Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Current opinion | Published 2 March 2012, doi:10.4414/smw.2012.13535
Cite this as: Swiss Med Wkly. 2012;142:w13535

HIV vaccines: an attainable goal?

Lucy Reynell[a,b], *Alexandra Trkola*[a]

[a] Institute of Medical Virology, University of Zurich, Switzerland
[b] PhD Programme in Microbiology and Immunology University of Zurich, Switzerland

Summary

Publication of the first efficacious large-scale HIV vaccine trial in 2009 prompted fresh hope that design of a protective vaccine against HIV may be achievable. In this review we explore the difficult task of eliciting protective immune responses to HIV and highlight the hurdles that vaccine design must still overcome.

Key words: *HIV; HIV vaccine; vaccine; antibodies; humoral immunity*

The quest for an HIV vaccine

In the almost 30 years since HIV was identified as the causative agent of AIDS, molecular characterisation of HIV pathogenesis has led to development and licensing of roughly 30 HIV inhibitors. When administered in certain combinations these drugs enable patients to control viral load for many years [1]. As a result, the prognosis following infection in most developed countries has improved dramatically, and AIDS-related deaths have been steadily declining worldwide [2].

In contrast to the success of anti-retroviral treatment, the search for an efficacious HIV vaccine has been slow to yield positive results. Despite enormous efforts over the past three decades, most attempts to design an HIV vaccine regimen have proved ineffective and were abandoned in the early stages of development. Only a handful of regimens were assessed in phase II/III studies, and neither antibody- nor T-cell-based vaccine regimens proved effective [3–7]. In 2009 the RV144 HIV Vaccine Trial, tailored to induce protective antibody responses, was the first to report partial efficacy with a 31% lower infection rate in vaccinees than in individuals receiving placebo [8]. Despite this modest effect, the results of this trial fostered fresh hopes that design of a protective vaccine against HIV may be achievable, and has focused unprecedented levels of resources on both defining the protection correlates of this regimen and the search for alternative approaches [9].

HIV vaccine design is at the crossroads. The recent identification of new antibodies which block HIV with unparalleled potency [10–12], target a wide variety of strains [13] and prevent infection in animal models [14–19] raise further hopes that engaging protective humoral responses to build an efficacious vaccine against HIV is possible. However, difficulties in devising vaccines and determining their efficacy have simultaneously highlighted the fact that the correlates of protection against HIV acquisition still await definition [20–22]. Additionally, as new means of pre-exposure prophylaxis are identified, the window of opportunity for conventional efficacy testing of HIV vaccines may soon be closing.

While HIV vaccine design has never experienced a period of such potential and (justified) optimism, development and testing may yet increase in complexity. In this review we highlight recent successes in antibody-based vaccine design and hurdles old and new that need to be overcome. We believe these factors will shape the future of antibody-based vaccine design, and need to be balanced in order to make HIV vaccines an attainable goal in reality.

HIV vaccines – how might one work?

That an HIV vaccine is a desirable goal has never been disputed. However, whether or not this goal is attainable has been differentially reflected over the years [9, 23–27]. Vaccines are indisputably the ideal means of protecting a large proportion of the healthy population [28]. They are cost-effective and are designed to involve low risks in use. When efficacious they confer immunity on individuals, and, importantly, if the required threshold of immunity in the population is reached, a given pathogen can be eradicated [29, 30]. Smallpox virus is the best example of this, as the virus was officially declared eradicated in 1979, 21 years after the World Health Organization initiated a focused vaccination-based eradication programme [31]. The more easily a virus is transmitted, the higher the degree of immunity in the population that needs to be reached. This factor has led to difficulties in eradicating the measles virus, where it is estimated that over 90–95% of the population would need to be vaccinated in order to halt the spread of this highly contagious virus [32]. However, in the case of HIV, where an easy accessible preventive measure is desperately needed, even a partially efficacious vaccine is currently considered highly desirable. Due to the comparatively restricted transmission routes of HIV, individuals at high risk of infection, such as men having sex with men (MSM), sex workers or discordant couples, can be more easily identified and targeted by preventive measures or,

once available, vaccines. In fact, even without targeting to high risk populations vaccination of a moderate proportion of the population is expected to achieve a substantial reduction in HIV transmission and save millions of lives [33].

All currently licensed antiviral vaccines protect by eliciting inhibitory antibodies [34]. HIV vaccine development also initially focused on attempts to elicit neutralising antibodies [9]. In addition, due to their confirmed protective role in natural infection, and the difficulties encountered in antibody based HIV vaccine design, vaccine strategies which evoke cellular immunity to HIV infection are also sought [25, 27].

Eliciting antibodies capable of neutralising the virus before it enters and infects target cells appears to be an ideal strategy for vaccine design. The mechanism of action and prevalence of these HIV neutralising antibodies has been studied in great depth over recent decades [35, 36]. Such antibodies act by binding specifically to the only accessible viral proteins on HIV's outer surface, the envelope proteins gp120 and gp41, arranged as trimers of gp120-gp41 heterodimers to form the so-called viral spikes [37, 38]. Depending on the region of the viral spike targeted, neutralising antibodies can interfere with engagement of cellular receptors or block fusion of the viral and host membranes [35]. Preventing this first step in the viral life cycle may be particularly important in HIV, which is capable of integration into the host genome and can persist in a latent state [39].

Whilst this activity is likely to be crucial for antibodies to mediate sterilising immunity [40], increased attention has recently been focused on the capacity of envelope binding antibodies to mediate additional antiviral activities. These antibody effector functions include immune complex formation, complement recruitment, Fc-receptor mediated phagocytosis and antibody dependent cellular cytotoxicity [41]. It has recently been suggested that the last two must be crucial for effective antibody-mediated immunity [42].

While neutralising antibodies act against virions, vaccine strategies targeted at conferring cellular immunity aim to induce killing of infected cells upon recognition by CD8 cytotoxic T lymphocytes. This activity targets cells in which viral protein synthesis is occurring and thus acting at a later step in the infection cycle [25]. While the prevention of infection achieved by neutralising antibodies may be conceptually more desirable, the multitude of difficulties experienced in eliciting sterilising immunity to HIV has resulted in the consensus that an effective HIV vaccine will need to induce both cellular and humoral immunity [25].

HIV vaccines – how can the hurdles be overcome?

The hunt for an efficacious HIV vaccination regimen faces several major obstacles, summarised in table 1. Firstly, immune correlates of protection need to be defined. However, as, once infected, humans do not naturally clear HIV, determining which immune responses are capable of clearing or even preventing infection, and thus which responses vaccine design must elicit, is not simple.

During the natural course of infection individuals produce HIV-specific antibodies and CD4 and CD8 T cell responses in abundance [43]. Studies to determine which of these specific immune responses effectively limit viral replication in vitro, and correlate with reduced viral load in vivo, have been employed to predict potential correlates of protection from HIV infection. While none of the immune responses elicited in natural infection are capable of clearing HIV infection, hope remains that blocking virus transmission may be easier to achieve. HIV transmission is a stochastic process, often involving only a single founder virus [44, 45]. In contrast, clearing an established retroviral infection, particularly once viral latency is established in long-lived cells, is likely to involve a higher magnitude and different type of response. This may provide a window of opportunity for HIV directed antibodies. Passive transfer of broadly neutralising antibodies to HIV infected patients can transiently suppress viral replication but does not lead to viral clearance [46]. However, animal challenge studies have demonstrated the ability of certain monoclonal antibodies to prevent acquisition with neutralising antibodies targeting specific epitopes [14, 16–18, 40, 47] or recruiting specific immune effector functionality [42].

Another potential obstacle facing vaccine design is the diversity of circulating HIV strains [34]. Due to an error-prone reverse transcriptase, and the capacity to recombine genetic information from different strands of genomic viral RNA during reverse transcription, HIV has the ability to mutate rapidly to avoid antibody and T cell responses elicited in natural infection [48]. As a result the virus exists within the population as a diverse range of clades, strains and quasispecies [34]. Historically efficacious vaccines for genetically diverse viruses have been difficult to develop; for example, the seasonal influenza vaccine, despite annual adaptation to antigenic drift and shift of the circulating viruses, achieves only moderate efficacy [49].

Yielding antibodies to specific epitopes through vaccination remains challenging [26]. In other viral infections simply administering recombinant viral proteins can yield protective antibody responses [28], but this has not been the case for the poorly immunogenic and genetically diverse HIV envelope. No HIV proteins are entirely conserved, and conserved epitopes that are accessible to neutralising antibody attack are especially rare within the external envelope proteins of HIV. This is particularly remarkable as the virus depends on several relatively conserved domains within these envelope proteins to recognise and enter its target cells [35]. As these domains, such as the binding sites for CD4 and coreceptors, are the prime targets for neutralising antibodies the virus has evolved to effectively protect these sites. The HIV envelope is camouflaged by dense, host-derived glycosylation which shields vulnerable sites and hampers immune recognition [reviewed in 35]. Key domains in gp120 and gp41 are further hidden by flexible and highly variable loops in gp120 and the quaternary association into the trimetric viral spike, and only exposed transiently on engagement with cellular receptors [50]. Defining a single immunogen that will elicit a protective immune response against all genetic subtypes may not be feasible. Consequently, vaccine immunogens may need to be tailored to geographical variability in HIV diversity, or present multiple antigens in order to elicit a broader response, both strategies employed in the seasonal influ-

enza vaccine (trivalent) or pneumococcal vaccines (up to 23-valent).

Administration of monomeric envelope immunogens has yielded only limited success so far, as the monomeric proteins expose epitopes hidden in the functional envelope trimer and thus primarily elicit non-neutralising antibodies [3, 4, 8]. Additionally, quaternary epitopes composed of multiple protomers are not represented on the monomeric proteins. Unfortunately, designing a stabilised immunogen which resembles the native trimer has proven challenging but becomes a more attainable goal as more is learnt about the structural organization of the viral spike [37, 38].

Another potential impediment to HIV vaccine design has been a narrow and perhaps naively optimistic vision of what a vaccine should achieve. Although sterilising immunity remains the ultimate goal, vaccine trial design must broaden to recognize additional potential outcomes [51]. Based on the results of RV144, it has also become evident that trial design needs to incorporate frequent measures of immune activity and breakthrough viruses in order to stratify analyses of protection, and characterise the type of protection elicited. Vaccine regimen may induce immune responses that do not protect against transmission, yet succeed in clearing virus after few initial rounds of replication. Hence, monitoring of vaccinees must include measures capable of detecting and confirming transient infections which may, for instance, be characterised by positive serology, but persistently undetectable viral load, an outcome that may be achieved by a vaccine that educates the immune system to recognize and eliminate HIV infection. Alternatively, long-term follow-up of vaccinated individuals who do become infected may detect vaccine-induced control of viral load and delayed progression to AIDS. These outcomes would also lead to reduced onward transmission of HIV from infected vaccinees to their partners, and thus could still have a dramatic impact on the epidemic [51].

HIV vaccines – where are we now?

Numerous preclinical studies and phase I and II clinical trials have been conducted over recent decades in an attempt to define immunogens capable of eliciting HIV-directed humoral and/or cellular immune responses [9, 52, 53]. In animal models, classical vaccine design strategies that have succeeded rapidly for other viral infections have failed to induce strong immune responses to HIV. Inactivated or killed virus, recombinant envelope proteins (gp120, gp160, gp140, trimer), peptides (V3, MPER), or various envelope scaffolds have been probed in various formulations, including adjuvants and DNA prime boost regimen [9]. DNA vaccine and various types of recombinant attenuated vector regimen have elicited cellular responses capable of controlling infection [25, 52, 53] or inducing protection against transmission of homologous challenge [54]. More recently, vaccine-induced antibodies have also been implicated in protection against heterologous challenge [55]. In these models the potential for passive immunisation of neutralising antibodies to provide sterilising immunity against viral challenge [14–17, 40], and for T cell responses to control viral load [54] have also been affirmed.

Considering the logistical problems associated with testing HIV vaccine efficacy in clinical trials (discussed in more detail below), non-human primate (NHP) infection models may need to be developed further to provide reliable indications that a regimen is immunogenic or efficacious before initiation of human trials. Ideally the demonstration of efficacy in NHP challenge models combined with established safety in human trials may qualify regimens for licensing. However, thus far protection induced in NHP has not translated sufficiently into clinical trial success [56–58]. One complication of current NHP studies is the need for hybrid SIV/HIV virus strains which produce similar pathogenicity to HIV and allow investigation of HIV-directed immune responses in NHPs. Few appropriate virus strains have been identified so far [59], limiting the breadth of elicited immunity that can be probed. While resembling HIV infection and pathogenesis in many aspects, since these models cannot recapitulate the human immune response or diversity of HIV infection, they cannot replace large-scale phase IIb proof-of-concept or phase III clinical efficacy trials.

Only a handful of immunisation regimens have been tested in large-scale clinical efficacy trials. The first, a protein immunogen composed of recombinant HIV envelope subunits, failed to demonstrate protection (in injection drug users, AIDSVAX B/E [3], or high-risk MSM, AIDSVAX B/B [4, 7]) despite eliciting antibodies capable of binding and neutralising the immunisation strain in some patients [4] and protecting chimpanzees from homologous challenge [57, 58].

Table 1: Remaining challenges in vaccine design.

General
• Correlates of protection remain undefined.
• Correlates of (mucosal) transmission remain undefined.
• Vaccines must elicit mucosal immune responses.
• Animal models capable of predicting efficacy of vaccines in human protection are required in order to reduce the need for human efficacy testing.
• Circulating strains of HIV demonstrate dramatic genetic diversity, rendering the development of a globally active vaccine difficult.
Antibody based vaccines
• The HIV envelope is poorly immunogenic.
• The HIV envelope shields conserved regions from antibody binding.
• An appropriate immunogen to elicit potent neutralising antibodies has not been identified.
• The in vivo mode of antibody activity (neutralisation and/or effector functions) remains to be ascertained.
T cell based vaccines
• Recombinant viral vector immunogens must be designed to induce protective cytotoxic and helper T cell responses in man.
• Safe immunogens which do not induce increased susceptibility to HIV infection must be defined.
• Pre-existing vector-directed immunity must be avoided.

Following much evidence that CD8 induced cellular immunity controls viral load during natural infection [60, 61], vaccine research shifted the focus towards recombinant viral vector immunogens which generate viral proteins in host cells and thus elicit T cell responses. Despite success in preclinical assessments, the vaccine regimen designed to elicit protective T cell responses has failed in human trials [62]. These regimens had no impact on acquisition or the viral load in those participants who became infected, despite exhibiting this ability in NHP models [56], eliciting HIV-specific T cell responses in most vaccinees [5] and exhibiting immune pressure on breakthrough infections [63]. The two phase IIb trials designed to probe the efficacy of a T cell based vaccine regimen using the replication-defective adenovirus type 5 (Ad5) MRK gag/pol/nef vector were stopped prematurely when the first interim analysis showed that it had no impact on infection rate or early plasma viral load. In fact, HIV infection rate was elevated amongst a subgroup of vaccinated men who were previously Ad5-seropositive and uncircumcised [62], raising safety concerns about this regimen. The mechanism causing this increase in susceptibility is not fully understood but the transmission mode may have played a role as the effect was observed in MSM but not in heterosexual participants [62]. As increased infection appears to be associated with pre-existing immunity to Ad5, the vector may have stimulated Ad5 specific CD4 T cells and Ad5 antibody immune complex formation in Ad5-seropositive individuals. This immune activation could stimulate CD4 T cells and dendritic cells, rendering cells more susceptible to HIV [64]. While the mechanism responsible for higher HIV acquisition during this trial has not been confirmed, the impact of vector-directed immune activity must be considered in future trials [62].

The vaccine regimen employed in RV144 combined a canarypox vector expressing LAI gag and protease, and CRF01_AE gp120 with an LAI gp41 transmembrane linker, followed by two protein boosters of AIDSVAX B/E, the protein used in the earlier protein-only vaccine trial study in Thailand [6]. Thus, in RV144 both B and T cell directed strategies, neither of which had been successful individually, were combined in a prime-boost regimen. The positive outcome of this trial, a 31% reduction in infection risk in a primarily heterosexual population in Thailand, thus surprised many and is still not fully understood since the immune mechanisms responsible for this protection have not yet been determined [8].

The quest for correlates of protection

The results of RV144 raised many questions. Although moderate efficacy has been reported, the low level of HIV acquisition occurring in the trial population of low-risk volunteers equips statistical analysis with low power to identify potential correlates of protection. Without further verification in clinical trials any immune responses found to correlate with reduced transmission may simply represent surrogate markers of immune activation. Extensive work to define the window in which protection occurred (persistence of protection), immune pressure exerted on breakthrough viruses in vaccinees (sieve analysis) and immune responses responsible for non-infection (immune correlates of protection) has involved rapid widespread international collaboration since the RV144 results were announced in 2009 [8]. Initial correlates analysis, thus far unpublished but reported at the AIDS Vaccine Conference 2011 in Bangkok [65], revealed that the protection induced by RV144 does not appear to be mediated by the usual suspects. Neutralising antibody responses were rarely elicited and did not correlate with reduced acquisition. Instead protection correlated with non-neutralising humoral responses directed towards a particular epitope in the HIV envelope, variable loop 2 (V2). Individuals with high V1V2 directed IgG experienced a 43% reduction in HIV incidence, and strains present in vaccinated but infected individuals possessed more highly mutated V2 loops, suggesting escape mutation from the elicited antibody response. However, the mechanism by which these antibodies elicit protection remains to be determined [65]. One possibility is that these V1/V2 binding antibodies mediated antibody-dependent cellular cytotoxicity (ADCC), an immune response that allows destruction of opsonised infected cells [66]. In NHP challenge studies it has been demonstrated that the protection mediated by passive transfer of a broadly neutralising antibody depends upon the ability of that antibody to mediate Fc-receptor effector functions [42], of which ADCC is one.

A feature of particular note is that the protective effect of RV144 was only transient and the protective effect was found to be statistically significant only during a relatively narrow time window [8]. The latter aroused controversy on the value of the observations, efficaciousness of the vaccine and the validity of the statistical methods employed [67–69]. The period of peak immunogenicity, as determined by analysis of infection incidence, occurred two weeks after the last boost vaccination and titres of V1/V2 binding IgG declined in the following 6 months, suggesting that any protection observed may have rapidly deteriorated. This observation raises further questions. Was this protection mediated by humoral or CD8 T cell responses, and did these responses act in concert with immunisation-induced stimulation of the innate immune system? Most importantly, could more frequent or further rounds of vaccination yield sustained protection?

The difficulty encountered in identifying correlates of protection in RV144 has highlighted the importance of designing trials in a way which will provide both enough transmission events to lend statistical power to sieve and correlates analysis and sufficient biological material for immune functionality to be thoroughly assessed. Simultaneously, standardised in vitro assays must be defined to dissect and assess the quantity and quality of specific humoral and cellular immune responses directed towards the immunogen administered.

Moving antibody based vaccines ahead

Whilst protein immunogen regimens have elicited antibodies capable of binding challenge strains, these immune responses appear to be limited by the same restricted breadth apparent in natural infection [9]. Recently, however, isol-

ated highly potent broadly neutralising antibodies have confirmed that HIV infected individuals are able to produce precisely the kind of antibodies that are thought to be ideal candidates to provide protective immunity [36]. Structural analysis of the epitopes targeted by broadly neutralising antibodies has highlighted sites of vulnerability in the HIV envelope that are conserved across multiple strains, such as the gp120 CD4 binding site [12], gp120 V2V3 loops [10], gp120 glycans [10, 70] and gp41 MPER region [71, 72]. However, such broadly neutralising antibodies appear to be rarely elicited in vivo and some well characterised broadly neutralising antibodies possess fairly unusual characteristics (such as domain-swapped structure [73] or self-reactivity [74]), long CDR3 regions [13, 75] and many are highly affinity matured [10, 76]. Nonetheless, eliciting such antibodies by presentation of appropriate protein immunogens remains one of the most promising yet challenging routes to vaccine design. The key lies in defining an immunogen capable of overcoming the barriers to the development of broad antibody responses encountered in natural infection and focusing the immune response solely on the desired domain. Conformational masking, glycan shields and a high degree of flexibility combine to render the natural conformation of the viral envelope spike poorly immunogenic [37, 38]. Presenting the required domains in an engineered immunogen capable of maintaining and presenting this conformation without interference from shielding factors is the ultimate goal [77]. This rapidly progressing field is termed reverse vaccinology or rational design [77].

As discussed, all isolated HIV broadly neutralising antibodies have undergone a high level of affinity maturation. Therefore, despite construction of antigens expressing the epitopes of these antibodies, vaccinees may not be able to elicit similar antibodies immediately. Instead, identifying the germline precursor and partially matured ancestor antibodies that lead to development of the broadly neutralising paratope may inform design of a series of immunogens capable of guiding antibody maturation in vivo.

How much antibody must a vaccine elicit to be protective? Maintaining high antibody levels for prolonged periods may be difficult if vaccination is not boosted at regular intervals. NHP passive transfer studies have determined that the protection conferred by neutralising antibodies typically requires sera antibody concentrations that exceed the in vitro inhibitory dose 100 fold [14, 16, 17, 40, 78]. The same range of activity was found in human passive immunisation [46, 79]. Thus, if a vaccine is capable of eliciting approx. 10 µg/ml of an antibody [80], then the potency of that Ab must provide broad neutralisation with an inhibitory dose of less than 0.1 µg/ml. If elicited individually or in combination, the new highly-potent highly-broad antibodies may achieve this with increased breadth [13].

Will anti-retroviral treatment thrive where HIV vaccines have failed so far?

While prophylactic measures such as condom use [81] and male circumcision [82] dramatically reduce HIV transmission, they have not been practised sufficiently to halt the epidemic. Although no pharmaceutical regimen has yet provided a cure, patients with undetectable viral load are certainly less infectious, emphasising that appropriate prescription of anti-retroviral therapy (ART) can have a significant impact on the epidemic [83]. Recent publications have highlighted the potential of "treatment as prevention" [84, 85], and evidence that the prescription of certain small molecule anti-retrovirals to uninfected individuals serves as a prophylactic prevention strategy (preexposure prophylaxis, PrEP) is accruing [86, 87]. Both of these strategies are more efficacious in preventing transmission than the only effective vaccine tested to date [8]. However, while compelling in terms of efficacy widespread implementation of PrEP faces enormous difficulties. The fact remains that the majority of those infected with HIV worldwide do not have access to expensive anti-retroviral drugs even to treat infection [2]. Extending provision of lifelong ART not only to all infected individuals but potentially all at-risk individuals also, faces significant operational and financial hurdles and is unlikely to be the most cost-effective route to HIV elimination. In contrast, even a moderately effective vaccine could rapidly have tremendous impact [33]. Employing PrEP as an eradication strategy would depend upon a high degree of compliance by a large proportion of the population for many years. Sustained systemic treatment of healthy individuals with the currently approved anti-retrovirals is likely to do more harm than good, in view of the adverse effects associated with these medications [88]. Therefore, it is likely that PrEP will be restricted to certain high-risk settings and administered as required.

Many of these concerns also apply to microbicides, topically applied anti-retrovirals [87], although topical application may circumvent adverse effects and allow more widespread administration. In contrast, an effective vaccine may provide sustained protection following only a few immunisations.

Combining PrEP and vaccination

Inclusion of efficacious PrEP provision in HIV vaccine trials would certainly change the landscape of vaccine trial design. Efficacy trials in high-risk populations (AIDSVAX [3, 4] and STEP [5]) have found an incidence rate of 3–6% per annum, and in RV144 the incidence was well below 1%. These relatively low incidences render efficacy, sieve and correlate of protection analysis low-powered, and thus limit capability of detecting moderate efficacy or determining the mechanism of protection. In comparison, a vaginal microbicide containing tenofovir studied in the CAPRISA trial reduced HIV transmission to women during heterosexual intercourse by 39% [87]. Once microbicide efficacy is confirmed, this intervention may need to be recognised as a new standard of care, and thus will need to be provided during vaccine trials to both vaccine and placebo arms [89, 90]. In these circumstances the incidence of infection would decrease by at least 30–50%; a trial such as RV144, which followed 16,402 participants for 3.5 years and detected only 125 infections, would be under-powered to retrieve data for outcome analysis.

Ignoring difficulties in distribution, PrEP and microbicides are currently the most effective pharmaceutical measures

we have to protect in high risk settings. It is clear that vaccine development will require many more years to yield potent protection. In the meantime, targeting a lower-efficacy vaccine to a high proportion of the population, with simultaneous implementation PrEP for those at high risk, may be the most efficient route to eradication.

Both antibody and T cell based vaccines depend on eliciting potent CD4 T cell responses. Inducing activated CD4 T cells, which are highly susceptible to HIV acquisition [91], maybe a risky undertaking if no countermeasures are employed, as the outcome of the STEP trial suggested [62]. A combination of vaccination with PrEP may, in fact, overcome this potential adverse effect and provide added protection during the time vaccination stimulates and builds up immunity to HIV.

The quest continues

Despite the many remaining challenges, the goal of an efficacious HIV vaccine is more attainable now than ever. The immunogens currently undergoing clinical investigation [53, 88] have benefitted from the development of strong animal challenge models, and standardised in vitro assays for detection of elicited humoral and cellular immunity. Correlates of protection may yet be forthcoming from the RV144 trial analysis and further ongoing trials.

If the window of opportunity for conventional vaccine trials is being closed by efficacious PrEP, alternatives to large-scale efficacy testing must be found before the potential for eradication of HIV through vaccination is lost. In our opinion precise definition of the correlates of protection, together with efficacy testing in improved animal models, appears to be the only solution. Once efficacy of a given vaccine regimen has been defined in animal models and correlates of protection for this regimen have been defined in both animal models and medium sized human trials, vaccine licensing requirements could be relaxed to allow specific measures of immunogenicity to stand in as a surrogate for efficacy.

Funding / potential competing interests: This work was supported by the Swiss National Science Foundation grant Nr 310030_135527.

Correspondence: *Professor Alexandra Trkola, rer. nat. tec, Institute of Medical Virology, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland,*
trkola.alexandra[at]virology.uzh.ch

References

1 Zolopa AR. The evolution of HIV treatment guidelines: current state-of-the-art of ART. Antiviral Res. 2010;85(1):241–4.

2 UNAIDS Global report 2010 | UNAIDS Report on the global AIDS epidemic 2010. Available from: http://www.unaids.org/globalreport/Global_report.htm

3 Pitisuttithum P, Gilbert P, Gurwith M, Heyward W, Martin M, van Griensven F, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis. 2006;194(12):1661–71.

4 Gilbert PB, Peterson ML, Follmann D, Hudgens MG, Francis DP, Gurwith M, et al. Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. J Infect Dis. 2005;191(5):666–77.

5 Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008;372(9653):1881–93.

6 Gray GE, Allen M, Moodie Z, Churchyard G, Bekker L-G, Nchabeleng M, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis. 2011;11(7):507–15.

7 Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis. 2005;191(5):654–65.

8 Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209–20.

9 Munier CML, Andersen CR, Kelleher AD. HIV vaccines: progress to date. Drugs. 2011;71(4):387–414.

10 Walker LM, Phogat SK, Chan-Hui P-Y, Wagner D, Phung P, Goss JL, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science. 2009;326(5950):285–9.

11 Zhou T, Georgiev I, Wu X, Yang Z-Y, Dai K, Finzi A, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science. 2010;329(5993):811–7.

12 Wu X, Yang Z-Y, Li Y, Hogerkorp C-M, Schief WR, Seaman MS, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010;329(5993):856–61.

13 Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien J-P, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature. 2011;477(7365):466–70.

14 Hessell AJ, Rakasz EG, Poignard P, Hangartner L, Landucci G, Forthal DN, et al. Broadly neutralizing human anti-HIV antibody 2G12 is effective in protection against mucosal SHIV challenge even at low serum neutralizing titers. PLoS pathogens. 2009;5(5):e1000433.

15 Parren PW, Marx PA, Hessell AJ, Luckay A, Harouse J, Cheng-Mayer C, et al. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. J Virol. 2001;75(17):8340–7.

16 Hessell AJ, Rakasz EG, Tehrani DM, Huber M, Weisgrau KL, Landucci G, et al. Broadly neutralizing monoclonal antibodies 2F5 and 4E10 directed against the human immunodeficiency virus type 1 gp41 membrane-proximal external region protect against mucosal challenge by simian-human immunodeficiency virus SHIVBa-L. J Virol. 2010;84(3):1302–13.

17 Hessell AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, et al. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. Nat Med. 2009;15(8):951–4.

18 Mascola JR, Lewis MG, Stiegler G, Harris D, VanCott TC, Hayes D, et al. Protection of macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. J Virol. 1999;73(5):4009–18.

19 Seaman MS, Xu L, Beaudry K, Martin KL, Beddall MH, Miura A, et al. Multiclade human immunodeficiency virus type 1 envelope immunogens elicit broad cellular and humoral immunity in rhesus monkeys. J Virol. 2005;79(5):2956–63.

20 Rolland M, Gilbert P. Evaluating immune correlates in HIV-1 vaccine efficacy trials: what RV144 may provide. AIDS Res Hum retroviruses. 2011 Sep 9;

21 Pantaleo G, Koup RA. Correlates of immune protection in HIV-1 infection: what we know, what we don't know, what we should know. Nat Med. 2004;10(8):806–10.

22 DeVico A, Fouts T, Lewis GK, Gallo RC, Godfrey K, Charurat M, et al. Antibodies to CD4-induced sites in HIV gp120 correlate with the control of SHIV challenge in macaques vaccinated with subunit immunogens. Proc Natl Acad Sci U S A. 2007;104(44):17477–82.

23 Kim JH, Rerks-Ngarm S, Excler J-L, Michael NL. HIV vaccines: lessons learned and the way forward. Curr Opin HIV AIDS. 2010;5(5):428–34.

24 Burton DR, Desrosiers RC, Doms RW, Feinberg MB, Gallo RC, Hahn B, et al. Public health. A sound rationale needed for phase III HIV-1 vaccine trials. Science. 2004;303(5656):316.

25 Walker BD, Ahmed R, Plotkin S. Moving ahead an HIV vaccine: Use both arms to beat HIV. Nat Med. 2011;17(10):1194–5.

26 Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. Curr Opin Immunol. 2010;22(3):358–66.

27 Barouch DH, Korber B. HIV-1 vaccine development after STEP. Ann Rev Med. 2010;61:153–67.

28 Plotkin SA. Vaccines: the fourth century. Clin Vaccine Immunol. 2009;16(12):1709–19.

29 John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. Eur J Epidemiol. 2000;16(7):601–6.

30 Anderson RM, May RM. Immunisation and herd immunity. Lancet. 1990;335(8690):641–5.

31 The global commission for the certification of smallpox eradication. The global eradication of smallpox 1979. Available from: http://whqlibdoc.who.int/publications/a41438.pdf

32 Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, Cochi SL. Measles eradication: is it in our future? Am J Public Health. 2000;90(10):1521–5.

33 IAVI. Estimating the potential impact of an AIDS vaccine in developing countries – policy note 2010. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/2c678572-e031-4fc2-b412-0794e04c9409/IAVI_Policy_Notes_Estimating_the_Potential_Impact_of_an_AIDS_Vaccine_in_Developing_Countries_2010_ENG.pdf

34 Ariën KK, Vanham G, Arts EJ. Is HIV-1 evolving to a less virulent form in humans? Nature reviews. Microbiology. 2007;5(2):141–51.

35 Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. Proc Natl Acad Sci U S A. 2005;102(42):14943–8.

36 Clapham PR, Lu S. Vaccinology: Precisely tuned antibodies nab HIV. Nature. 2011;477(7365):416–7.

37 Wyatt R, Kwong PD, Desjardins E, Sweet RW, Robinson J, Hendrickson WA, et al. The antigenic structure of the HIV gp120 envelope glycoprotein. Nature. 1998;393(6686):705–11.

38 Schief WR, Ban Y-EA, Stamatatos L. Challenges for structure-based HIV vaccine design. Curr Opin HIV AIDS. 2009;4(5):431–40.

39 Pace MJ, Agosto L, Graf EH, O'Doherty U. HIV reservoirs and latency models. Virology. 2011;411(2):344–54.

40 Burton DR, Hessell AJ, Keele BF, Klasse PJ, Ketas TA, Moldt B, et al. Limited or no protection by weakly or nonneutralizing antibodies against vaginal SHIV challenge of macaques compared with a strongly neutralizing antibody. Proc Natl Acad Sci U S A. 2011;108(27):11181–6.

41 Huber M, Trkola A. Humoral immunity to HIV-1: neutralization and beyond. J Intern Med. 2007;262(1):5–25.

42 Hessell AJ, Hangartner L, Hunter M, Havenith CEG, Beurskens FJ, Bakker JM, et al. Fc receptor but not complement binding is important in antibody protection against HIV. Nature. 2007;449(7158):101–4.

43 Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. N Engl J Med. 2011;364(20):1943–54.

44 Keele BF, Giorgi EE, Salazar-Gonzalez JF, Decker JM, Pham KT, Salazar MG, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. Proc Natl Acad Sci U S A. 2008;105(21):7552–7.

45 Haaland RE, Hawkins PA, Salazar-Gonzalez J, Johnson A, Tichacek A, Karita E, et al. Inflammatory genital infections mitigate a severe genetic bottleneck in heterosexual transmission of subtype A and C HIV-1. PLoS pathogens. 2009;5(1):e1000274.

46 Trkola A, Kuster H, Rusert P, Joos B, Fischer M, Leemann C, et al. Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. Nat Med. 2005;11(6):615–22.

47 Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, et al. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. Nat Med. 2000;6(2):207–10.

48 McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol. 2009;10(1):11–23.

49 Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2011 Oct 25;12(1):36–44.

50 Kwong PD, Doyle ML, Casper DJ, Cicala C, Leavitt SA, Majeed S, et al. HIV-1 evades antibody-mediated neutralization through conformational masking of receptor-binding sites. Nature. 2002;420(6916):678–82.

51 Gupta SB, Jacobson LP, Margolick JB, Rinaldo CR, Phair JP, Jamieson BD, et al. Estimating the benefit of an HIV-1 vaccine that reduces viral load set point. J Infect Dis. 2007;195(4):546–50.

52 Brian Foley, John Mokili, Robert Funkhouser, Norman Letvin, Kalpana Gupta, Jon Warren, et al. Non human primate HIV/SIV vaccine trials database [Internet]. Available from: http://www.hiv.lanl.gov/content/vaccine/home.html. 2011

53 IAVI. Database of AIDS Vaccine Candidates in Clinical Trials [Internet]. Available from: http://www.iavireport.org/trials-db/Pages/default.aspx.

54 Hansen SG, Ford JC, Lewis MS, Ventura AB, Hughes CM, Coyne-Johnson L, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. Nature. 2011;473(7348):523–7.

55 Barouch DH, Liu J, Li H, Maxfield LF, Abbink P, Lynch DM, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. Nature. 2012 Jan 4;

56 Shiver JW, Fu T-M, Chen L, Casimiro DR, Davies M-E, Evans RK, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. Nature. 2002;415(6869):331–5.

57 el-Amad Z, Murthy KK, Higgins K, Cobb EK, Haigwood NL, Levy JA, et al. Resistance of chimpanzees immunized with recombinant gp120SF2 to challenge by HIV-1SF2. AIDS (London, England). 1995;9(12):1313–22.

58 Berman PW, Gregory TJ, Riddle L, Nakamura GR, Champe MA, Porter JP, et al. Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160. Nature. 1990;345(6276):622–5.

59 Sina ST, Ren W, Cheng-Mayer C. Coreceptor use in nonhuman primate models of HIV infection. J Transl Med. 2011;9(Suppl 1):S7.

60 Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, et al. Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. Science. 1999;283(5403):857–60.

61 Jin X, Bauer DE, Tuttleton SE, Lewin S, Gettie A, Blanchard J, et al. Dramatic rise in plasma viremia after CD8(+) T cell depletion in simian immunodeficiency virus-infected macaques. J Exp Med. 1999;189(6):991–8.

62 Gray G, Buchbinder S, Duerr A. Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. Curr Opin HIV AIDS. 2010;5(5):357–61.

63 Rolland M, Tovanabutra S, deCamp AC, Frahm N, Gilbert PB, Sanders-Buell E, et al. Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. Nat Med. 2011;17(3):366–71.

64 Benlahrech A, Harris J, Meiser A, Papagatsias T, Hornig J, Hayes P, et al. Adenovirus vector vaccination induces expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1. Proc Natl Acad Sci U S A. 2009;106(47):19940–5.

65 Haynes B, The RV144 Immune Correlates Working Group. The RV144 ALVAC/HIV Prime, rgp120 B/E Trial: Immune correlates analysis. In: AIDS VACCINE 2011, editor. AIDS VACCINE 2011. Bangkok, Thailand. Available from: http://www.hivvaccineenterprise.org/conference/2011/sites/default/files/PL01.04%2C%20Haynes.pdf

66 Chung A, Rollman E, Johansson S, Kent SJ, Stratov I. The utility of ADCC responses in HIV infection. Curr HIV Res. 2008;6(6):515–9.

67 Gilbert PB, Berger JO, Stablein D, Becker S, Essex M, Hammer SM, et al. Statistical interpretation of the RV144 HIV vaccine efficacy trial in Thailand: a case study for statistical issues in efficacy trials. J Infect Dis. 2011;203(7):969–75.

68 Cohen J. Unrevealed analysis weakens claim of AIDS vaccine "Success." Science Insider. 2009; Oct 5.

69 Leavy O. HIV vaccine results controversy. Nat Rev Immunol. 2009;9(11):755–755.

70 Trkola A, Purtscher M, Muster T, Ballaun C, Buchacher A, Sullivan N, et al. Human monoclonal antibody 2G12 defines a distinctive neutralization epitope on the gp120 glycoprotein of human immunodeficiency virus type 1. J Virol. 1996;70(2):1100–8.

71 Stiegler G, Kunert R, Purtscher M, Wolbank S, Voglauer R, Steindl F, et al. A potent cross-clade neutralizing human monoclonal antibody against a novel epitope on gp41 of human immunodeficiency virus type 1. AIDS Res Hum Retroviruses. 2001;17(18):1757–65.

72 Muster T, Guinea R, Trkola A, Purtscher M, Klima A, Steindl F, et al. Cross-neutralizing activity against divergent human immunodeficiency virus type 1 isolates induced by the gp41 sequence ELDKWAS. J Virol. 1994;68(6):4031–4.

73 Calarese DA, Scanlan CN, Zwick MB, Deechongkit S, Mimura Y, Kunert R, et al. Antibody domain exchange is an immunological solution to carbohydrate cluster recognition. Science. 2003;300(5628):2065–71.

74 Mouquet H, Scheid JF, Zoller MJ, Krogsgaard M, Ott RG, Shukair S, et al. Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation. Nature. 2010;467(7315):591–5.

75 Saphire EO, Parren PW, Pantophlet R, Zwick MB, Morris GM, Rudd PM, et al. Crystal structure of a neutralizing human IGG against HIV-1: a template for vaccine design. Science. 2001;293(5532):1155–9.

76 Wu X, Zhou T, Zhu J, Zhang B, Georgiev I, Wang C, et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. Science. 2011;333(6049):1593–602.

77 Nabel GJ, Kwong PD, Mascola JR. Progress in the rational design of an AIDS vaccine. Philosophical transactions of the Royal Society of London. Series B, Biological sciences. 2011;366(1579):2759–65.

78 Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, et al. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. J Virol. 2002;76(5):2123–30.

79 Trkola A, Kuster H, Rusert P, von Wyl V, Leemann C, Weber R, et al. In vivo efficacy of human immunodeficiency virus neutralizing antibodies: estimates for protective titers. J Virol. 2008;82(3):1591–9.

80 Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol. 2010;17(7):1055–65.

81 Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database System Rev. 2002;(1):CD003255.

82 Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev. 2009;(2):CD003362.

83 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657):48–57.

84 Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. 2011;365(6):110718073018079.

85 Anglemyer A, Rutherford GW, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database System Rev (Online). 2011 Jan;(8):CD009153.

86 Roehr B. Tenofovir works as pre-exposure prophylaxis against HIV, two studies confirm. BMJ (Clinical research ed.). 2011 Jul 15;343:d4540.

87 Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168–74.

88 Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. Antiviral Res. 2010;85(1):201–9.

89 Philpott S, Heise L, McGrory E, Paxton L, Hankins C. The challenge of defining standards of prevention in HIV prevention trials. J Med Ethics. 2011;37(4):244–8.

90 Rennie S, Sugarman J. Developing ethics guidance for HIV prevention research: the HIV prevention trials network approach. J Med Ethics. 2010;36(12):810–5.

91 Sodora DL, Allan JS, Apetrei C, Brenchley JM, Douek DC, Else JG, et al. Toward an AIDS vaccine: lessons from natural simian immunodeficiency virus infections of African nonhuman primate hosts. Nat Med. 2009;15(8):861–5.

92 Lloyd AL. The dependence of viral parameter estimates on the assumed viral life cycle: limitations of studies of viral load data. Proc Biol Sci. 2001;268(1469):847–54.