Monthly Focus: Anti-infectives

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Review

Vaccines for HIV

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A preventive vaccine for HIV is urgently needed to curb the AIDS pandemic. Research and development of HIV vaccines is accelerating and there is increasing evidence that a viable market will be identified. The basic approaches to HIV vaccine design (HIV protein vaccines, live vector, DNA vaccines and live attenuated vaccines) are all undergoing rapid improvements to their design and delivery techniques; patents since 1997 in this field are reviewed. Many of the techniques being pioneered for HIV vaccines will be applicable to vaccines for other pathogens. Although some candidate HIV vaccine approaches have demonstrated at least partial efficacy in animal models and have been shown to be safe and immunogenic in early human trials, no human efficacy trials of HIV vaccines have been completed. The final utility of the many clever techniques now available to produce novel HIV vaccines remains unknown.

Keywords: adjuvant, cellular immunity, HIV, immunity, vaccine

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1. Introduction

1.1 The HIV pandemic

It is estimated that over 15,000 new HIV infections occur daily, largely in developing countries which have little or no access to effective therapies. Over 40 million people worldwide are either now infected with HIV or have died of AIDS and seroprevalence rates are estimated to be as high as 30% of entire populations in several countries [1]. Since HIV is predominantly transmitted sexually, it affects men and women in the most productive phases of their working life and of childbearing age. HIV epidemics in many countries are now causing severe economic hardship as the working population is increasingly affected. The loss of both parents to HIV/AIDS is now resulting in an enormous orphan problem in many countries.

Educational programs, behavioural modification programs and sexually transmitted diseases control programs could (and should) have substantial impacts on HIV-1 acquisition rates. However, many such programs have either lacked the political will to implement, are difficult to sustain in the long-term or, in the case of mass treatment for sexually transmitted diseases, have been disappointing in their affect on HIV transmission [2]. Further advances in measures to prevent HIV-1 are desperately needed. There is now a growing social and political will to develop a safe and effective HIV vaccine. The spectacular worldwide successes with vaccines against smallpox and polio suggest great promise for vaccines to curb HIV-1 transmission. Equally, however, there has been a failure in some of the worse affected parts of the world to adequately deliver reasonably cheap

Table 1: HIV vaccine approaches.

Vaccine approach	Typical example	Advantages	Disadvantages	Status
Protein vaccines	Subunit envelope protein	Safe	Limited efficacy in animal models	Phase III trials started
Whole inactivated viruses	Inactivated HIV	Commonly successful for other pathogens	Inactivation must be complete. Limited efficacy to date.	Novel inactivation methods being assessed in animal models
Live attenuated vaccines	Nef-deleted HIV-1 strains	Good efficacy in animal models	Unsafe to date	Safer versions being constructed and assessed in animal models
Live vector vaccines	Attenuated poxviruses	Safe; some induction of cellular immunity	Immunity to the vector may be limiting	Extensively assessed in Phase I/II trials
DNA vaccines	HIV-1 *env-rev* HIV-1 *gag-pol*	Safe to date Simple to engineer	Early versions have limited immunogenicity alone	Phase I/II trails underway

and effective vaccines such as hepatitis B vaccines. Whether the promise of intensive research into HIV vaccines at present will be ultimately fulfilled is an open question.

1.2 General types of HIV vaccines

Most HIV vaccines can be placed into five categories, each with inherent potential advantages and disadvantages (**Table 1**). Subunit protein vaccines and whole inactivated HIV vaccines were the first vaccines studied. These vaccines have proven to be safe, but their efficacy, utilising the macaque monkey model challenged with the simian immunodeficiency virus (SIV), has been disappointing [3]. This may be due to the poor induction of key immunologic parameters that are widely believed to be required for HIV vaccine efficacy, particularly neutralising antibodies or cytotoxic T-lymphocytes (CTL). Equally, since no human efficacy trials have been completed, it is possible that the SIV/macaque model may not reliably predict HIV vaccine efficacy [4] and the results of an HIV envelope subunit approach now being assessed in Phase III studies in the US and Thailand are eagerly awaited.

Although live attenuated HIV vaccines have shown promising efficacy in SIV/macaque models, many versions have resulted in pathogenic disease in a proportion of macaques [5,6]. Some human subjects infected with naturally attenuated HIV mutants have also progressed to AIDS [7]. Nevertheless, it remains possible that only live attenuated vaccines will prove efficacious and research on both safe and effective live attenuated HIV vaccines is ongoing.

Live vector and DNA vaccines against HIV are widely believed to be the most promising approach to prevent HIV today. Recombinant attenuated poxviruses (e.g., modified vaccinia Ankara, fowlpoxviruses and canarypoxviruses) expressing HIV genes were among the first live vector approaches tested and are capable of safely inducing CTLs in at least a minority of subjects. Many other recombinant live vectors, such as adenoviruses and alphavirus replicons such as Venezuelan equine encephalitis viruses also show considerable promise [8]. Many poxvirus and other vector approaches have been combined with subunit protein vaccines as boosting vectors and this poxvirus/protein 'prime and boost' approach induces higher levels of non-neutralising antibodies (but not CTLs) compared to poxviruses or protein vaccine approaches alone [9]. Recombinant canarypoxvirus HIV vaccines together with envelope subunit boosting are poised to enter human efficacy trials in the near future.

'Naked' DNA vaccines, first described in the early 1990s [10], have been heralded as a potentially cheap and effective HIV vaccine approach [11]. Although it is remarkable that injected DNA vaccines are immunogenic at all, many initial versions were poorly immunogenic and only weakly protective in animal models [12]. Considerable effort is now being directed towards improving this approach, including expression of adjuvant polynucleotide sequences termed CpG motifs [13] and the enhancement of antigen expression by optimising the antigen codons for human cells [14]. Additionally, it is now clear that DNA vaccines very efficiently prime CTL responses that are greatly enhanced following boosting with attenuated poxvirus-HIV vaccines [15-17]. The DNA/poxvirus

Table 2: Obstacles to HIV vaccine development.

Scientific obstacles	Political or practical obstacles
HIV is highly polymorphic. Protection against heterologous strains may be limited.	Efficacy trials may need to be performed in developing countries
Correlates of protective immunity unclear	Standard of care for individuals (eg. expensive anti-HIV medications) infected with HIV during efficacy trials may be different in country of sponsor
Difficult to generate neutralising antibodies against HIV-1	
Induction of sustained immunity, particularly at mucosal sites, may be difficult	Concern that a viable market for HIV vaccines may not exist

prime/boost approach is considered a highly promising HIV vaccine approach at present.

The best outcome from HIV vaccination would be complete 'sterilising' immunity following HIV exposure, however this may be difficult to achieve and non-sterilising immunity may be ultimately more feasible. Different approaches for immunisation against HIV/AIDS are generally aimed at either inducing sterilising immunity *via* neutralising antibodies (such as whole inactivated viruses or those based on the virus envelope), or to block the progression of infection or disease by inducing cellular immunity and/or targeting regulatory proteins, such as a vaccine based on HIV Tat.

1.3 Obstacles to HIV vaccine effectiveness

In the face of intense research, why has the development of an HIV vaccine been so slow? There are many obstacles, both scientific and political (**Table 2**). HIV is highly mutagenic, leading to both an enormous diversity of strains throughout the world and an ability of HIV to mutate to escape immunologic control. Permanent immunity following HIV exposure appears to be a rare or non-existent event and therefore the determinants of immunity to HIV and how difficult this will be to achieve are unknown. Neutralisation of HIV by antibodies has not been reliably achieved following protein or live vector approaches to date. The lack of a validated, small animal model of HIV disease has also hampered vaccine development since challenge studies must be performed in primate models. Induction of effective, long-lived responses at genital mucosal surfaces, where HIV is most commonly encountered, has also proved difficult. Although none of the many scientific obstacles to HIV vaccine development are insurmountable, together they pose a formidable challenge.

Political and social obstacles to HIV vaccine development are also substantial. Most of the large global vaccine development companies have viewed HIV vaccine research as both risky and one whose market may largely be areas of the world that may not be able to afford the ultimate product. The World Bank and organisations such as the International AIDS Vaccine Initiative are now working to ensure that viable markets for HIV vaccines exist, while ensuring that areas of the world that most desperately need HIV vaccines have access to them once they are developed [201]. Human HIV vaccine efficacy trials will need to be done in regions of high HIV seroincidence and therefore most likely in developing countries or amongst other marginalised groups. Conducting HIV vaccine efficacy trials in many countries will be difficult and fraught with ethical dilemmas. The United Nations has recently released a paper on the many issues to be faced in HIV vaccine clinical trials [202]. Although the political and social issues are also not insurmountable, they could significantly delay the development and subsequent availability of effective HIV vaccines.

1.4 Therapeutic HIV vaccines

Although the greatest public health benefit is likely to come from preventive HIV vaccines, there has been increasing interest in vaccinating individuals already infected with HIV in an attempt to slow or halt the course of infection. It is generally felt that a more viable market for therapeutic (as compared to preventive) HIV vaccines exists. Several clinical trials of therapeutic HIV vaccines have been performed and have shown neither a clinical benefit nor sustained or substantial improvements in the surrogate markers of HIV progression, such as HIV viral load or CD4+ T-cell depletion [18]. However, most vaccines studied to date have been protein vaccines not capable of enhancing CTL responses. Additionally, most published studies to date have vaccinated individuals with active HIV replication and it is now thought that high levels of HIV replication abrogate the induction of HIV specific cellular immunity [19]. Several trials are

ongoing studying subjects on effective antiretroviral drugs and/or those with very recent HIV infection; scenarios where induction of effective HIV-specific immunity may be easier to achieve. In addition, new generation vaccines, such as DNA vaccines, are being assessed as therapeutic HIV vaccines with the hope that more effective immunity may be induced [20].

2. HIV vaccine approaches

2.1 Whole inactivated vaccines

Whole inactivated SIV vaccines delivered in adjuvant were among the first vaccines reported to prevent SIV infection in macaques. The success of the vaccines led to much optimism about the development of vaccines for HIV. However, the search for the correlates of immune protection against the inactivated viruses revealed that the protective immune responses were raised against the human host cell proteins used to grow the challenge virus and not to the SIV antigen [3]. When early versions of whole inactivated vaccines were evaluated which did not contain human proteins, such as HLA-DR molecules, the vaccines were not found to be effective in SIV models.

However, whole inactivated HIV vaccines have recently shown some promise [21]. Many inactivation methods for HIV whole inactivated virus vaccine approaches (such as heat or formalin) disrupt surface proteins on the virion [21]. A promising technique to inactivate HIV-1 is to use aldrithiol-2 to attack the highly conserved zinc fingers of the nucleocapsid protein and render the virus non-infectious [101]. This technique preserves the virion external proteins and the immune responses against the virus are retained [21]. Other processes to inactivate HIV have been claimed, including the use of metal cations [102] and inactivation by ethylene imine oligomers to selectively modify nucleic acids [103].

2.2 Subunit protein/peptide vaccines

Recombinant subunit HIV-1 protein vaccines (e.g., Env and/or Gag proteins administered in adjuvant) were initially attractive to vaccine developers following the success of recombinant Hepatitis B surface protein vaccines. However, recombinant SIV proteins have demonstrated limited ability to protect macaques against SIV challenge, the most common primate model of AIDS employed [22]. Neutralising antibody and CTL responses are poorly elicited against recombinant protein vaccines for HIV and recombinant protein vaccines may require further refinements to increase their efficacy. It has been realised that the neutralising antibody epitopes of HIV are hidden within the envelope, may be highly conformational and only displayed during the transient fusion event when HIV enters target cells [23-25]. The recent solving of the crystal structure of the HIV-1 envelope protein, together with the demonstration that hidden neutralising epitopes can be displayed by fixing envelope bound to it's receptors, offers hope that viable improvements in the ability of HIV-1 Env subunit vaccines to induce protective immunity will be achieved [23-25].

Several recent patents have been filed claiming novel HIV-1 protein or peptide formulations that may be capable of improving the immunogenicity and efficiency of HIV-1 protein vaccines. Envelope proteins or peptides have been intensively studied because, as the surface protein, they may be capable of inducing effective neutralising or fusion-inhibiting antibodies. Haynes *et al.* [104] have used a hydrophilic peptide corresponding to the antigenic determinants of the envelope glycoprotein as a therapeutic or preventive HIV vaccine. Use of disulphide bonds to stabilise Env preparations has been studied [105,106]. Epitopes of the variable domain of gp120 (V1/V2) of the HIV-1 envelope are claimed in patent [107] to generate neutralising antibodies against primary isolates of HIV-1. Berman *et al.* [108] claim a composition of polypeptides from the envelope of HIV-1 from a number of HIV-1 isolates with the potential to provide broad protection against the different isolates. Helical peptides from HIV gp41 may induce antibodies which can prevent viral membrane fusion [109]. Polypeptides which can inhibit the binding of the HIV gp120 to its CXCR4 and CCR5 viral co-receptors have also been studied [110].

Other protein targets include HIV P17 gag peptides, for which both T-cell and B-cell epitopes are claimed as a vaccine for HIV-1 in patents [111,112]. An HIV-1 Tat vaccine has shown utility in primate models [26,113]. Tat and Nef fusion proteins have been suggested to be useful HIV vaccines [114,115]. The coupling of synthetic polypeptides encoding HIV-1 Tat epitopes with carrier proteins to impair HIV multiplication is claimed in patent [116]. The HIV-1 Vif protein has recently been studied as an HIV vaccine antigen [117]. Novel HIV-1 peptides and carrier molecules to enhance immunogenicity are claimed in patent [118]. Tandem HIV peptides which form a

tetrameric structure have been shown to enhance immunogenicity [119].

HIV protein vaccines are likely to be more effective if delivered in an appropriate adjuvant and many novel adjuvants have been claimed to be specifically useful for HIV vaccines. Adjuvants to enhance mucosal immunity, believed to be of specific importance to HIV-1, have been claimed, including an exogenous hydrophobic sequence complexed with a proteosome [120], an enterotoxin adjuvant [121] and ISCOM particles [122]. Broadly applicable adjuvants are claimed for vaccine use with HIV and a number of other pathogens. Bacterial toxins as HIV vaccine adjuvants [123-125], oil in water emulsions [126], novel poly(dl-lactide-co-glycolide) (PLG) microparticles [127], macroglobulin complexes [128], polyphosphazene polyelectrolyte [129], peptide linkers [130] and liposome delivery methods [131,132] may find utility as HIV-1 vaccine adjuvants. Specifically targeting antigen presenting cells (APCs), either using chimeric APC-specific mAbs [133] or antigen pulsed dendritic cells isolated from an affected patient and then infused back into the patient [134], may also eventually prove useful for HIV-1 vaccine research and development.

2.3 DNA vaccines

The discovery that injection of plasmid DNA alone could lead to expression of encoded proteins [10] has spawned enormous interest in DNA vaccines [135,136]. DNA vaccines are generally relatively simple to design, construct and manufacture. DNA vaccines could prove to be a relatively inexpensive method to induce cellular immunity, long believed to be required for protective immunity to HIV-1. However, immune responses elicited by DNA vaccines are generally poor in larger animals and hence much work and many recent patents claim methods to increase the potency of the immune response following DNA vaccination and targeting the vaccine to sites to stimulate the desired immune responses.

Important recent patents in this field include increasing the efficiency of antigen expression by optimising the codon usage from HIV-1 *env* and *gag* DNA for expression in mammalian cells [137,138]. The use of specific nucleotide motifs, either CpG motifs or other hexamer molecules, can very efficiently enhance the generation of cellular immunity [139].

2.3.1 DNA vaccine delivery

DNA vaccines can be delivered by a wide variety of physical means or in specialised adjuvants which may enhance their expression and immunogenicity. Delivery of DNA vaccines *via* a topical adhesive contact device is claimed by Tang *et al.* [140]. Claims for specific adjuvants include liposome complexes [141,142], incorporating histones [143], microencapsulation of DNA in a polymer [144], saponin adjuvants [145], peptide/DNA conjugates [146,147], binding the DNA vaccine to target cells [148] and other adjuvants [149,150]. Mucosal immunity to HIV may be enhanced by a number of novel methods to deliver DNA vaccines, including particle-mediated delivery to mucosal tissues [151], incorporating DNA into human papillomavirus (HPV) vectors [152] and improving the transfection efficiency of DNA vaccines into mucosal tissue [153].

2.4 Live vector vaccines

Recombinant microorganisms genetically engineered to express HIV-1 antigens are promising HIV-1 vaccines. Amongst the first live vectors described was the genetically engineered vaccinia virus (the former smallpox vaccine) [154,155]. Recombinant poxvirus approaches have been improved and a recent patent describes recombinant vaccinia vectors including a very large number of different HIV-1 envelope (polyenv) sequences which are immunogenic against many HIV isolates [156]. Since wild type vaccinia can cause disease in immunodeficient humans, attenuated poxviruses, such as canarypoxvirus, fowlpoxviruses and modified vaccinia Ankara, have been studied and improved upon [157-160]. Immunisation with poxvirus vaccines to one mucosal surface may improve the broad mucosal immunogenicity of these vaccines [161]. Novel poxviruses such as parapoxvirus and povapoxvirus vectors encoding HIV-1 antigens have recently been described [162].

Alphaviruses such as sindbis virus, semliki forest virus and Venezuelan equine encephalitis virus can be engineered as replicons to efficiently express inserted HIV genes and show considerable promise as HIV vaccine viral vectors [163]. Adenoviruses have been extensively engineered as gene delivery systems and aslo show some promise as HIV vaccine vector [164]. Other non-poxvirus viral vectors showing promise include alfalfa and tobacco mosaic viruses fused to antigenic peptides [165], viral vectors encoding antigen and immunomodulating co-factors [166], recombinant Sabin poliovirus vectors [167],

enteroviruses such as coxsackieviruses [168], and a non-integrating retrovirus vector [169]. Recent bacterial vectors showing some promise include attenuated Listeria carrying HIV antigens [170].

There has been a 'cross-fertilisation' of DNA vaccine and live vector vaccine approaches recently. Salmonella strains have been used for oral delivery and mucosal immunogenicity of DNA plasmids encoding HIV antigens [171]. The use of DNA vaccines to prime the immune system prior to viral vector boosting, such as modified vaccinia Ankara has been shown to be efficient at inducing cellular immunity to malaria [160]. There is a body of prior literature on this approach, including the use of fowlpoxvirus HIV-1 vaccines as the boosting vaccine [15,17,27].

2.5 Co-delivery of immune-modulating molecules

Vaccine potency can be improved by delivering immunomodulatory proteins such as cytokines and chemokines, as originally described in the 1980s utilising cytokines encoded by recombinant vaccinia viruses [28,172]. The co-expression of immunomodulatory proteins with vaccines can enhance the immune response by directing the type of immune response required for a particular vaccine. Co-expression of IFN-α, a Th1 cytokine, by a fowlpoxvirus-HIV vaccine has recently been shown to enhance HIV-specific immunity [173]. The cytokine co-expression concept was specifically studied for a variety of cytokines co-delivered with DNA encoding HIV immunogens in 1998 [174]. The utility of colony stimulating factors (e.g., granulocyte monocyte-colony stimulating factor) co-delivered with HIV DNA vaccines has also been demonstrated [175]. The efficacy of recombinant protein or DNA vaccines against HIV-1 may be enhanced by including chemokines with the vaccine preparation [176,177]. The timed release of immunostimulatory cytokines with a vaccine to direct the immune response (Th1/Th2) and the fusion of the cytokines with antibody fragments which can suppress or induce an immune response is claimed in patent [178]. Co-inoculation of IL-12 intranasally with a viral vaccine has also been studied [179] and IL-11 has also been claimed as a useful cytokine co-expressed with viral vaccines [180].

2.6 Live attenuated vaccines

Attenuated strains of HIV that can potentially promote antigenic and protective immune responses against the wild type HIV are claimed as vaccines. A non-pathogenic strain of HIV-1 was isolated from an Australian cohort and found to contain deletions in the *nef* gene and U3 region of the long-terminal repeat [29]. Deacon *et al.* [181] claim this attenuated HIV strain has the potential to elicit protective immunity against HIV. Lentivirus strains that contain engineered mutations in the *nef* gene alone or with mutations in one or more of the non-essential genetic elements are claimed to be capable of eliciting protective immunity [182,183]. Molecular clones of HIV or SIV which remove Rev activity, glycosylation sites in envelope, or antibody-dependent enhancing domains in gp41, are claimed to be potentially useful live attenuated HIV vaccines [184-186]. A *tat*-deleted strain of HIV-2 is claimed to be replication competent but non-pathogenic with vaccine potential against HIV [187]. Deletions downstream of the primary binding site also attenuate HIV-1 [188]. Non-integrating, or conditionally replicating, lentivirus or retrovirus vaccines have been studied and may be safer than classical live attenuated HIV vaccines, although their ability to induce protective immunity has not been studied [189,190]. Cross-protection against HIV may be possible using other viruses, such as the caprine arthritis-encephalitis virus [191].

3. Expert opinion

The HIV epidemic, beginning in the 1980s, initiated an enormous burst of knowledge about the immune system and the detailed study of retroviruses. Although HIV vaccines have been very slow to enter efficacy trials (with only one product, an envelope protein, now being assessed in the USA and Thailand), the intense research activity now underway is likely to provide a large number of spin-offs. Many of the vaccine concepts being developed and evaluated for HIV, even if they fail to demonstrate utility as HIV vaccines, may well find utility as vaccines or treatments of other pathogens, and this is quite evident in the claims made for most HIV vaccine related patents.

It is difficult to speculate on the potential utility or otherwise of many HIV vaccine approaches, since no HIV vaccine has passed the ultimate test, providing protection against HIV in human efficacy trials. As such, the precise immune correlates of protective immunity to HIV in humans (a sought-after surrogate marker for efficacy) are not known. Attempts to claim that a vaccine capable of stimulating any particular

immune response in mice, non-human primates, or even humans, is of great utility as an HIV vaccine are of dubious value. As noted above, a body of circumstantial evidence suggests cellular immune responses may be critical in providing protective immunity. Therefore, at present great interest focuses on live vector and DNA vaccine approaches since these approaches appear most promising in this regard. Combining vaccine approaches in 'prime/boost' regimens (e.g., consecutive immunisations with a DNA vaccine and poxvirus vaccine) appears promising. Additional manipulations, such as encoding immune-stimulating cytokines or CpG motifs, could further enhance specific immunity. If such combination approaches are found effective, a large number of patents on the various components and concepts would have claims to the ultimate, rather complex, vaccine regimen. Other viral vectors, such as Venezuelan encephalitis virus, or novel combinations of DNA and viral vectors vaccines, perhaps combined with novel additional targets such as HIV-1 Tat could also prove to be efficacious against HIV and are currently being supported through the lengthy clinical trial process.

Many of the early (Phase I/II) clinical trials of HIV-1 Env subunit vaccines, while not powered to detect vaccine efficacy, have resulted in small numbers of 'breakthrough' HIV-1 infections despite extensive counselling. Detailed analysis of the breakthrough infections in such trials, although conflicting, did not find convincing evidence that any protection was afforded against HIV-1 strains closely related to the strains utilised in the vaccine formulations [30,31]. As such, the requirement for HIV-1 antigens used in the vaccine to closely match those in the exposed population is unknown. Small studies have suggested antigenic variation between vaccine strains and exposed viruses may be important [32], but the extent of this problem is not known. Strategies to overcome the problem of antigenic variation across HIV strains, such as utilising antigens from multiple HIV-1 strains or focusing on highly conserved targets, are of interest but have unclear utility. Given the breakthrough infections observed in current Phase I/II trials, it seems unlikely that anything close to 90% protection will be achieved when efficacy trials are completed. As such, partially effective vaccines may be marketed first with subsequent rounds of improvements made. Improving upon partially effective vaccines will, however, require even larger sample sizes and amounts of funding.

Live attenuated HIV vaccines, although of promising efficacy in primate models, are generally considered unsafe in current formulations and will not enter clinical trials in the near future [7]. However, should current generations of safer approaches, including protein, DNA and a number of live vector HIV vaccines, prove poorly efficacious over the next decade, a push to seriously re-evaluate live attenuated vaccines is likely to emerge. The time delay between invention and eventual marketing of this approach may undermine the utility of some HIV vaccine patents, perhaps particularly in the live attenuated HIV vaccine field.

Many social, political and market factors will have a bearing on the ultimate utility of HIV vaccines. Conducting Phase III efficacy trials requires substantial funding and generally will be performed in underdeveloped countries, raising many ethical issues. While these issues can, and will, be resolved in the many settings where such trials will eventually occur, solutions may be both time-consuming to achieve (such as the delays which occurred in initiating HIV vaccine trials in Uganda). In addition, funding for the provision of expensive medications to those infected during the course of HIV vaccine trials may be required in some settings. These factors will be an additional hurdle for vaccine developers and perhaps lessen the inherent value of the patents. Working towards developing a viable market for HIV vaccines is likely to encourage the full assessment of more HIV vaccine approaches and increase the value of successful vaccine strategies. In the meantime, the option of studying many HIV vaccine approaches either as therapeutic HIV vaccines or against other pathogens, will continue to drive innovation in this field. Since the humanitarian value of an effective preventive HIV vaccine would be enormous, fuelling both innovation and development of HIV vaccines should continue to be vigorously encouraged.

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