complicated by an animal reservoir of SIV in feral chimps and African monkeys, from which multiple independent transmissions to humans have been documented. Finally, HIV evades effectively both humoral and cellular immune responses. This is mainly due to a high antigenic variability facilitated by a combination of an error-prone reverse transcriptase (10−4 per base), recombination between the diploid HIV genome during reverse transcription, and a high replication rate (10⁹ new virions per day in an infected individual) even during the asymptomatic phase of infection. Also, other sophisticated strategies that HIV employs contribute to the immune evasion.

Thus, the structure of the HIV envelope glycoprotein protects effectively HIV from neutralization by antibodies. In viral and cellular membranes, the envelope forms a trimer of gp120–gp41 heterodimers, which is mediated by the interaction between the most conserved surfaces on the heterodimers. This makes these conserved regions on the virus inaccessible, while the exposed areas are highly variable and masked by bulky polysaccharide structures. The CD4-binding site is buried deep in the molecule and can be more easily reached by the
extended CD4 loop than the complementarity-determining regions of antibodies. The chemokine co-receptor-binding site is hidden and becomes available only after the gp120 interaction with the CD4 receptor. Both of these sites are guarded by flexible V1, V2 and V3 loops with highly variable amino acid sequences, which obscure the neutralization epitopes and contribute to the inefficiency of affinity maturation of the antibody responses. In summary, the biggest problem of neutralization is reaching the neutralizing epitopes on HIV by antibodies.

There is much more hope in killing of HIV-infected cells by CTL, but it is not without challenges either. A quick accumulation of mutations cause an escape from the CTL by altering epitopes so that they either cannot be recognized or antagonize the index peptide-specific responses. Down-regulation of MHC class I molecules was described, although this may be insufficient to prevent CTL killing. A selective loss of HIV-specific T cell responses may occur through exhaustion, anergy and up-regulation of Fas ligand (CD95L) on HIV infected cells, which may induce apoptosis in approaching CTL.

All these mechanisms come down to a single fact: HIV persists in the face of vigorous anti-HIV immune responses, which do abate the initial viraemia, but in a vast majority of cases fail to clear the virus from the body or provide a life-long protection from progression to AIDS. Therefore, a successful vaccination strategy has to train the immune system to respond faster and/or elicit qualitatively or quantitatively better immune responses than the natural HIV infection does. The immune response has to win the battle very early during the primary infection (Fig. 1; see below).

![Fig. 1](https://example.com/figure1.png)

**Fig. 1** Protective immune responses have to act very early to minimize HIV replication, generation of HIV variants and the damage which HIV inflicts. As a result of a successful vaccination, HIV is never detected in the body (A), only a transient replication occurs after which HIV is cleared (B), or the level of HIV viraemia is kept below the threshold of transmission and development of AIDS (C).
Light at the end of the HIV tunnel

Despite these multiple defences that HIV employs, observations and experimental data are accumulating which suggest that an immunological protection against the HIV infection is achievable. The identification of exposed seronegative/uninfected individuals with CTL responses against HIV raised the possibility that the CTL responses could have at least contributed to the prevention of infection\(^5\). The immunological bases of this protection was further supported\(^6\) by the fact that re-exposure to HIV appeared necessary for maintaining the ‘resistance’. Furthermore, in the SIV and HIV infections of non-human primates, complete resistance or partial protection has been achieved by an active immunization employing a series of vaccine modalities. Recently, promising subunit vaccine approaches inducing protection are on the increase\(^7\text{--}^\text{11}\).

Aims of a preventive vaccine

Ideally, the goal of an effective prophylactic vaccine is to prevent HIV infection or induce so-called ‘sterilizing immunity’ so that, after exposure, the virus is never detected in the body. However, most vaccines in use today work by preventing disease symptoms rather than the infection itself. For HIV, sterilizing immunity may not be an achievable objective either. Rather, vaccination may aim at elicitation of such an immunity that allows a limited and transient virus replication, after which the virus is cleared from the body, there are no signs of disease and no transmission to other individuals. Alternatively, a potentially successful vaccine may induce immune responses that decrease the primary viraemia and suppress virus load to levels so low, that both progression to AIDS and transmission are totally prevented (Fig. 1). Anything less would constitute a partial protection, but even a partially protective vaccine may be useful in some parts of the world. While in the industrialised countries, a prophylactic vaccine only delaying disease may not be that advantageous because of the highly active anti-retroviral therapy (HAART), vaccinated individuals infected with HIV in non-industrialised countries, i.e. without the possibility of HAART, may benefit enormously just from a substantial delay of the disease.

Importance of HIV clades

The significance of the genetic diversity among individual HIV isolates and its implication for vaccine design have been long debated. The predominant HIV-1 clade in Europe and North America is clade B, which
is also the most studied one. In central and Eastern Africa, the predominant circulating HIV-1 strain is clade A, while clade C is dominating Southern Africa, India and China. Generally, a clade-specific vaccine design requires a more careful consideration for the induction of nAb than for CTL. Although there are some important inter-clade differences in CTL epitopes, many epitopes are conserved across-clades partially due to structure/function constraints. However, to facilitate the interpretation of efficacy studies, vaccines should attempt to match the local strains prevalent in the trial population with the view that any successful approaches can be adapted for other clades if cross-protection is not achieved.

**Non-human primate models of AIDS**

Central to the development and preclinical evaluation of new vaccine strategies is the use of suitable animal models. They allow the assessment in a relatively faster and cheaper way the basic safety, immunogenicity and in some instances efficacy of new vaccines, and provide a platform for a more effective planning of clinical trials. Infection of non-human primates with immunodeficiency viruses offers a spectrum of models in terms of difficulty in preventing virus infection and severity of disease. These models range from the non-pathogenic infection of chimpanzees with HIV-1 SF2, in which a protection is achieved relatively easily, to infection of rhesus macaques with simian immunodeficiency virus (SIV)mac, which usually causes AIDS within the first year after infection and in which protection is much harder to obtain. Infection of humans with HIV-1 lies somewhere in the middle and it still remains to be determined which of the above models are the most useful ones and for what, i.e. immunopathology, vaccine immunogenicity, protection against infection or disease, and determination of protection correlates. While a vaccine-induced immunity is enormously encouraging, the interpretation of a failed protection is less clear. First, to establish an infection in all of a small number of control animals, monkey challenge doses are at least 100-fold higher than the estimated HIV doses infecting humans and, second, the challenge viruses are usually more pathogenic. Thus, a vaccine protecting monkeys against an experimental SIV challenge may not have any protective effect in humans, while an immunogenic vaccine failing to protect monkeys may still be beneficial for people. Therefore, a ‘fine-tuning’ of immunogenicity in, and/or protection of, monkeys may be a useful exercise only as far as providing a starting basis for clinical trials; the final optimization of vaccination parameters for humans will have to be carried out in humans. In essence, certain level of vaccine immunogenicity in non-human primates should be the necessary condition and sufficient drive for testing that approach in humans. For such vaccines, the bridging
process between the laboratory and clinic should be facilitated and accelerated. (A near complete list of all monkey challenge experiments is published biennially14.)

**Live attenuated vaccines**

Live attenuated vaccines have undergone an extensive evaluation in non-human primates. Studies showed that it was possible to engineer viruses with mutations in several genes, all of which to some degree attenuated the virus and provided a protection against infection greater than other vaccine strategies15. However, most attenuated viruses retained pathogenicity and caused AIDS in both adult (after a long incubation period) and new-born monkeys16. Also, detection of virulent revertants in monkeys originally immunized with nef-deletion mutants may signal that this protection is not always complete17. In humans, several subjects in a small group of patients, the Sydney Blood Bank Cohort, experienced a decline in the CD4+ T-cell counts after about 12 years of infection with a nef-deleted virus and several developed AIDS18. Thus, the development of a safe attenuated HIV vaccine, which replicates sufficiently to confer protection, seems remote. Furthermore, the advent of a number of very safe technologies, which can induce good immune responses, may make the deployment of a potentially lethal preventive vaccine very difficult to justify.

**Whole killed vaccines**

Whole killed vaccines are non-infectious non-replicating virus particles that have been used successfully as vaccines for other infections such as polio, mumps, influenza and typhoid fever. As AIDS vaccines, inactivated SIV showed some promise in the SIV monkey model. However, while there is no doubt that HIV can be safely inactivated, these vaccines are relatively inefficient in the induction of both neutralizing antibodies and particularly CTL.

**Subunit vaccines**

Subunit vaccines represent a more rational approach to the vaccine development, which for practical, safety and immunogenicity reasons is almost certain to be favoured for AIDS vaccines to attenuated or whole inactivated HIV preparations19. Conceptually, subunit vaccines are
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Table 1 Most commonly studied vehicles for genetic vaccines

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<th>DNA-based vaccines</th>
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<tr>
<td>Live bacterial vectors</td>
<td>Mycobacteria&lt;br&gt;Salmonella&lt;br&gt;Listeria monocytogenes&lt;br&gt;Shigella</td>
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<td>Live viral vectors</td>
<td>Retroviruses&lt;br&gt;Adeno-associated virus&lt;br&gt;Adenoviruses&lt;br&gt;Alphaviruses&lt;br&gt;Sindbis virus&lt;br&gt;Senliki forest virus&lt;br&gt;Venezuelan equine encephalitis virus&lt;br&gt;Poxviruses&lt;br&gt;Modified vaccinia virus Ankara&lt;br&gt;NYVAC&lt;br&gt;ALVAC&lt;br&gt;Fowlpox virus&lt;br&gt;Herpes simplex virus</td>
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composed of up to three major components: (i) the compulsory immunogen, which is an HIV-derived molecule, most frequently and especially for CTL a protein, to which the immune responses are directed; (ii) a vaccine vehicle, which is a carrier facilitating the delivery of the immunogen or its gene to the host’s body; and (iii) an optional immunomodulator, which can be a molecule, signal or adjuvant, often an integral part of the vehicle, modulating the induction of immune responses in terms of type, potency and longevity. While the immunogen defines vaccine specificity and provides a basic level of ‘intrinsic’ immunogenicity, vaccine vehicles and immunomodulators help to optimize the elicitation of immune responses. Although many processes involved in the induction of immune responses are currently unknown, it is very likely that the immunogenicities of subunit vaccines are in great part determined by the choice of a vaccine vehicle (Table 1) and route of administration.

Furthermore, there is a growing body of data demonstrating that heterologous vaccine vehicles delivering a common immunogen in a sequential prime-boost protocol are more potent inducers of specific immune responses than single vaccine modalities8,10,20–26. It is intriguing that some vectors are better for priming and others for boosting. The reasons for the efficiency of the heterologous prime-boost strategies are not clear, but may have to do with: (i) different ‘professional’ antigen-presenting cells and processing pathways, to which the immunogens are introduced; (ii) focusing of immune responses to the immunogens by priming with simple vectors and boosting with more complex, but at the same time more immunogenic, ones; (iii) allowing for better affinity maturation by initial
low level expression of immunogens from a non-complex vehicle; or (iv)
inducing the desired Th1/Th2 cytokine milieu during the priming
immunization. For the same reasons, certain combinations of vehicles
more than others may induce longer-lasting immunological memory.

**Antibody responses**

As most vaccines currently in use work by inducing virus-neutralizing
antibodies, also for the development of HIV vaccines the HIV envelope
glycoprotein has been the immunogen of choice. Although some success
was reported in inducing nAb against laboratory HIV strains, extreme
difficulties with neutralizing primary isolates halted the progress in this
area. To date, only a few antibodies neutralizing a broad range of primary
HIV isolates have been identified: two bind to the CD4-binding-site and
2G12 epitopes on gp120, and one recognizes the 2F5 epitope on gp41.

Nevertheless, approaches focusing on the induction of a strong HIV nAb
response continue to be a high priority research area. A vaccine utilizing
monomeric HIV gp120 is the only AIDS vaccine so far that has reached
phase III efficacy trials in humans. Although the outcome of these trials will
not be known for several years, the expectation are low due to the results
of phases I and II. In these trials, vaccinees have developed little, if any,
antibodies capable of neutralizing field HIV isolates and no differences
were observed in breakthrough infections between placebo- and vaccine-
immunized subjects. Various other approaches under investigation
include the use of gp160 and gp140 oligomers, variable loop deletion
mutants, stabilized gp120–gp41 subunits, env deglycosylation mutants,
envelopes from CD4-independent viruses, gp120–ligand complexes,
fusion-competent antigens, gp41 peptides and envelopes presented on a
carrier which facilitates trimer formation. Many of these strategies are
novel and promising, although they may not solve the main problem of
accessibility, *i.e.* even if neutralizing antibodies were generated by active
immunization, they might not readily reach the neutralizing epitopes on
HIV which they recognize. This was reflected in experiments passively
transferring antibodies capable of HIV neutralization, in which sterilizing
immunity was achieved, but only with very high concentrations which
would be hard to achieve and maintain by active vaccination. Moreover,
there is a danger of inducing infection-enhancing antibodies. Studies
demonstrated that sera neutralizing HIV at high titres (10^{-3} to 10^{-2}) may at
lower concentrations (10^{-3} to 10^{-6}) increase its infectivity. Thus, induction
of env-specific antibodies by vaccination may not be desirable at all, a
possibility that should be resolved by the phase III trial of gp120. In any
case, a reliable method for induction of antibodies neutralizing primary
HIV isolates by active immunization is still awaited.
**Cytotoxic T-lymphocyte responses**

CTL are usually CD8+ cells, which defend an organism against intracellular pathogens such as HIV. They do so through a recognition of 8–10 amino acid-long HIV-derived peptides, which the infected cells process and display on their surface. Upon recognition, CTLs kill virus-infected cells and thus limit the production of new virions, and secrete a variety of soluble factors that directly or indirectly contribute to the suppression of virus replication. Just like for antibodies, these effector functions are adaptive, require a cascade of specific molecular and cellular interactions for their generation, and display a long-term memory.

The immunological correlates of protection against HIV remain undefined, but a picture is emerging. While there is still only limited evidence from humans for a protective ability of neutralizing antibodies, compelling data from several laboratories point to the central role of CD8+ CTL for containing viral replication in both acute and chronic simian and human immunodeficiency virus infections.

**CTL and prevention of HIV infection**

For a successful control of HIV replication, CTLs have to kill virus-infected cells before they shed new virions. The exact timing of the expression of the first viral proteins, i.e. susceptibility to CTL killing, and virus release may depend on the cell type and activation status. Thus, although tat and nef mRNAs were detected in H9 cells as early as 2–3 h postinfection, HIV-infected cells are generally believed to produce rev, tat and nef at about 8–12 h and release new viruses at about 24 h postentry. In vitro, this left enough time for CTL to kill HIV-infected cells before these produced new virions and inhibit HIV spread through a release of soluble factors. Therefore, in vivo, CTL may be able to clear the initial small number of infected cells before HIV establishes generalized infection. This might explain detection of HIV-specific CTL responses in exposed, but uninfected, commercial sex workers whose cells were fully susceptible to infection with HIV, in uninfected infants born to HIV-infected mothers and seronegative health care workers occupationally exposed to HIV-contaminated body fluids.

At the organism level, CTLs have to suppress HIV replication very early after transmission, which in turn can be done most efficiently by targeting the transmitting virus. The more HIV is allowed to replicate, the better chance it has to generate escape mutants and the bigger insult it delivers to the immune system, from which this may never recover completely. In humans, many CTL responses and corresponding epitopes were identified during the asymptomatic phase of infection, i.e. weeks to years after the initial CTL response. It is almost by definition that the identified
CTLs were directed against viruses that had been unaffected by or escaped the initial immune responses. And even studies that looked at CTL during the acute HIV infection are likely to have missed the most important events\textsuperscript{34}. In addition, analyses of the CTL-HIV interactions usually suffer from not knowing the sequences of the transmitting viruses. Thus, definition of the very first CTL responses induced by natural transmission may pave the way towards an effective prophylactic vaccine. It is in this area that the non-human primate models can become extremely useful as demonstrated by an elegant work, which pointed to the tat protein as being one of the first CTL targets \textit{in vivo} imposing a selective pressure on HIV\textsuperscript{35}. 

Another potential caveat of the current approaches lies in the fact that our knowledge of the CTL responses is based, with a few exceptions\textsuperscript{36}, on the circulating peripheral blood lymphocytes. However, as the most common route of HIV transmission is through a heterosexual contact, \textit{i.e.} via mucosa, the early battle may not be won in the blood. Although there is a belief in a close correspondence between the blood, lymphoid organs and mucosal CTL, which is supported by limited reports mainly from primate models, a more comprehensive analysis of the mucosal CTL responses in man may have to await further technological advances.

The effectiveness of vaccination is going to be determined by several characteristics of the CTL population. First, the sheer numbers of vaccine-induced memory CTLs influence critically the head-start of the immune system\textsuperscript{37}, which may require regular boosts to stay above the protection threshold\textsuperscript{6}. Second, the homing pattern of memory CTL effectors may affect the HIV control. Third, the specificity of CTL for the transmitting virus\textsuperscript{35}, proteins expressed early rather than late in the replication cycle\textsuperscript{9,23,37}, and epitopes derived from structurally constrained regions of proteins, which limits the generation of escape mutants, is likely to be important. Fourth, CTL responses against multiple epitopes may be required for the control of HIV replication\textsuperscript{4}. Finally, the CTL success in the time-race with HIV may depend on the CTL killing efficiency, which is determined by, for example, their overall functionality, perforin load, T-cell-receptor affinity for MHC-peptide complexes, and surface density of Fas-ligand and other functional or auxiliary molecules.

**Subunit vaccine challenge experiments in non-human primates**

Protecting monkeys with semi-rationally designed subunit vaccines has been harder to achieve compared to vaccines based on live attenuated viruses. This is especially true for the early experiments when the knowledge of the HIV pathogenicity was limited. This situation may now be changing due to our increased understanding of the HIV-host interaction.
and more advanced vaccine vehicle technologies. Thus, protection of macaques may depend on the route of immunization. Subunit DNA vaccines have protected chimpanzees from infection with HIV-1, but provided very limited protection of macaques against pathogenic SIV and non-pathogenic SIV/HIV chimera (SHIV)\textsubscript{HXBc2} challenges. A control of viremia and prevention of clinical AIDS was achieved by a vaccine combined from three plasmids expressing gag, env and an IL-2/Ig fusion protein and was mediated by cellular immune responses. Env protein boosting after DNA priming increased antibody, but not CTL responses and protected macaques against a non-pathogenic SHIV\textsubscript{HXBc2} challenge. Trivalent modified vaccinia virus Ankara (MVA) immunization reduced post-challenge virus burden, recombinant vaccinia virus-based regimens gave some protection against an SIVmac challenge and in a combination with DNA significantly decreased virus loads after infection. Adjuvanted tat protein and recombinant Semliki forest virus priming followed by MVA boosting delivering tat and rev protected macaques against pathogenic challenges with SHIV\textsubscript{89.6PD} and SIVmacJ5, respectively. A containment of challenge infections by subunit vaccines was also achieved by DNA prime-recombinant fowlpox boost vaccinations, which held non-pathogenic HIV\textsubscript{8} and non-pathogenic SHIV\textsubscript{IIIb} below the level of detection.

**Candidate HIV vaccines in clinical trials**

There has been about 30 different types of vaccine candidates tested in about 60 clinical trials involving about 5000 HIV-uninfected volunteers (http://www.scharp.org/public/home.htm).

In terms of formulations, the candidate HIV vaccines taken into the phase I studies include peptides mostly corresponding to gp120 V3 loop, but also gag- and nef-derived lipopeptides, yeast transposon-derived Ty virus-like particles carrying p17/p24, DNA-based vaccines, recombinant vaccinia virus, ALVAC (canarypox virus) and *Salmonella typhi* of which the last two vaccines are tested in a combination with monomeric env protein boosts. The majority of these vaccines employed HIV clade B immunogens. New trials are in the pipeline of recombinant MVA leading to a DNA prime-MVA boost protocol, Venezuelan equine encephalitis virus and a novel *Salmonella* vector, all using clade A or C immunogens. The vast majority of the above strategies attempt to induce nAb, about half of the studies also include other than env HIV proteins and only a few focus solely on the elicitation of CTL. Recombinant monomeric gp120 protein and ALVAC vectors have reached phase II trials and adjuvanted monomeric gp120 from clades B and E is the only HIV vaccine candidate that has been taken as far as phase III efficacy trials.
So far, the reported immunogenicities in humans of the above vaccines have been unimpressive. Nevertheless, these studies have provided a ‘baseline’ for new technologies including novel immunogens for induction of neutralizing antibodies, and early proteins, better vaccine vehicles and their combinations for induction of CTL, which showed promise in non-human primate models.

**Therapeutic vaccines**

Similar immunogenic strategies as employed for a prophylactic vaccine may be used for immunotherapy of HIV-infected individuals. As the replication fitness of HIV within an individual does not correspond directly to the efficiency of transmission, i.e. there appears to be a certain transmission ‘bottleneck’, therapeutic vaccines may require a different set of immunogens and possibly vaccine vehicles for an optimal induction of both humoral and cell-mediated immune responses. Also, therapeutic vaccines may have to be used together with HAART to suppress HIV replication resulting from immune activation.

**Perspectives**

So what is the prospect of a prophylactic vaccine for HIV? Providing that scientists can outsmart 10,000 nucleotides (the size of the HIV genome), the collection of all the safety, immunogenicity and efficacy data necessary for a deployment of a successful HIV vaccine may still take up to 10 years. The final delivery of an effective vaccine to the people who need it the most and in as short a time as possible will require intense international commitment, collaboration and co-ordination in areas such as preparedness for and management of clinical trials, trial ethics concerning (e.g. inclusion of placebo groups and the level of care offered to volunteers infected in the course of the trials), agreements on the intellectual property rights, product manufacture and price. Although vaccine research is an inherently slow process, the recently acquired scientific and political momentum has put the HIV vaccine development back on the road, possibly on a motorway.

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