Review

Scientific and regulatory challenges in evaluating clinical trial protocols for HIV-1/AIDS vaccines – A review from a regulatory perspective

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Clinical development of prophylactic HIV/AIDS vaccines presents many scientific challenges that result in challenges for regulators reviewing clinical trial applications (CTAs). The World Health Organization (WHO) has the responsibility to provide technical support to these regulators. The search for an HIV/AIDS vaccine will only succeed through well-designed, -conducted and -controlled human efficacy studies reviewed and approved by regulators in countries worldwide, particularly in countries where the epidemic has hit hardest, such as in sub-Saharan Africa and Asia. This review summarizes the current candidates in development and focuses on challenges regulators face when reviewing CTAs, such as the evolving landscape of “standard of prevention,” trials in adolescents, adaptive trial designs, correlates of protection and their analysis, and access to successful vaccines. There are many unknowns in the field of HIV/AIDS vaccine development and often, there is not a clear right or wrong approach because of the scientific challenges described in this review. Consequently, regulators should not feel that decisions need be made in isolation, when there are many available international collaborative efforts and opportunities to seek expert advice. The WHO provides many such opportunities and support to regulators across the globe.

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1. Introduction – scope and purpose of review

Currently, the development of experimental preventive Human Immunodeficiency Virus Type 1 (HIV) vaccines includes a wide variety of innovative and complex approaches without precedent in other, licensed vaccines. International harmonization and standardization of regulatory practices will help to ensure that HIV vaccines are evaluated and licensed based on internationally accepted scientific criteria and standards. However, there are no international guidelines specific for the evaluation of HIV vaccines available, though a wide range of guidelines covering various aspects such as the production and quality control, nonclinical and clinical evaluation of biological products are available from WHO and UNAIDS and other international or national regulatory bodies (International Conference on Harmonisation — ICH, Food and Drug Administration — US FDA, and the European Medicines Agency — EMA; see Tables 1 and 2 in Appendix 1). Many of the principles are applicable to HIV vaccines. The new approaches that are being taken for HIV/AIDS vaccine development, e.g., vectored vaccines or heterologous prime-boost immunization, are not adequately covered by existing guidelines. Specific guidance and technical support are therefore, required to help regulators from all countries, particularly those in low- and middle-income countries (LMIC), understand the scientific rationale and challenges for HIV vaccine development and regulatory evaluation in order to build technical expertise for HIV vaccine evaluation and licensure.

Prophylactic HIV vaccine clinical trials, including efficacy trials, have been conducted worldwide. Many of the countries hardest hit...
by the HIV/AIDS (Acquired Immunodeficiency Syndrome) epidemic are in sub-Saharan Africa or Asia and most of those are LMIC or emerging market countries. Regulation of clinical trials in many LMIC, in which some HIV vaccine clinical trials are taking place, is still new and evolving. In some countries, regulators are primarily pharmacists and often they have more of a pharmaceutical background and are less experienced with vaccines or biologicals. Although they have extensive experience with registration of drugs, regulation of clinical trials of unlicensed biologicals, like HIV/AIDS vaccine candidates, can be more challenging. LMIC regulators often have experience with registration of vaccines that are included in the WHO Expanded Programme for Immunization (EPI) or certain other key vaccines relevant to their populations (e.g., malaria or meningitis A), but HIV/AIDS vaccine candidates differ in several key facets from childhood vaccines that have been in use for decades. However, LMIC regulators are gaining experience with HIV/AIDS clinical trial reviews and evaluation because of the number of clinical trials that have been conducted to date. With this experience comes the recognition that there are aspects of regulating HIV/AIDS clinical trials, borne from the scientific challenges and gaps in knowledge, which are not only challenging for regulators, but may create barriers to vaccine development and evaluation. It is these aspects that will be the focus of this and the companion review.

It should also be acknowledged that each country has its own legal framework that invests the regulators of that country with authority to oversee clinical trial authorization. Some countries do not have such legislation, and only drug registration is the legal authority of regulators. This diversity in legal frameworks poses an additional challenge to regulators in various countries, as well as to applicants who wish to work in a country in compliance with the law and established ethical principles. It should go without saying that a population for a clinical trial should not be chosen on the basis of a lack of legal authority for regulatory oversight of clinical trials in that country, but instead selected on the basis of established cohorts of HIV-at-risk populations who have the potential to benefit from the trial. In cases where the regulators do not have sufficient legal authority, trial sponsors/applicants should consider strongly engaging the WHO in trial review, through one of their advisory committees or through the Article 58 procedure, as well as informing in some manner, the local regulatory agency of their plans. In all cases, local ethics committees should have oversight.

Many of the aspects that challenge regulators reviewing HIV/AIDS vaccine clinical trial protocols were requested to be addressed in queries to WHO from regulators, manufacturers and vaccine developers. In particular, information regarding the status of the most promising/most advanced HIV vaccine candidates, appropriate methods for their evaluation and guiding principles that are applicable to specific vaccine formulations and their intended use were part of frequently asked questions. It will be important for regulators to distinguish between issues relevant to Phase 1 and 2 trials, which are not intended to address efficacy, but only preliminary safety and activity measures, from review issues specific to Phase 2b and Phase 3 trials, intended to demonstrate efficacy, and which may form the basis for ultimate licensure decisions.

2. Scientific challenges that create regulatory challenges for HIV/AIDS vaccine development

The scientific challenges faced by HIV/AIDS vaccine development are innumerable and have been reviewed many times over [1–9]. Nonetheless, from the perspective of regulators tasked with reviewing vaccine clinical trial applications (CTA), there are some scientific challenges that warrant reiteration, as they result in regulatory challenges.

2.1. Lack of human survivors

Often, empirical development of a vaccine starts by evaluation of the types and magnitudes of immune responses elicited in humans who survived the infection or disease (convalescents) or who clinically managed well the infectious organism to which a vaccine is sought. By understanding the immune responses in individuals who did well despite infection, one has a target response to aim a vaccine to meet. However, human survivors (“cures”) of HIV infections consist only of case studies, like the stem cell transplant recipient known as the “Berlin patient” [10]. These anecdotal case studies rarely result from a strictly immunological clearance of infection, but represent medical interventions with rare and extraordinary success. Simply put, once infected with HIV, the best that can be hoped at present is that the disease will be chronically managed with anti-retroviral and other therapies. There are no descriptions of immunologically-produced survivors from infection. So, there is no clear immunological target for how to prevent infection or disease. Thus, regulators, when faced with the review of immunological data for a candidate vaccine, have no greater insight than any other scientist in the HIV/AIDS vaccine field as to whether those data actually support advancing the candidate further in clinical studies. At best, a regulator must judge whether the candidate vaccine or regimen2 elicits the types of immune responses that the applicant claims to be the mode-of-action for the vaccine. Judging whether that claim of the mode-of-action may actually result in efficacy is not truly possible at present.

2.2. Lack of predictive animal model of efficacy

The next step in the development of a successful vaccine, after identifying what the target immune response to vaccination should be, is often to attempt to protect from an infectious challenge in an animal model using a candidate vaccine. Although there exist several animal models of HIV/AIDS that have yielded significant insight into HIV disease pathogenesis and other scientific insights, none have yet been fully predictive of the outcomes seen in the human efficacy studies performed to-date. In fact, each efficacy study performed in humans has had some supportive animal data suggesting efficacy would be seen, but in the end, the human efficacy study results were unpredictable and unpredicted by the animal data. One NHP model used in studies performed after the conclusion of RV144 was able to recapitulate the findings [11]. Whether this model will help predict future successful candidates remains unknown. For regulators, this means that the requirement of particular animal models to support clinical advancement of a candidate vaccine or candidate regimen would be an unreasonable expectation. While some animal data are needed to verify safety and activity (immunogenicity), challenge–protection models may be misleading and should be interpreted with significant caution. Such models may provide insight into a potential mechanism or mode-of-action, but cannot be taken to predict success of a candidate vaccine or regimen in humans.

2 Many HIV/AIDS vaccine candidates actually consist of complex regimens, termed prime-boost regimens, in which more than one immunogen may be given at the same or separate times, e.g., three primes with a DNA plasmid followed by a viral vector boost or primes with a poxvirus vector followed by boosts with a combination of poxvirus vector and proteins. Throughout the review, reference to vaccine or vaccine candidates or regimens will mean whatever complex regimen is proposed in a particular HIV vaccine clinical protocol rather than a single candidate immunogen as might be used in other diseases, e.g., measles.
2.3. Lack of validated correlate of protection

As a result of the two challenges described in Sections 2.1 and 2.2, the lack of human survivors and the lack of a predictive animal model for efficacy, immune correlates of protection remain poorly understood and poorly defined. Some data have emerged from the single efficacy study in which modest efficacy was achieved and these are discussed in the companion review and elsewhere [11,12]. Whether these potential correlates will hold true for other candidates or regimens or even be substantiated with similar regimens or highly related candidates, when studied in other populations of higher incident infection rates or infected by different routes of transmission or infected with different clades of HIV, remains to be tested. Plans are underway to do just that. Other vaccines have been licensed without identifying a definitive correlate of protection, e.g., although Human Papillomavirus (HPV) vaccine efficacy correlates with antibodies, the high efficacy seen in efficacy trials precluded identifying a level of antibodies below which efficacy was not established, i.e., an actual correlate. Likewise, pertussis vaccines, tuberculosis vaccine and rotavirus vaccines have all been licensed without definitively identifying the type or geometric mean titer (or concentration) of antibody (or immunological) responses required for protection. In the case of HIV/AIDS vaccines, not only is the type or titer of antibody needed undefined or the epitope target of such antibodies uncertain, it is unclear whether antibodies alone will be sufficient or if various types of T cell responses, or even innate immune responses, may also be required to achieve efficacy with a particular candidate or regimen. Likewise, it is unclear whether “sterilizing” immunity will need to be achieved or whether it might be possible for a successful immune response generated by a vaccine to abort an infection, i.e., whether transient infection that is cleared could be a clinically meaningful benefit to target.

For regulators, this makes review of the design of certain types of vaccine clinical trials more challenging, e.g., bridging studies, comparability or non-inferiority studies (e.g., lot consistency studies or clinical studies to support changes to manufacturing, if required). Even efficacy study design will be tricky. Efficacy will need to be established on the basis of prevention of acquisition of the HIV infection itself and not on the basis of any immunological correlate. Furthermore, virological or cellular correlates that have proven useful in drug approvals for anti-retroviral drugs, may be useful or important secondary endpoints of vaccine efficacy studies. Whether a vaccine can cause an infection to be transient, i.e., to be cleared or aborted, might be able to be addressed with a virological endpoint. However, immunological correlates will have to be identified, if possible, in the conduct of human efficacy studies (i.e., prevention of HIV acquisition in humans) and if they cannot be identified, then the design of bridging or lot consistency studies, etc., will remain a challenge. Similarly, the timing of conducting such studies (after the successful efficacy study is completed and the correlate of immunity identified, if it can be) can be challenging for a regulator to know what to require of an applicant. Ideally, they would be conducted before the end of the efficacy study to speed time to licensure after successful efficacy results are seen, but this may be infeasible for the reasons noted. Regulators should gain agreement with clinical trial applicants on these points well in advance of marketing authorization applications.

What is known, however, is that the immune response in an infected individual does drive escape mutations to arise in the virus with which s/he is infected, as well as reducing the viral load from the peak at acute infection before the immune system can fully respond to the infection down to a “set-point.” Mutations arise both in known antibody epitopes and in known T cell epitopes [13,14]. In many individuals, even effective neutralizing antibodies develop and these drive viral evolution [15]. However, these neutralizing antibodies develop rather late in the infection, after months of chronic infection. The virus seems to always stay one step ahead of the infected person’s immune response against it. Thus, which immune response might correlate with protection has not been identified, and various scientists have differing opinions on this matter. However, the fact that the immune system does drive viral evolution and immune escape demonstrates the effectiveness of some immune responses. In natural infections, the immune response may be too little or too late, but vaccination might be able to tip those scales in favor of the immune system.

2.4. Variability

Another scientific challenge is that of variability. Strain variability is greater for HIV than any other viral infection. Infected individuals do mount immune responses to their infecting strain, but these immune responses do not clear the viral infection completely. In many individuals, neutralizing antibodies arise, but they arise late in the infection. As stated above, both T cell responses [14] and neutralizing antibodies [13] in the infected individual can generate immune pressure causing the infecting virus to mutate to escape this immune pressure. These escape mutants seem to keep continually ahead of the immune response. However, as a consequence, novel viruses are transmitted to others, ever expanding the viral diversity. Consequentially, strains differ by their relative sensitivity or resistance to antibody-mediated viral neutralization. Also, there are a variety of routes of transmission against which one would like an HIV vaccine to protect. Populations vary in their degree of risk of exposure and infection and whether or not the degree to which a vaccine might be protective against occasional and unpredictable exposure (e.g., general population) or against relatively frequent exposure [e.g., discordant couples or commercial sex workers (CSW) working within populations with high prevalence] could be variable.

2.4.1. Viral genetic or strain variability

HIV-1 consists of four major types (M, N, O, and P), each of which represents an emergence of HIV in humans from SIV of chimpanzees; thus, having occurred on four separate occasions [16]. Within the main group, there are sub-types or genetic clades grouped into six sub-types (A, B, C, D, F, and G) and numerous circulating recombinant forms (e.g., A/E, A/G, B/C). In part this is due to the relative lack of fidelity of the HIV polymerase, as with many RNA viruses. In part it is due to immunological pressure, or in the case of those on anti-retroviral therapy, pressure to resist the therapy and continue to replicate in the face of it. The meaning of this genetic variability on immunological variability is unclear, as HIV has never been “serotyped” per se, like many other viruses have. In part, this is because it is so unclear what type of immune response is protective (antibodies or cells, systemic or mucosal, neutralizing or non-neutralizing, against which viral protein, etc.). As a result, some vaccine candidates or regimens strive for clade-matching to the region or population in which studies will be performed, whereas others have attempted to address global variability with a multi-clade or mosaic/consensus approach. Likewise, some candidates have been focused on the envelope glycoprotein and others have taken a multi-genic approach. It remains unclear which will be needed for success. Thus, when regulators review a clinical trial application (CTA), they should evaluate which approach is being taken and expect the applicant to justify their approach in some reasonable manner, e.g., providing immunology data that scientifically support that the approach might achieve its aim.
2.4.2. Immunological variability or variability in sensitivity to antibody neutralization

It was observed in the early 1990’s that some strains of HIV seemed much more resistant to antibody-mediated neutralization than others [17]. Neutralization assays were developed over the whole of the 1990’s and the 2000’s to become better able to distinguish between these differences. To date, no vaccine candidate or regimen has been successful at eliciting broadly neutralizing antibodies against the toughest-to-neutralize strains, despite the fact that such antibodies do develop in some infected individuals. Efforts are underway to rationally design immunogens capable of eliciting broad neutralizing antibodies. In the meantime, such broadly neutralizing antibodies, recombinantly made into monoclonal antibodies, are being explored as research reagents and for clinical use. Importantly, to aid distinguishing the ability of various sera, either from infected individuals or from vaccinees, or monoclonal antibodies to neutralize various strains of HIV, a tier-based ranking system was devised [18]. Strains of HIV are designated as being “Tier 1” if they are relatively easy to neutralize by many antisera. “Tier 2” strains are more difficult to neutralize and may only be recognized by a few, more potent or broader antisera. Often, there may be good recognition by an antiserum or antibody of strains within a clade, but significantly less across clades. Even within clades, there is significant variability by antiserum to recognize strains. The most potent and broadest of the new generation of monoclonal antibodies can neutralize across clades to a considerable extent [19–23]. Regulators may need to consider the existing human clinical immunogenicity data (as well as animal data) for a vaccine candidate or regimen, which is expected to elicit antibodies, for which they are reviewing a CTA for an efficacy trial (or advanced phase trial) to evaluate the ability of that regimen to elicit antiserum that will recognize the predominant clade of strains in their country or region. While the regimen may not elicit broad neutralization, the applicant should have evaluated this aspect and should provide information in this regard for regulatory review, in the cases of regimens expected to elicit antibodies.

Additionally, non-neutralizing antibodies can have positive impact on killing infected cells or preventing infection of new cells. These functions have been recently reviewed [24]. If the applicant proposes a mode-of-action through such non-neutralizing antibodies, they should provide evidence that their candidate vaccine elicits them (either from animal studies or early human trials or both).

2.4.3. Variability in route of transmission

HIV can be transmitted sexually by penile exposure (heterosexual or MSM), vaginal exposure (heterosexual), or rectal exposure (MSM or heterosexual in women), as well as intravenously (Intravenous Drug Users/People Who Inject Drugs, unsafe blood supply, or tainted needles/needle sticks) or from mother to fetus or neonate intrapartum, peripartum, or post-partum during breastfeeding. Depending on the route of transmission, one could envision that it may be easier or more difficult for a vaccine to protect against infection. Similarly, different types of immune mechanisms may play a role in protection against different routes of transmission, e.g., mucosal immunity vs. systemic immunity. One could argue that in the case of intravenous exposure, it may be easier to protect (robust antibody response in blood stream immediately “on the scene”) or more difficult (entry bypasses normal immune mechanisms and provides ready access to target cells for infection) than other routes of transmission. Whether this variability in routes of transmission will impact vaccine efficacy remains unknown. Certainly, the amount of virus in the exposure inoculum is expected to vary by route of exposure. The impact of this fact on whether a vaccine will protect some populations with lower exposure doses and not those with higher exposure doses is concerning. Consideration will need to be taken by regulators regarding whether to require different efficacy trials in each population or enrollment in the same efficacy trial of various populations, or whether bridging into various populations might be considered upon completion of a successful efficacy trial in one or more populations. Likewise, the uniformity or variability of the population to be enrolled (all by similar or same route of exposure or enrollment for risk by various routes) should be justified by the applicant and that justification should be evaluated by the regulator.

2.4.4. Variable epidemiology

Some scientists have suggested that the modest efficacy seen in the RV144 study (described in the companion review) was as a result of the low incidence of HIV infection found in the general population in Thailand of those enrolled in the study. They have further suggested that success might not be recapitulated in a higher risk population (e.g., the general population in sub-Saharan Africa, discordant couples, CSW in high prevalence settings). However, arguably, anyone who becomes infected with HIV has had a high risk exposure by definition. What is unclear is whether a “high risk exposure” in the general population in Thailand resulted as a lower viral load transmission (fewer viruses in the exposure inoculum?) than would be a “high risk exposure” in the general population in some countries in sub-Saharan Africa (more viruses in the exposure inoculum?). It certainly could be easier for a vaccine to protect someone from a lower inoculum than a higher one. In most cases of sexual transmission, infection appears to be established by a single or no more than a few viruses, based on studies of viral diversity in acute infections [25,26]. It is nonetheless unclear whether this variability in HIV prevalence in different populations makes a difference for efficacy of a protective vaccine. Another aspect of note is the risk per exposure. Populations in which more encounters with HIV-infected individuals are likely per potential exposure, the higher overall risk for infection. Evidence from NHP studies with repeated low-dose exposures permit estimates of vaccine efficacy per risky exposure. The combination of inoculum size and repeated risky exposures may increase risk of infection in higher prevalence populations; hence, such populations may need a more potent vaccine in order to have efficacy. A corollary to this might be that a vaccine effective in a lower prevalence population may not be effective in a higher prevalence population. However, should discordant results be seen if multiple efficacy studies (or in sub-group analyses within a single one) are undertaken in different populations with varying risks of exposure, regulators need to consider what indication they might approve for such a vaccine, i.e., in which populations might the vaccine be indicated in the label. Regulators will need to consider also whether foreign efficacy data will support approval in their country, based on similarity or differences of the risks and routes of transmission and clades of circulating strains. It will be logistically impossible to recapitulate efficacy trials in every region/population type. What is scientifically needed to support label claims remains unclear.

2.5. Vaccine-induced sero-positivity or sero-reactivity (VISP or VISR)

Although this issue is less “scientific” and more a pragmatic one with potential to result in social harms, it does raise a regulatory challenge. In the United States, where more than 100 HIV/AIDS vaccine clinical trials have been conducted, the U.S. NIH and the U.S. Food and Drug Administration (FDA) have worked together to ensure that labeling of licensed HIV test kits make clear that participation in an HIV/AIDS vaccine study may result in a positive or indeterminate test. So, such a result leads to the need to rule out
the possibility that the individual is not, in fact, already infected with HIV, but is sero-positive or sero-reactive due to having been vaccinated with an investigational vaccine candidate in a clinical trial. Regulators in other countries may need to consider working with the blood industry in their countries to raise awareness of this possibility, as trials become more prevalent or large studies are undertaken. Particularly when efficacy studies are performed, as they generally enroll subjects at some risk of HIV infection, means to distinguish between sero-positivity or sero-reactivity due to vaccination vs. due to actual infection will be needed. As many HIV/AIDS vaccine candidates have become complex, containing many, if not most, of the HIV proteins, antibodies may be generated against most, if not all, of the antigens detected by test kits approved and commonly used in your country. Consequently, it may be necessary to rely on plasma RNA tests or other tests developed for the specific purpose of distinguishing between vaccination and true infection (DIVA), as no viral RNA would be present in the plasma of individuals who had been vaccinated in a clinical trial but was not infected. Additionally, once a successful vaccine is demonstrated and licensed, screening practices for HIV infections within countries that take up the successful vaccine may need to rely on plasma RNA test kits rather than serological ones. A workshop on this subject was held in 2012 and consultation of the meeting report may be insightful.

3. Vaccine candidates that may advance towards efficacy trials

The companion review outlined the outcomes of the completed efficacy studies performed to date. At present, there are no ongoing efficacy studies. HIV/AIDS vaccine development must continue with as much urgency as ever. Future efficacy studies are being planned with candidates similar or related to the modestly successful regimen from RV144 and with candidates and regimens that have shown promising safety profiles and immunogenicity results in Phase 2a studies. These will be described below. Many other candidates are in the pipeline, either in Phase 1 or 1/2, or in preclinical development. Primarily, clinical candidates will be described below. Regulators may receive CTAs for review to support future clinical trials of some of these investigational candidates. Existing data are, thus, summarized in this section.

It will be important for regulators to distinguish between early phase trials they may be asked to review and efficacy trials (either pilot or pivotal). As explained in the companion review, regulators should not focus on the nomenclature of the trial phase, but instead focus on the principal aims of the study to either gain preliminary data of safety and immunogenicity or to gain efficacy data. For those studies aimed at efficacy, a distinction exists between those intended to primarily generate hypotheses to be tested in pivotal efficacy trials and those testing such hypotheses, i.e., the pivotal, licensure-supporting trials. Concurrence from regulators must be gained for all phases and types of clinical trials of HIV/AIDS vaccines. However, regulators may wish to focus their energies on the most careful review and consideration of the pivotal trials, the data from which they will subsequently be asked to review for licensure or registration (marketing authorization).

3.1. Reprise of RV144 in South Africa

Because the RV144 regimen was designed specifically to match the epidemic in Thailand, where the study was performed, plans to move forward with efficacy testing in South Africa, where clade C infections predominate, requires redesigning the candidate regimen. A new ALVAC related to vCP1521, but expressing clade C antigens, is in development by Sanofi Pasteur (http://www.sanofipasteur.com/, accessed 10/14/2014, France and USA). They have partnered with Novartis (http://www.novartis.com/, accessed 10/14/2014, USA), another major global vaccine manufacturer, to develop the protein components, which will also be clade C. Novartis also brings to the regimen a potentially more potent (and possibly one that will result in more durable immunity) adjuvant, MF59, which has an established safety profile and is contained in a licensed influenza virus vaccine. The plans for this new regimen of ALVAC and MF59-adjuvanted protein may include incorporation of additional boosts to extend the durability of the immune response. In addition, due to evolving business relations between Novartis and GlaxoSmithKline (http://www.gsk.com/, accessed 10/14/2014, UK), other adjuvants may be considered, such as GSK’s “Adjuvant System” (AS##).

The plans for moving rapidly from Phase 1 to Phase 3 are supported by the P5 partnership, described in the companion review. Initial studies are underway in South Africa and this may be extended to also include Thailand. Thus, a regional approach to this vaccine combination is being considered, with the first place that licensure would likely be sought being South Africa or southern Africa, where clade C infections predominate. The extent of the epidemic in this region supports the concept of seeking licensure there first. As the new regimen is highly similar or related to the RV144 regimen, regulators will likely be asked to consider data from RV144 to support licensure, should the new regimen also prove efficacious and safe. However, because all of the components of the new regimen are in fact, new products, prudence warrants conduct of Phase 1 studies initially. If safety and immunogenicity profiles seem similar to those established for the RV144 regimen, rapid advancement to Phase 3 seems likely. Due to the urgency to find and license a successful HIV/AIDS vaccine, all due haste should be taken by the P5 to advance candidates related to those that have shown modest efficacy already. In fact, spokespersons for the P5 have stated that their goals are “to substantiate and extend the RV144 results.” [27] Further goals include: to extend the results to a higher risk population, to expand geographic scope, to enhance level of efficacy, to prolong duration of protection, to identify immune correlates of protection and to continue to build a public-private partnership for success. A successful outcome of an efficacy study in South Africa would substantiate the controversial results of RV144. By enhancing the efficacy or durability of efficacy with the new regimen and testing in a new region and population with increased incidence of HIV acquisition, P5 hopes to extend the RV144 results.

3.2. Phase 2A headed to phase 2B

There are some candidate vaccines that have successfully conducted or are currently conducting Phase 2a studies. These candidates are likely to move forward to pilot efficacy testing or Phase 2b studies. The most advanced candidates include DNA priming with poxvirus boosting or alternative (to ALVAC) poxvirus priming with protein boosting or more complex regimens with DNA priming, followed by poxvirus, then protein.

There has been considerable discussion about conducting pilot efficacy trials with adaptive trial designs, in which multiple candidate regimens would be compared to a single placebo arm. Futility analyses and analyses that would rank the various regimens at interim timepoints in the study would permit “dropping” the arms that are not likely to demonstrate efficacy or which are more poorly efficacious and continuing the study with only the most
promising regimens. This approach, which is perceived to be more efficient, hinges on all candidate regimens being ready for efficacy testing at approximately the same time and that the study design for efficacy testing of each regimen be the same. It may be that such a study design would be conducted for scientific research purposes, rather than strictly to support vaccine development leading to licensure. Such a “research track” design is being considered. The purpose would be, in addition to the gaining of scientific knowledge and potentially, identification of correlates to formally hypothesis-test in subsequent studies, to down-select from various potential candidate regimens, since animal models have not proven predictive for this purpose, as down-selection with other drug development often occurs through the use of animal studies.

3.2.1. Geovax Labs, Inc. (http://www.geovax.com/, accessed 10/14/2014, USA) has been developing products that are the result of the scientific concepts of Dr. H. Robinson, formerly of Emory University (USA), and Dr. B. Moss and colleagues of the NIH (USA). Dr. Robinson developed DNA plasmid vaccine candidates to serve as a prime in conjunction with the Modified Vaccinia Ankara (MVA) vectors developed by Dr. Moss et al. The DNA plasmid vaccine candidates include JS-2 and JS-7, along with JS-7 adjunction with a GM-CSF-expressing plasmid, which is in early development. JS-7, the current lead candidate, expresses most of the genes of HIV, with several inactivating mutations and/or deletions — gag, pro, RT, gp120, gp41, tat, rev, and vpu from clade B. Of note however, is the fact that the vaccine does generate viral-like particles, because the expressed Gag polypeptide is myristoylated. The current lead MVA vector, MVA/HIV62, expresses Gag, Pro, RT, gp120 and a truncated gp41, also from clade B and also containing certain inactivating mutations [28]. The DNA priming series is delivered at doses of 3 mg followed by MVA boosts at 10^8 PFU, although lower doses have also been studied. Furthermore, different regimens have been studied — either two DNA primes followed by two MVA boosts at 0, 2, 4, and 6 months or 3 MVA's (without DNA priming) at 0, 2, and 6 months. Each of these regimens has strengths, as will be discussed below in Section 3.2.1.2.

MVA is a poxvirus vector, like ALVAC, although the species of origin is cowpox. Derived from a strain of vaccinia by serial passage through chicken eggs, MVA spontaneously lost several genes as a result of an induced mutagenic event, which is of major degree in human cells and is not propagated to any significant degree in human cells and is not believed to replicate in humans. So, like ALVAC, MVA is considered to be a non-replicating (in humans) poxvirus vector. MVA was used in Germany as a smallpox vaccine in the 1970’s, so there is considerable human experience (>100,000 people) with the non-recombinant virus, as a prophylactic vaccine. MVA has also been licensed in the current era for use in biological-warfare-at-risk populations like deployed military personnel, or has been stockpiled for this purpose (for use in the general population at the time of a biological attack).

3.2.1.1. Safety. Several clinical trials have been completed, including a Phase 2A trial [28]. The most common adverse experiences included pain and tenderness at the injection site — ~75% of recipients of DNA plasmid or placebo experienced mild to moderate pain and/or tenderness (1st boost) and ~25% (2nd boost) of recipients of the MVA or placebo experienced mild to moderate pain (27%). Systemic reactions were experienced at no more than moderate severity with the majority experiencing no or mild reactions in recipients of DNA plasmid, MVA boost, or placebo. Around 40% of subjects experienced mild systemic reactions with the initial prime (DNA plasmid or placebo), with decreasing percentages with each subsequent inoculation. Among other types of adverse experiences, ~20% of subjects had mild experiences that were possibly-related to vaccination and only ~2% of subjects had moderate experiences that were possibly-related to vaccination. Less than 10% of subjects had AEs that were probably or definitely-related to vaccination, with the majority of those being mild. One SAE considered definitely-related to vaccination was an allergic reaction starting within 15 min of receipt of the second dose of MVA. The symptoms resolved within 2 h and no further vaccinations were given to this participant. HVTN 065 [28], a Phase 1 study, demonstrated a similar safety profile. Approximately 20% and 50% of subjects experienced mild pain and/or tenderness at the injection site following the DNA plasmid primes or MVA boosts, respectively. Approximately 20% of subjects experienced moderate pain and/or tenderness at the injection site following the MVA boosts. When MVA was given as a series of three inoculations, each was accompanied with nearly 100% of subjects experiencing pain and/or tenderness at the injection site, the majority of these being mild in nature, and ~20% being moderate. In comparison, among placebo recipients, only mild pain and/or tenderness at the injection site was observed in less than or approximately 50% of subjects. The profiles of mild to moderate systemic reactions looked nearly identical between placebo recipients and vaccinees who received either the DNA-DNA-MVA (DDMM) regimen or the DNA-DNA-MVA-MVA (MMM) regimen, with perhaps slightly more reactions in those getting MMM. It was stated that 7 AEs were probably or definitely-attributed to vaccination and six of these were mild local reactions. The last of these was an individual who had a moderate decrease in neutrophil count 14 days after the initial DNA priming dose, which resolved and did not recur on subsequent doses. No other laboratory abnormalities and no findings of abnormal EKG findings were observed in this study, which could be attributable to vaccination.

In theory, concern raised by clinical trials of new generation smallpox vaccines (vaccinia grown in cell culture systems) of cardiac complications, particularly myocarditis or perimyocarditis, could be of issue with poxvirus-vectored vaccines and regulators have expected increased scrutiny for such AEs. This theoretical concern has not been observed so far with MVA. The findings of abnormal EKGs were less than or approximately 50% mounted neutralizing antibodies against Tier 1 (more difficult-to-neutralize) viruses.

3.2.1.2. Immunogenicity. Immune responses in HVTN 205 [29] were as follows, with the initial number being for the DDMM regimen and the second number being for the MMM regimen:

- 66% and 43% mounted CD4 responses;
- 21% and 15% mounted CD8 responses;
- 47% and 70% mounted antibodies against gp120;
- 93% and 95% mounted antibodies against gp41;
- ~30% and ~65% mounted neutralizing antibodies against Tier 1 (easier-to-neutralize) viruses;
- ~15% and ~40% mounted neutralizing antibodies against Tier 2 (more difficult-to-neutralize) viruses.

Thus, the DDMM regimen elicited higher percentages of responders with CD4 responses (p = 0.01). However, the MMM regimen elicited higher percentage of responders with antibodies against gp120 (p = 0.0001) and neutralizing antibodies against Tier 1 and Tier 2 (p = 0.02) viruses. Among responders, the highest frequency CD4 cell responses were against Env (mean of ~0.1% and ~0.2%, respectively for DDMM and MMM) and Gag (mean of ~0.1% and ~0.1%, respectively for DDMM and MMM). Only 2 responders to pol were noted in the DDMM group. The magnitude of CD8 cells was somewhat higher as follows: means of ~0.3% (DDMM, against Env), ~0.1% (MMM, against Env), ~0.2% (DDMM, against Gag), ~0.4% (MMM, against Gag), and ~0.09% (DDMM, against Pol).
Binding serum IgG antibody magnitudes were on the order of mean reciprocal titers of 6800 and 25,000, respectively for DDMM and MMM, for a consensus gp140 (a truncated gp160 without the transmembrane domain and cytoplasmic tail), 24,000 and 25,000 for gp41, and 29,000 and 29,000 for p24 (Gag). Mean titers were similar with DDMM and MMM, though MMM trended to higher means, particularly for gp120 and gp140. Serum IgA binding antibodies were low in terms of responders, with almost none against gp120, and less than 13% of responders with IgA in the serum against gp41 or p24. Strong responses were seen to the immunodominant gp41 epitope and antibody avidity was higher in the MMM group.

The data published from HVTN 065 provides the following immunogenicity information: CD4 responses were observed in 77% of subjects receiving the DDMM regimen that was also used in HVTN 205, i.e., the “full dose.” Whereas only 44% of subjects receiving the MMM regimen mounted CD4 responses to vaccine antigens. The magnitudes of these responses were between 0.07 and 0.17% of total CD4 cells. These CD4 responses persisted, and at six months post-last-dose, 38% and 8%, respectively, in the DDMM and MMM groups. CD8 responses developed in 42% and 17% of subjects on the DDMM and MMM regimens, with magnitudes between 0.06 and 0.065%. Like the CD4 responses, the CD8 responses persisted to six months post-last-dose with 38% and 4% responders, respectively, in the DDMM and MMM groups. It was stated that responses did not differ between genders. Responses were directed primarily to Gag and Env antigens.

Although T cell responses were better for the DDMM group, in regards to antibody responses, the MMM group appeared superior. 96.6% of subjects receiving MMM seroconverted to HIV antigens. The magnitudes of these responses were between 0.07 and 0.17% of total CD4 cells. These CD4 responses persisted, and at six months post-last-dose, 38% and 8%, respectively, in the DDMM and MMM groups. CD8 responses developed in 42% and 17% of subjects on the DDMM and MMM regimens, with magnitudes between 0.06 and 0.065%. Like the CD4 responses, the CD8 responses persisted to six months post-last-dose with 38% and 4% responders, respectively, in the DDMM and MMM groups. It was stated that responses did not differ between genders. Responses were directed primarily to Gag and Env antigens.

The safety of the DNA plasmid prime has been demonstrated in EV02 and EV03. The EV03 study, although completed, is not yet published. In EV02, all participants experienced local reactogenicity following the DNA priming doses, mostly pain and/or erythema at the injection site. All of these reactions were mild, except for two subjects with moderate pain. No differences were noted between reactions following the first or second vaccination. Systemic reactions were noted in 57% of subjects following DNA priming doses, mostly malaise and headache, while at the same time, 35% of subjects who would later receive NYVAC, but had received no vaccinations in the other arm of the study, experienced similar events. These reactions were mostly mild, with a few reactions of moderate malaise, myalgia, and/or headache. Two events of malaise lasted for more than seven days. Descriptions of lab abnormalities, SAEs, and withdrawals related to AEs are described in McCormack et al. [31].

The safety of the NYVAC vector has been demonstrated expressing various antigens. The exact construct, NYVAC-C, has been tested in EV01, EV02, EV03 and HVTN 078. HVTN 078 contained regimens with Ad5 and is not summarized here, as these will not advance. See Bart et al. (2014, 32). In EV01, there were no serious AEs or severe ones (grade 3 or 4). Only one grade 2 local reaction, induration, was observed after the second inoculation and none after the first. The most common local reactions were pain (after either dose) and/or erythema (after the 2nd dose) at the injection site. The proportion of subjects experiencing erythema was significantly greater after the second than the first immunization (p < 0.002). Systemic reactions included the following: chills/rigors, malaise, myalgia, headache, nausea. These were experienced quite infrequently after the first dose and after the second dose by less than half of subjects, with malaise being the most frequent at 40%. Laboratory abnormalities and other AEs are described in Bart et al. (2008, 33).

In EV02, most subjects experienced pain and/or erythema at the injection site following a NYVAC injection. The majority were mild in severity. Four subjects experienced moderate local reactions of pain, swelling, and/or itching. Two subjects experienced severe induration or pain, respectively, after NYVAC either as a boost or when given alone without a DNA prime. There were no significant differences in the pattern of local reactions following NYVAC given as a boost or when given without a prime. Likewise, the majority of systemic reactions were mild. Four moderate events were observed following NYVAC inoculation: headache, malaise, myalgia, and/or
chills/rigors. One subject had severe myalgia. Laboratory abnormalities and further description of AEs may be found in McCormack et al. [31].

Like MVA, NYVAC vectors could also be associated with cardiac-related AEs (myopericarditis) that were seen in clinical trials of vaccinia produced in cell culture. Monitoring for such AEs, either symptomatic or asymptomatic, have been included in various trials of NYVAC vectored HIV/AIDS vaccine candidates. This is an important issue for future regulatory oversight of these vaccines.

Overall, the regimen (2 DNA primes at 4 mg each followed by 2 NYVAC boosts at >10⁶ TCID50) appears to be well-tolerated, with most subjects experiencing some local reactions, mostly mild and transient in nature, with mild pain at the injection site being the most frequent experience. Mild malaise was the most frequent systemic complaint.

3.2.2.2. Immunogenicity. In EV02, immunogenicity for one of the regimens that may be the most likely to move forward, 2 DNA primes followed by 2 NYVAC boosts, was 83% responders as measured by ELISpot assay. For those who completed the full regimen, the response rate was 90%. At peak response, two weeks post-last-vaccination, ELISpot values ranged from 100 to 1100 SFU/million cells. Almost half of responders (median response) had ELISpot values exceeding 600. Responses to Env were the most frequent with fewer than half responding to Gag or Pol and only one responder to Nef. Fewer than half responded to Env and one other peptide pool. All responders generated CD4 responses and 47% generated CD8 responses. The CD4 cells generated expressed (1–40%), 2 (40%), or 3 (20%) cytokines (γ-interferon, IL-2, and/or TNF-alpha). The CD8 cells expressed 1 (25%), 2 (35%), or 3 (slightly more than 25%) cytokines, or all 3 cytokines and CD107a (10%), a degranulation (killing) marker. Epitope mapping for responders to Env revealed an average of 4.2 peptides (range 2–8) being recognized. There was a trend for women to respond better than men. Prior vaccinia receipt did appear to impact the magnitude of responses to the DNA prime, NYVAC boost regimen, in men (p = 0.03) and women (p = 0.05) at the peak time point. Approximately half of responders retained CD8 responses as long as one year post-last-vaccination, with magnitudes that were not significantly different from earlier timepoints (p = 0.09) [31,34].

Also at two weeks post-last-vaccination, 75% of subjects had developed antibodies to the Env in the vaccine. However, these responses were transient and only one subject had detectable antibody responses six months after the last vaccination. The antibodies generated in responders did not have neutralization capacity.

In EV03 [35], in which three DNA primes and a NYVAC boost were compared to the regimen described above (two primes, two boosts), 94% of subjects responded at the peak time point in the regimen with three primes vs. 81% in the regimen with two primes. The peak magnitudes were a mean of 774 SFU/million cells (three primes) vs. 398 SFU/million cells (two primes). Antibody responses were not described for this study.

3.2.3. Karolinska Institutet DNA plasmid prime with USMHRP MVA boost

Scientists at the Karolinska Institutet in Sweden have teamed up with those at the USMHRP to develop a prime-boost regimen with a DNA plasmid vaccine, termed HSIV, expressing Env from clades A, B, and C. Gag from clades A and B, and clade B RT and Rev and the USMHRP MVA, termed MVA-CMDR, expressing Env from clade E and Gag-Pol fusion protein from clade A. Not only is the regimen heterologous for the vectors but also heterologous for the antigens expressed. The regimen has included use of the Biojector® 2000 to deliver the DNA plasmids i.m. (doses of 3.8 mg total of the 7 plasmids) or i.d. (0.6 or 1 mg total). The DNA plasmids have been given with or without protein GM-CSF at 150 mcg at the site of injection of the plasmids, if given i.m., or by the s.c. route; or under the site of injection of the plasmids, when given i.d.. The MVA boost is given at a dose of 10⁶ PFU (generally i.m., although i.d. was also explored with a dose of 10⁵ PFU). One schedule of the regimen that has been explored is 0, 1, and 3 months for the DNA plasmid primes and month 9 (and in one trial, 21) for the MVA boost. Another schedule explored in TaMoVac-01 was DNA priming at 0, 1, and 3 months with MVA boosting at months 7 and 10.5.

Trials have been conducted in Sweden and in the United Republic of Tanzania (Tanzania). Studies HIVIS 01/02 were Phase 1 studies. The HIVIS 03 study conducted in Tanzania was a Phase 1/2 study. Additional Phase 1/2 studies include: HIVIS 04, HIVIS 06, TaMoVac-01 in Tanzania and HIVIS 05 and HIVIS 07 in Sweden. Only the results of HIVIS 01, HIVIS 02, HIVIS 03, and TaMoVac-01 are published at present [36–39].

3.2.3.1. Safety. In HIVIS 01 and 02 [36], in the arms that did not receive the protein GM-CSF, which could confound the safety profile of the DNA plasmid prime, MVA boost regimen, the vaccines were well-tolerated. Only four subjects experienced grade 2 AEs following the DNA plasmid primes. All other AEs were mild. Following the MVA boost, when given i.d., there were mild local reactions, while when given i.m., there were more mild systemic reactions. One subject experienced a grade 2 fatigue following the MVA boost given i.m. No laboratory abnormalities were found attributable to vaccine. ECGs were unremarkable.

In HIVIS 03 [38], of the AEs that were experienced within two weeks of a priming dose, 40% occurred in those who received the vaccine i.d., 36% in those who received the vaccine i.m., and 24% occurred in those who received placebo. Most AEs were mild, with eight events considered moderate (four in those who received the vaccine i.d., three in those who received the vaccine i.m., and one in a placebo-recipient). One event, a headache, was deemed probably related to study agent, but this was in a placebo-recipient. Likewise, the one SAE that occurred was in a placebo-recipient. The most common events were headache (21%) and pain at the injection site (12%). Of the AEs that were experienced within two weeks of a booster dose, 77% occurred in vaccinees and 23% in placebo recipients. All of these AEs were mild with the exception of an event of moderate pain possibly associated with vaccination. The most common event was pain at the injection site (30%). There was no increase in severity of AEs on subsequent doses. 11 SAEs occurred on study from time of dosing through the six months following the last vaccination. Only two of these events occurred within two weeks after a dose and only one in a vaccinee. A subject receiving his/her last vaccination (2nd MVA), developed hematemesis, considered unrelated to vaccination. The remaining nine SAEs occurred outside the window of two weeks post-inoculation and included: injury in a motor vehicle accident, fainting, fissure in ano, mild head injury, musculoskeletal chest pain, epistaxis, acute gastroenteritis, paralytic ileus and hemoptysis. Two were considered probably not related and the rest unrelated to vaccination. No laboratory abnormalities were noted and there were no remarkable ECG results.

In the Phase 2a trial TaMoVac-01 [39], 120 subjects received either placebo or 3 i.d. inclusions of DNA (plasmids pooled or separated) at 0.3 mg per arm (right & left) at 0, 4, and 12 weeks followed by placebo or 10⁷ PFU MVA-CMDR i.m. (left arm) at 30 and 46 weeks. Most subjects regardless of regimen experienced some local and/or some systemic reactions. The majority of these were mild, with a few moderate and very few severe (local only) reactions. The most common (68%) local reaction was pain, including the three severe reactions (1 following DNA, 2 following MVA). The
most common (54%) systemic reaction was headache. One reaction that resulted in discontinuation of vaccination was in an individual who experienced moderate itching and excoriations after a second DNA inoculation. Three SAEs included two HIV infections and a skull fracture complicated with osteomyelitis. Other severe AEs were not SAEs nor associated with vaccination. Other lesser AEs were not associated with vaccination, with the exception of possibly-related events of altered menstrual cycles, herpes zoster, herpes labialis, and allergic conjunctivitis. Infections were frequent on study, including malaria, gastroenteritis, URI, and tonsillitis. Anemia was frequently noted & subjects treated with iron sup-
plementation. Laboratory events were mostly mild with 12 par-
icipants having events of grade 3 or higher. The majority of severe events were asymptomatic neutropenia.

Overall, the vaccinations were well-tolerated in healthy adults in Sweden and in Tanzania.

3.2.3.2. Immunogenicity. In HIVIS 01/02, following the priming series, 30% of subjects developed T cell responses to vaccine anti-
gens as assessed by ELISPot to ≥1 peptide pools. Following booster doses, 92% of subjects had T cell responses. 86% of subjects responded to Gag, 65% to Env, and 59% to both Gag and Env. Only one subject responded to RT. The best response rates following the priming series were in those who received the DNA plasmid i.m. However, following boosting, the i.d. and i.m. routes primed equivalently. The addition of protein GM-CSF reduced the magnitude of the responses. Response rates and magnitudes were better in those who received the booster dose i.m. than in those who received it i.d. The mean response to Gag was 358 SPU/million cells. Age was noted to influence response magnitudes with no high responses in subject >40 years of age. Seven of 38 vaccinees sero-
converted as assessed by a routine HIV ELISA kit. By Western blot, all seven reacted to Gag p24, one to Gag p17, and 1 to Env gp120. An in-house ELISA assay revealed anti-Gag titers ranging from 50 to 10,200, but only one subject developed anti-Env (gp160) antibodies of low titer, insufficient to warrant conducting a neutralization assay [36,37].

In HIVIS 03, response rates for ELISPot were similar following the priming series, whether given i.m. or i.d., with the i.d. route trendi
ting to higher response rates. Following the initial MVA boost, response rates were consistently higher among those receiving the priming series i.d. and response rates tended to drop off following the second booster dose, evening out the response rates between the two routes. Magnitudes of responses were in the low to mid-
hundreds of SFC/million cells following the first boost. As with response rates, magnitudes of responses tended to drop off following the second MVA boost. While age did impact response rates, evidence of prior vaccination (vaccinia scars) did not impact the immunogenicity of the regimen. Subjects receiving the priming series i.d. also tended to recognize more peptide pools, as many as 5 with a median greater than 3, than those receiving it i.m., who responded to no more than 3 pools with a median of 2. Samples were assessed by ICS after the second booster dose in 29 vaccinees. 86% developed CD4 and/or CD8 responses to Gag with 55% having CD4 responses and 59% having CD8 responses. The response rates and magnitudes by ICS did not vary between the priming routes. Median magnitudes of CD4 ICS responses were on the order of 0.2% against various Gag peptide pools (range 0.06–3.67). Likewise, for CD8 responses, median magnitudes were higher than with CD4 with ranges from 0.1 to 1.15 against various Gag peptide pools. Binding antibodies to gp160 were found in 21% of vaccinees after the first boost and in 90% following the second boost. Median titers were the same whether the subjects were primed i.d. or i.m. (me-
dian 800 in both cases, with ranges from 200 to 3200 for i.d. and 200 to 6400 for i.m.). No one seroconverted based on a routine diagnostic ELISA following the first boost, but all did following the second boost. Neutralization was assessed following the second MVA boost by the TZM-bl assay, in which none was found, and by the PBMC assay, in which high response rates were observed – 83% against an AE strain, CM235, and 72% against the clade B SF162 strain. However, only 31% of subjects had neutralizing activity against another clade B strain, BAL. Responses rates did not differ by priming route [38].

In TaMoVac-01, ELISPOT responders were frequent, whether the DNA plasmid primes were given in pools (90%) or separated (97%). The second MVA boosted the frequency of Env responses in at least one regimen. The magnitude of responses to Gag and Env, respec-
tively, ranged from 100 to 660 or 80 to 335 SFC/10⁶ cells. There were no obvious differences between regimens. Two placebo recipients scored positive on either one occasion or sporadically (4/7 time-
points). ICS analyses revealed the following: CD4 responses be-
tween 41 and 67% for any peptide (Gag, Env) with highest frequencies following the first MVA. CD8 responses between 7 and 50% with highest frequencies clearly following the second MVA (i.e., the second MVA boosted CD8 cells), as was seen with the GeoVax products. Magnitudes of CD4 and CD8 responses generally fell between 0.1 and 1% of total cells regardless of regimen. Mean antibody titers were above 400 with ~95% of vaccinees responding. The authors concluded that they could simplify the regimen to three i.d. inoculations at a visit (0.6 mg) from the prior 5 (1 mg) of DNA without deleterious effects on the potency of the regimen [39].

3.2.4. Chinese DNA plasmid prime, Tian tan poxvirus (vaccinia) boost

Chinese scientists, Dr. Shao Y. and Dr. Ruan L., Chinese CDC, have been working on use of the Chinese vaccinia virus (smallpox vac-
cine) strain, Tian Tan, as both a replicating and a non-replicating vector, to express HIV antigens. The antigens are primarily clade C or B/C (the predominant circulating clade in China). The non-
replicating vector has been tested clinically. They are also work-
ing on DNA plasmid vaccines and a heterologous prime-boost approach. The Phase 2A study of this combination is ongoing or recently completed in China and results are under analysis.

There are current plans to move towards a Phase 2B with some combination regimen in China. Clinical trial data are not yet pub-
lished, although there are publications by Dr. Shao et al. on animal studies with the various candidates.

3.3. Phase 1/2 potentially headed to phase 2A

In addition to the poxvirus–protein and DNA plasmid–poxvirus regimens already described, another DNA plasmid prime-MVA (poxvirus) boost regimen has been tested in Phase 1 or Phase 1/2 and may advance to Phase 2A. This candidate regimen contains a clade C-expressing regimen developed by the South African AIDS Vaccine Initiative (SAAVI) and tested by the HVTN in South Africa and the USA.

3.3.1. SAAVI DNA plasmid prime MVA boost

SAAVI has developed a DNA plasmid prime-MVA boost regimen expressing Gag, RT, Tat, Nef, and Env of a clade C strain originally isolated in South Africa. The products were supported by NIAID (USA) through regulatory support and contracts to manufacturers. Unfortunately, the company that manufactured the MVA boost has closed, so this product can no longer be manufactured there. However, if an alternative manufacturer can be identified, progress may resume. It is hoped that a South African manufacturer would be able to tech-transfer and make these products. Meanwhile, laboratory work continues on an improved version of the vaccine candidate regimen at the University of Cape Town.
The DNA plasmid prime is given at a dose of 4 mg and uses the same plasmid backbone, though a different construct, as the one from the VRC that was used in HVTN 505 (see relevant safety and immunogenicity data from sections 4.3.6.1 and 4.3.6.2 in the companion review, respectively). In general, three priming doses are given by needle and syringe rather than by Biojector, as VRC used. Also, generally, two MVA boosts are given at doses on the order of $10^3$ PFU, but other regimens have been explored in HVTN086. HVTN086 added a clade C protein boost from Novartis (adjuvanted with MF59) to the regimen. It is not clear which regimen would advance to further studies. The Phase 1 study results remain unpublished at this time.

### 3.3.1. Safety
In HVTN 073 [35], in information reported publicly at conferences, the safety profile was reported as favorable, with only three of 48 subjects withdrawing from the study: one relocated away from the study site, one experienced schizophrenia and one developed a swollen tongue (it was not clear whether this was in association with vaccination or what was the timing of this event to know whether it was an allergic reaction to vaccination or not).

#### 3.3.1.2. Immunogenicity
Likewise, in preliminary information reported at conferences [40,41], the immunogenicity profile was favorable. With regard to T cell responses, 69% of subjects developed CD4 responses and 33.3% developed CD8 responses. Mean response magnitudes of 0.002% of total T cells were observed, with ranges from 0.008 to 0.07%. Median responses were stated to be between 0.02 and 0.04%. The T cell responses were mainly directed to Env (66.7% for CD4, 8.3% for CD8) and Gag (as high as 34.4% after the first boost, but falling to 15.2% after the second for CD4, 5.6% for CD8), although there were better CD8 responses to Pol (25% for CD8 vs. 9% for CD4). CD4 cells were not boosted by the second MVA dose, but CD8 cells were. T cell response rates were similar between the USA and South African sites, although there were more responders among the USA subjects. The predominant cytokine expression in CD4 cells was IL-2 and/or TNF-alpha, whereas the predominant profile in CD8 cells was interferon-gamma and/or TNF-alpha. Antibody responses were not reported in these presentations.

### 3.4. Phase 1
The pipeline for development of HIV vaccines continues to expand at the earliest stages of clinical evaluation, with many preclinical concepts remaining to enter the clinical pipeline. Some of the preclinical vaccine concepts are incremental improvements on existing products in the clinical pipeline, while others are completely novel. New vector systems, new adjuvants, and new delivery devices or systems are in preclinical development. In early clinical development there are several familiar vector systems in clinical development in combination, e.g., alternative adenovirus-prime with a heterologous alternative adenovirus-boost, or delivered by a novel delivery system, e.g., DNA plasmids accompanied with electroporation. Other novel vector systems, e.g., Vesicular Stomatitis Virus (VSV) or Sendai Virus, are also in clinical development. The following sub-sections will describe some of the candidate vaccines in clinical Phase 1. Depending on the safety profiles emerging in Phase 1 and the immunogenicity, in terms of potency and the ability to fill a niche not filled by other candidate vaccines or regimens, i.e., filling a novel immunological “space,” decisions will be made by funders whether to advance these candidates further.

#### 3.4.1. Electroporated DNA or DNA with cytokine adjuvants
At least two companies have developed electroporation devices that are intended to improve the uptake of plasmid DNA vaccine candidates in vivo. These devices may theoretically have slightly more safety risks than delivery by needle and syringe or by Biojector® 2000 delivery systems, which are already marketed. However, the safety profile remains to be elucidated to determine this. This may be balanced by the potential benefit of enhanced potency of the DNA plasmid vaccines delivered in conjunction with electroporation. Whether the promise of this technology will be fulfilled remains to be seen. Data to date suggests that electroporation might not lead to the number of inoculations being decreased, but that the immunogenicity may be improved or that dose-sparring may be observed. Devices include those accompanying intramuscular injections and those accompanying intradermal injections.

Inovio Pharmaceuticals, Inc. (http://www.inovio.com/, accessed 10/15/2014, USA) is a developer of such electroporation devices, which have been tested with a number of candidate vaccines, including those to prevent influenza, malaria, and HIV, as well as therapeutic products against cancer, which are in preclinical or early clinical development. Their subsidiary, VGX International, Inc. (VGXII, http://vgxii.com/, accessed 10/15/2014, USA), manufactures the DNA plasmids used in conjunction with the device produced by Inovio. The HIV DNA plasmid vaccine concepts are those of Dr. D. Weiner from the University of Pennsylvania. Funding and/or clinical trials support for HIV vaccine development have been provided by NIAID and USMHRP.

Ichor Medical Systems (http://www.ichorms.com/, accessed 10/15/2014, USA) is also a developer of such an electroporation device, which has been tested with a number of candidate vaccines, including those to prevent HIV, influenza and malaria, as well as therapeutic products against cancer, immunotherapeutics, proteins, and monoclonal antibodies. The Ichor device has been used with a DNA plasmid candidate vaccine being developed by FIT Biotech (http://www.fitbiotech.com/, accessed 10/15/2014, Finland), referred to as a Gene Transfer Unit or GTU®.

In addition to plasmid antigens, some developers, e.g., Dr. Weiner (discussed above) or Dr. Robinson (discussed in section 3.2.1), are testing DNA plasmid candidate vaccines adjuvanted with cytokines expressed on plasmids and injected simultaneously with the DNA plasmid vaccines. Such cytokines include interleukin 12, interleukin 15, and GM-CSF, among others. Funding and clinical trial support have been provided by NIAID, USA.

#### 3.4.2. Electroporated DNA with cytokine adjuvant prime with VSV boost
Profectus Biosciences, Inc. (http://profectusbiosciences.net/ accessed 10/15/2014) has also developed DNA plasmid vaccines adjuvanted with a plasmid expressing IL-12. Furthermore, they have developed novel vectors based on Vesicular Stomatitis Virus (VSV). The VSV concept was originated by Dr. J. Rose of Yale University. Dr. Weiner (mentioned above in section 3.4.1) has also collaborated with the scientists at Profectus on DNA plasmid vaccines and cytokine adjuvant plasmids. Funding and clinical trial support has been provided by NIAID and IAVI. Information on the first-in-human study can be found in Fuchs et al. [42].

#### 3.4.3. Novel adenovirus serotypes with MVA vector in prime—boost combinations
Dr. D. Barouch, Beth Israel Deaconess Hospital and the Ragon Institute of Harvard University, USA, has been developing prime-boost combinations based on heterologous rare-serotype (e.g., type 26 or 35) human adenoviruses or adenovirus in a heterologous prime-boost combination with MVA. The individual vectors have been tested independently in Phase 1 and the most likely candidate regimen to advance further is an Ad26 prime-MVA boost combination. The Phase 1 results are published [43–45]. The choice of Ad serotypes was based on seropositivity rates being low in human
populations in various countries and potency in preclinical animal models. His corporate partner in the development of these products is Crucell (http://crucell.com/, accessed 10/15/2014, the Netherlands), with funding from NIAID, USA. Dr. Barouch also receives funding from the Bill & Melinda Gates Foundation though a Collaboration for an AIDS Vaccine Discovery (CAVD) grant. Other serotype adenovirus vectors are in preclinical development and they are based on serotypes derived from chimpanzees, such as chAd6 and chAd7 (Dr. H. Ertl, University of Pennsylvania, USA) and chAd3 and chAd63 (collaboration between Okairos, Italy, and the VRC, NIAID, USA). Other rare human serotypes, such as Ad35, Ad28, etc. have been tested, even clinically (Ad35), but it is likely that these will not advance further as they appear to be less potent.

3.4.4. Replicating adenovirus vector

PaxVax, Inc. (http://www.paxvax.com/, accessed 10/15/2014, USA) is developing a replicating adenovirus type 4 vector. Discovery work on this concept has been performed by Dr. M. Robert-Guroff (NIH, USA), who originally collaborated with Wyeth Research, USA, which developed the vector system based on their oral Ad4 and Ad7 vaccines previously licensed for use by the United States military (Wyeth no longer makes these vaccines, and has subsequently been purchased by Pfizer). A Phase 1 study is underway comparing delivery by oral, tonsillar, and intranasal routes.

3.4.5. Other replicating and non-replicating vectors

There are other replicating vector approaches in development. The concept of a replicating vector is to trade on the benefits afforded with a live, attenuated vaccine, but without using live, attenuated HIV, which would not be safe. By expressing HIV proteins in a viral vector that replicates in the vaccinee, the endogenous expression and amplification of expression through replication, along with limited spread of the vector, may achieve a similar effect as infection, without the risks. For example, as described above in section 3.2.3, the Chinese CDC has a replicative-competent Tian Tan (vaccinia) vector. Other vectors not yet in the clinic or in initial studies, but worth mentioning and under development by IAVI include Canine Distemper Virus, Sendai Virus (this clinical study initiated in the fall of 2013, though results are not yet published), and Adeno-Associated Virus (AAV, developed by Dr. Phil Johnson, Children’s Hospital of Philadelphia, USA and expressing a monoclonal antibody rather than an antigen gene). Sendai virus (not as a vector) has been tested clinically by Drs. J. Hurwitz and K. Slobod (St. Jude’s Hospital, USA) as a vaccine against parainfluenza virus 3, so there are some preliminary safety data on this virus as a vaccine or vector. AAV has been tested clinically expressing various antigens by several companies, mostly as a therapeutic agent, but IAVI’s AAV vectors were vaccine candidates.

Many other novel vectors, either as replication-competent or non-replicating vectors, in preclinical development, are being funded by NIAID and include vectors such as Listeria, rabies virus, SV40, measles virus, and others. Both IAVI and NIAID are supporting preclinical research on rhesus cytomegalovirus as an analogue vector in the rhesus animal model. Translation of this concept to use of human cytomegalovirus as a vector has yet to occur and may be difficult, as rhesus and human CMVs are different viruses. Nonetheless, plans to move this concept forward exist.

3.4.6. Mosaic antigens or consensus antigens

Another approach to improving the global applicability of candidate vaccines is to incorporate T cell linear peptide epitopes from strains of varying clades into an artificial construct that results in a natural-looking protein, often functional, which is constituted of natural epitopes, but which, in that order and arrangement of epitopes, does not exist in any particular strain of HIV. This so-called mosaic approach was intended to improve the breadth of T cell responses by expressing in a single, two, or three constructs the most common epitopes found in strains of every clade. Vaccine candidates will likely move forward containing these antigens, even though the concept of a strictly T cell-based vaccine is no longer considered a viable approach to achieve efficacy. At least one vaccine candidate with mosaic antigens has already entered the clinic. These mosaic antigens may also elicit antibody responses, if the protein is functional (and most of these constructs do generate functional proteins) and thus, folds properly to present conformational epitopes. But, the design was not innovated for the purpose of antibody-generation, but really to expand the breadth of T cell recognition with a single antigen representing multiple clades and strains. The bioinformatics used to design these mosaic constructs are well-described in Fischer et al. [46].

Some researchers, e.g., Dr. B. Haynes (Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, USA) and colleagues, are also studying consensus antigens, which are also bioinformatically determined to contain the sequences most closely matched to an “average” strain of HIV. Consensus or “center-of-the-tree” approaches attempt to minimize the sequence divergence of the immunogen candidate from all known strains within a clade or within the M group of HIV. These approaches all attempt to make a sequence that is as closely related to all known strains as possible in an effort to “average” out strain divergence and attempt to generate a universal approach to a problem of diversity.

4. Adolescents

The tremendous uncertainties about which vaccine candidates will prove to be efficacious in humans has stymied the efforts of many to advance efforts for the inclusion of adolescents in HIV vaccine studies. While no one wishes to bring harm to adults, most adults have the capacity to make their own informed decisions about trial participation. Children, in contrast, have limited autonomy and are recognized to require additional protections to prevent causing them harm in clinical research. This desire and necessity to protect children from clinical research is in sharp contrast to the need to protect children with clinical research. Without performing research with children included, one cannot discern how children may respond differently. There are biological and sociological reasons to expect differences, and some of these have been reviewed elsewhere [47]. Both in the European Union (EU) and the USA, legislation has been enacted to require developers to study how to appropriately and safely dose children with medicinal products. This legislation is in recognition of the imperative to protect children with clinical research into the right ways to prevent or treat their diseases or conditions rather than the current practice of using in children products that have only been approved for adult use; without knowing the proper doses, or even formulations, appropriate for pediatric use, because there are no data in children to guide these decisions.

In many, if not most, parts of the world, adolescents are at highest risk of acquiring HIV infections. The epidemiological statistics speak for themselves and therefore, adolescents should be the target population for a successful vaccine, when one becomes available. Like Human Papillomavirus vaccine (HPV) and Hepatitis B virus vaccine, vaccination of children before they become sexually

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active and at risk of acquiring these sexually transmitted diseases is the optimal approach to protecting adolescents at high risk of infection. It is for these reasons WHO held two consultations; the first, in Lausanne, Switzerland in 2004, which covered the inclusion of women, adolescents, children, and diverse racial groups in HIV vaccine studies [48] and the second, in 2006, in Gaborone, Botswana, which focused on inclusion of adolescents specifically [49].

In the current situation, the timing of when or whether to include at-risk adolescents in efficacy studies or to attempt to bridge in the absence of validated immune correlates by performing an immunological bridging study after efficacy is shown in adults remains an even more daunting dilemma. However, HIV/AIDS vaccine studies, whether efficacy or safety and immunogenicity studies, need to be performed in an adolescent population in order to assure that the ultimate target population for vaccination can be safely, effectively and ethically vaccinated once a safe and efficacious vaccine has been discovered. The debate of how (and when) best to do this continues. Regulators may be asked to consider protocols that may include enrollment of individuals younger than the age considered to be an adult in their respective country. The cited meeting reports from the WHO consultations may aid in consideration of the relevant issues.

5. Special considerations in trial design and efficacy endpoints

The conduct of efficacy studies for HIV vaccines has become increasingly complex as more knowledge has been gained from scientific advances and from the efficacy studies that have been completed. Particularly, going forward, the success of other prevention modalities, the improvement in availability in even the most-resource limited settings of antiretroviral therapy for those who become infected on study through their own risk behavior and the development of a new wave of potential monoclonal antibodies that will be studied for prevention will increase this complexity.

5.1. Trial design in era of circumcision, PEP, PrEP, microbicides, and other prevention modalities

In the past decade, considerable progress has been made in demonstrating the efficacy of various prevention modalities in various at-risk populations. To take male circumcision as an example, three separate efficacy studies conducted, respectively, in Kenya, South Africa and Uganda, demonstrated 48%, 53% and 60% reduction in HIV-acquisition in heterosexual men who were voluntarily circumcised [50]. As a consequence, when enrolling men in HIV/AIDS vaccine studies, it is appropriate and ethical to offer circumcision to those men who are eligible to participate in the study, but who are uncircumcised at baseline. In doing so, though, researchers must expect approximately half of the infections that might have occurred in the men enrolled in the HIV/AIDS vaccine efficacy study will be averted due to the preventive efficacy of circumcision. Thus, in deciding sample size and calculating expected event rates to determine efficacy of the investigational vaccine, the measured rate of events in a population of uncircumcised men can be anticipated to be halved and so, twice as many previously uncircumcised men would need to be enrolled [if all were to accept circumcision] to observe the same number of events. In this way, sample size calculations must be adjusted to account for all of the various prevention modalities that might be introduced in the conduct of an HIV/AIDS vaccine efficacy study, because they are or are likely to become standard-of-prevention and thus, reduce the event rate that would otherwise be expected, based on epidemiology in the study population. When regulators review CTAs for HIV/AIDS vaccine efficacy studies, they need to assess whether and how the clinical trial sponsor plans to offer standard-of-prevention and how they have calculated the impact of other prevention modalities on event rates, for the purposes of establishing relevant sample size of their study.

Additionally, some of the prevention modalities are transitory in their effect. While circumcision, once performed, will continue to exert its protective effect thereafter, in contrast, use of Pre-exposure Prophylaxis (PrEP) will only protect while it is being taken. If a subject enrolled in an HIV/AIDS vaccine efficacy study decides to begin to use PrEP while on study, his/her risk will be reduced by PrEP use. If, s/he is non-adherent to PrEP use, or discontinues it, then his/her risk of HIV acquisition will return, assuming his/her behavior that puts him/her at risk is unchanged. Determining the exact amount by which such non-continuous risk-reduction will occur in a study is unlikely to be able to be calculated accurately. Thus, statisticians may need to make certain assumptions or model expectations in calculating sample sizes and power calculations. In addition, it is paramount that information about use of other prevention modalities be tracked over the course of the study in order to assist in evaluating the data at the conclusion of the study. Regulators reviewing CTAs need to assess whether these aspects have been clearly addressed and how the use of other prevention modalities will be monitored in the HIV/AIDS vaccine efficacy study.

All trial protocols should include some aspect of providing risk reduction counseling to all participants. This counseling should be conducted in line with UNAIDS guidelines. In addition, HIV testing is generally part of the protocol both to ensure enrollment of only subjects who are HIV-seronegative at baseline and for monitoring for incident HIV infections that occur while on study. This counseling and testing approach is a successful prevention modality.

Another aspect to consider is which populations to enroll. It may become impossible to consider conducting a study in discordant couples, e.g., because treatment of the infected partner to prevent transmission to the uninfected partner and/or PrEP for the uninfected partner should be able to be accessed while on study. Thus, transmission rates should theoretically fall to near zero in discordant partners afforded these other prevention modalities. What used to be considered a prime population to enroll into HIV/AIDS vaccine and other prevention efficacy studies may no longer be considered a useful population to enroll. Regulators should consider the populations sponsors propose to enroll and the other prevention modalities to which those populations now have access or should be afforded on study.

Finally, when considering viral load and CD4 counts as endpoints in an HIV/AIDS vaccine efficacy study, early initiation of antiretroviral therapy will censure data collected after it is initiated, as it has such a profound effect on these parameters and any additional effect of vaccination will not be able to be disentangled. Therefore, collection of information about when and what types of antiretroviral therapy is initiated in those subjects who become infected on study is also crucial to the data analysis. A plan for how these statistical analyses will be handled should be clear and regulatory concurrence on the analyses gained before they are implemented.

5.2. Endpoints and futility analyses

Previously, slowing the progression of the disease or onset of AIDS or reducing viral load, while maintaining CD4 counts, in individuals who became infected through their own risk behavior after vaccination, were considered reasonable primary endpoints for a prophylactic HIV vaccine efficacy study. Those goals are no longer primary in the development of an HIV/AIDS vaccine. Given
the modest efficacy to prevent acquisition of HIV infection in the RV144 study, the ability of other prevention modalities (discussed above) to prevent acquisition of HIV infection, and the ethical mandate in clinical trial design to improve on existing therapies, the primary endpoint of an efficacy study should be prevention of acquisition of HIV infection. Of course, safety should also be a primary endpoint, although in some trials, it might be considered a secondary endpoint.

Reduction of viral loads and maintenance of CD4 counts in vaccinees, who subsequently become infected (i.e., vaccine breakthroughs), should be considered as important secondary analyses. Immune responses (a few targeted main assays) to vaccination and efficacy (prevention of acquisition) in particular subgroups might be included among secondary endpoints. Social harms, as a specific type of safety analysis, may be considered as a secondary or tertiary endpoint in an efficacy study. Other immunological assays could be considered tertiary or exploratory endpoints. Of course, study design and the aims of the study drive which analyses are primary, secondary, etc. and these comments should be construed as advisory only for general principles. As always, judgment must be used in determining what is appropriate in given studies a regulator may be reviewing.

It is important when there are multiple endpoints considered in a clinical trial that a clear rank-ordering of analyses be prospectively defined. Not simply, primary, then secondary, then tertiary, but rather, within the secondary endpoints, which analyses will be considered first and which subsequently should be pre-defined. In other words, secondary analyses should be rank-ordered. Because of the potential confounding by multiple testing, if the most important secondary analyses fail, then less important analyses become less relevant or less convincing. In this way, labeling claims can be supported by the most important endpoints that are most credible statistically and meaningful clinically. Data from pilot efficacy studies may guide decisions about the rank-ordering of endpoints in pivotal efficacy studies.

Also, while the general approach to a “per-protocol” analysis of the primary efficacy endpoint is to include only those subjects enrolled in the study confirmed to be uninfected at baseline and who received all study vaccinations or placebo inoculations (or in some cases, the priming series, but not necessarily the boost). A more realistic view of vaccine efficacy and an approach that most regulators would want to see analyzed would be the modified intent-to-treat (MITT) analysis of the primary efficacy endpoint. This would include all subjects enrolled in the study confirmed to be uninfected at baseline and who received at least one study vaccination or placebo inoculation. This is to be contrasted with an ITT analysis in which all subjects enrolled were included, regardless of whether they were actually uninfected at baseline or received any inoculations. For vaccine efficacy studies, it is generally the MITT analysis that is most relevant to judge vaccine efficacy. The per-protocol analysis generally is the “optimal” situation, but the realistic situation that may reflect real world situations most closely would be the MITT. A statistician should advise in individual cases what is most appropriate.

Finally, considering the outcomes of the various vaccine efficacy studies that have been completed to date, it is crucial that a futility analysis be planned. In order to be able to do this, interim analyses under the purview of an independent Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) are required. As a consequence, the study sample size should be adjusted to account for the loss of power from interim “looks” at the efficacy data. Several journal articles discuss these aspects in greater statistical detail [51, 52].

From a regulatory perspective, in review of a CTA, a regulator should confirm that these facets have been addressed prospectively in the protocol. Sometimes, a precise statistical analysis plan may not be included in the protocol, but rather provided prior to unblinding and analyzing data. If that is the trial sponsor’s plan, then agreement between the trial sponsor and the regulator about the timing of submission of the final prospective statistical analysis plan in relation to the analysis of the trial should be gained prior to initiation of the study. Obviously, if interim analyses are planned, these must be planned well before the end of the study, so either that statistical analysis plan (for the interim analyses) should be provided in detail in the protocol, or a clear indication of the timing of the planned interim analysis and the timing of submission of the statistical analysis plan for the interim analysis should be agreed upon in advance of the trial initiation. Statistical adjustments for such interim analyses should be considered and also agreed upon.

5.3. Adaptive design

There is considerable interest in clinical trials to incorporate adaptive design, which originally gained favor in cancer therapy studies. One concept of this approach is that a study can be designed to compare multiple therapeutic arms and as each endpoint occurs, judgment made in favor or against a particular arm of the study. In this manner, less therapeutically beneficial study arms may be halted early and more subjects enrolled in the more beneficial study arms. However, these are not the only adaptations that can be made. In reality, any changes (adaptations), made to the study design after a study has been initiated, but which have been planned in advance (usually based on reaching certain contingencies), can be considered an adaptive design. Vaccine studies permit certain adaptations to be made, but often, the study will be fully enrolled and most participants will have completed their vaccination series (or at least, their priming series, if there are booster doses), well before a sufficient number of endpoints are accrued to be able to gauge whether or how to adapt the study design. Nonetheless, some research studies (non-licensure-enabling) are being planned with the intent of taking an adaptive design approach. More information may be found in the article by Gilbert et al. [51]. It is possible that regulators may be more accepting of use of adaptive trial designs in non-licensure studies, but may expect more rigor or use of more traditional statistical approaches in pivotal licensure trials. Sponsors should discuss these issues with regulators in advance of execution of any statistical plan and regulators need to consider their comfort level and willingness to accept an adaptive trial design for regulatory decision-making. In the end, the analysis of the trial results must be credible and reliable, and hopefully compelling, for regulators to base decisions with any confidence or certainty.

5.4. Correlates analysis

Future efficacy studies should be planned and designed with an aim to collect the correct samples at the correct timepoints, processed and handled in the correct manner, and stored stably, to permit a correlates analysis at the end of the trial, should efficacy be observed. HVTN 505 (described in the companion review) was designed and planned in such a manner, although unfortunately, no efficacy was observed in that study. Nonetheless, defining immune correlates of protection is a top priority for efficacy studies of HIV/AIDS vaccines. Although many vaccines have been licensed successfully without correlates, for the reasons discussed in Section 2.3, as well as the discussion about bridging to an adolescent target population (Section 4), it is highly desirable to identify immune correlates of protection for HIV/AIDS vaccines. In addition, because initial candidates are likely to be no more than modestly efficacious, knowing what immune correlates are may permit the rapid, iterative development needed for highly efficacious vaccine candidates or regimens to follow.
As a successful HIV/AIDS vaccine may act through a variety of mechanisms, neutralizing antibodies, non-neutralizing but protective antibodies, mucosal immune responses, CD4 or CD8 cellular responses, even innate responses, sampling and planning for storage and analysis is more complex than might normally be the case for vaccines that act solely through a systemic antibody correlate. Some samples may require large volumes of blood cells or samples taken from anatomical sites that might require somewhat invasive procedures and such samples may realistically only be taken from a subset of individuals during a large efficacy study. Unfortunately, there is no a priori way to know which participants will become infected to be sure to collect such samples for those specific individuals. So, this complicates planning for a correlates analysis further.

Regulators should determine what a sponsor plans to do to support a correlates analysis in their efficacy study protocol. The design should fit with the proposed mechanism of action of the vaccine candidate. For example, if the proposal is that the vaccine will act through non-neutralizing antibodies, then a variety of immunological assays to measure such non-neutralizing but potentially protective antibodies should be planned. Some of these assays, like antibody-dependent cell-mediated cytotoxicity assay (ADCC) or antibody-dependent cell-mediated virus inhibition assay (ADCVI), are not as well developed and validated as a standard ELISA or neutralization assay may be. So, the protocol should be clear on the validation status and thus, credibility and reliability, of such assays, if they are intended to support regulatory decision-making. If they are proposed as exploratory endpoints, then they do not necessarily need to be validated, but if they are central to a correlates analysis (rather than just exploratory), then more information about their performance parameters should be provided for regulatory review. Although the ICH Q2 document on Validation of Analytical Methods is intended for lot release, rather than clinical assays, consideration of the principles in the ICH Q2 document for quantitative methods should be given to clinical assays that will be used to support licensure or bridging on the basis of correlates.

Another facet that should be borne in mind is that by the time an efficacy study is completed, it will be a good four to five years after it was planned, if not longer. Many new immunological assays will have been developed in the meantime. Some flexibility to incorporate new assays into the correlates analysis should also be considered. Furthermore, an assay that may not be validated at the time the efficacy study is initiated, may become validated by the time the correlates analysis will actually be performed, so some flexibility to review and decide-upon certain assays before they are used in the analysis, but well after the study is under-way, should be considered. This may require agreements be put into place between applicant and regulator at the onset of the study to leave some flexibility at the outset, but gain concurrence before analyses are undertaken and regulators are asked to review the resulting data.

6. Access issues when a successful HIV/AIDS vaccine is developed

It would be ethically unacceptable at the completion of an efficacy study of a clearly successful vaccine candidate or regimen to be unprepared for access to the safe and efficacious vaccine by the placebo-recipients of the study (and continued boosters, if called for, by the vaccinees), by the communities from which the study drew participants, and by the countries where the study was performed. Consequently, it is critical that study sponsors work with communities and countries to plan for access and for communities and countries to demand that these plans be made, even before the trial initiates, and implemented. While not a regulatory requirement, regulators should be mindful, as members of communities and representatives of their country, that such plans be in place, if not incorporated into the actual study protocol (however, if the sponsor plans to amend the study to vaccinate placebo-recipients at completion of the study or to continue to boost vaccinees, then such plans, albeit without the details of the planned amendment, should be made clear to regulators before the initiation of the study, at the time of the original CTA review). Additional aspects, including considerations for adolescents and women, on this topic of access were discussed at a number of WHO/UNAIDS consultations [53,54].

6.1. Planning for a partially effective vaccine

Considerable efforts have been undertaken to model in the context of different epidemic settings the utility of a partially effective vaccine. In each case, vaccines of modest efficacy if implemented in high risk groups with sufficient coverage could have a dramatic impact to curb the epidemic.

6.2. Planning for success

Because HIV vaccines are such a high risk venture for industry, often (if not in all cases to date) they are more prepared for iterative product development or for failure than to dare hope for success. This perspective is supported by the relative lack of success in the field thus far, so it should not be surprising that industry (and other researchers) would think and plan taking this perspective. However, when considering the appropriateness of the conduct of an HIV/AIDS vaccine study, regulators should be prepared to consider and question potential applicants whether they are prepared for success in the following ways:

- do they have sufficient doses of the vaccine to rapidly vaccinate placebo recipients in the efficacy trial who remain uninfected at study endpoint, if the trial demonstrates moderate to high efficacy? Do they plan to amend the study to permit vaccination of placebo recipients subsequent to achieving the primary endpoint of the study? If not, why not?;
- what are the planned timelines for scale-up to commercial manufacture and provision of licensure dossier for review subsequent to study outcomes being known (if scale-up was not performed prior to the conduct of efficacy studies)?;
- what are the planned timelines for additional Phase 3 studies, such as consistency lot studies, bridging studies (e.g., to adolescent populations) and large safety studies (if additionally needed), necessary to support the licensure dossier? Also, when (at the outset, during the review, or post-licensure) in the review of the licensure dossier will such data be provided for regulatory review? Do you agree with the proposal or do you have the necessary regulatory framework or mechanisms in place to accommodate the proposal?;
- what are the plans for access subsequent to licensure or registration in the communities in which the trial(s) was conducted? Although this latter question is less a regulatory question and more a public health question, the appropriate national authorities should consider this question. For regulators, has the correct populations been studied in clinical trials to permit the access plans, e.g., trials in adolescents?

7. Conclusion: how should regulators be prepared?

Regulators facing the evaluation of a clinical trial application of an HIV vaccine clinical trial, particularly Phase 2b and 3 studies, have significant challenges. In this and the companion review, efforts have been made to frame the scientific issues and challenges in terms of regulatory challenges. Key among these scientific
challenges that present regulatory challenges are the lack of human survivors from whom immune responses might guide vaccine development; the lack of an immune correlate of protection; the lack of predictive animal models for vaccine protection; the high degree of variability with regards to strains of HIV, immunological responses, routes of infection, populations at risk and the associated epidemiology. Additionally, issues surrounding vaccine-induced seropositivity (seroreactivity), inclusion of adolescents in HIV/AIDS vaccine clinical trials, conduct of future efficacy trials in an era of changing and evolving standard-of-prevention, concepts behind adaptive and other innovative trial designs (including accompanying statistical issues and the need to analyze the data for potential immune correlates of protection) and access to a successful HIV/AIDS vaccine once one is discovered present challenges.

Many of the challenges described herein have, at present, no clear-cut answer or specific “right” course to take. The answers to many of these questions are “gray” or “hazy” and there may be a lack of consensus about such answers. The HIV/AIDS vaccine field itself struggles with these challenges and international efforts such as the HIV Vaccine Enterprise and various public/private partnerships and networks, as well as the WHO, are always continuing scientific discussions on these challenges as more data emerge. Many of these discussions are taken in as publicly transparent a fashion as possible. Regulators are encouraged to take advantage of various fora for such public discussions. Collaborations among regulators within/across regions are encouraged by WHO, such as the African Vaccine Regulatory Forum (AVAREF) and the Developing Country Vaccine Regulatory Network (DCVRN), to foster regulatory convergence on common topics and to foster common regulatory practices. Regulators may also find collaboration or consultation with independent researchers in their own countries or regions to be useful for bringing strong scientific principles to bear on regulatory matters. Regulators need always put in context not only the scientific and technical aspects of the application, but also integrate their concerns about future ef
cind itself.

tacy trials to be conducted in their countries. The most advanced concept is the reprise of the RV144 regimen; however, due to various reasons, the products that will be studied are essentially new products. In addition, other poxvirus vectors, DNA plasmid vaccines (with or without various adjuvants or novel delivery devices), other viral vectors and subunit protein vaccines potentially with novel adjuvants are likely to be the subject of future efficacy trials. Because of the novelty of the products in comparison to licensed vaccines (live attenuated or inactivated organisms, conjugates), regulators may need to become more technically prepared for this review. With this aim in mind, we advise regulators to familiarize themselves with the various existing guidance documents and WHO publications, such as consultation reports, developed to assist them in this regard and which we have compiled a list to aid them in finding. It is important that WHO has been in collaboration with other bodies to derive consensus and provide guidance. Appendix 1 provides two tables for guidance and reports, as examples, from WHO and UNAIDS (Table 1) and from ICH, FDA, and EMA (Table 2) with associated weblinks to find the documents with ease. The majority of guidance provided are not specific to HIV/AIDS vaccines, but most, if not all, concepts and principles contained within them are as applicable to HIV/AIDS vaccines as to any other. In addition, Table 3 (Appendix 2) summarizes the regulatory challenges presented in this review.

Table 1
Examples of available WHO and UNAIDS documents that may provide useful information to regulators.*

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<tr>
<th>Title, source and reference</th>
<th>Topics covered/Issues discussed</th>
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<tr>
<td>WHO Good Manufacturing Practices for active pharmaceutical ingredients. WHO TRS No. 957, Annex 2 (2010).</td>
<td>Guidance on GMP for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. The special guidance for APIs manufactured by cell culture or fermentation is provided.</td>
</tr>
<tr>
<td>Guidelines for National Authorities on Quality Assurance for Biological Products. WHO, TRS No. 822, Annex 2 (1992).</td>
<td>General guidance for National Regulatory Authorities (NRAs) and National Control Laboratories (NCLs) on quality assurance for biological products (including vaccines) to assure their safety and efficacy.</td>
</tr>
<tr>
<td>Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities, WHO TRS No. 978, Annex 2 (2010).</td>
<td>General guidance to NRAs and/or NCLs for setting national requirements and system for independent vaccine lot release. Document also provides useful guidance to vaccine manufacturers.</td>
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Table 1 (continued)

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<th>Title, source and reference</th>
<th>Topics covered/Issues discussed</th>
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<td>Recommendations for the Evaluation of Animal Cell Cultures as Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell banks. Replacement of Annex 1, TRS No. 878. WHO TRS No. 578, Annex 3 (2010). <a href="http://www.who.int/entity/biologicals/vaccines/TRS_578_Annex_3.pdf?ua=1">http://www.who.int/entity/biologicals/vaccines/TRS_578_Annex_3.pdf?ua=1</a></td>
<td>Guidance to NRAs, NCLs and manufacturers on basic principles and, in some cases, on detailed procedures, that are appropriate to consider in the characterization of animal cells that are proposed for use in the manufacture of biological products, including vaccines. Document also provides useful guidance for establishing and maintaining cell banks.</td>
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**Report:**


**Report:**


**Report:**


**Report:**


Guidance and general principles of nonclinical evaluation of vaccines, with particular attention being given to the regulatory expectations for new and novel vaccines. Both prophylactic and therapeutic vaccines for infectious disease indications are considered in this document.

Guidance on consistent and harmonized nonclinical testing approaches to support the use of candidate adjuvanted vaccines in all stages of clinical development and ultimately for marketing authorization of the adjuvanted product. This document covers adjuvanted vaccines used in both prophylactic and therapeutic indications against infectious diseases.

(continued on next page)
Meeting reports from the consultations with the experts for other WHO-HIV/UNAIDS (HVI) publications regulators may wish to consider:

http://www.who.int/immunization/research/development/hiv_vaccdev/en/

WHO-UNAIDS HIV Vaccine Initiative:


WHO catalogue of international reference preparations

Useful Weblinks


Guiding principles for regulatory review for the purposes of clinical trial approval and licensing, which apply to a broad range of vaccines. Document serves as basis for setting or updating national requirements, as well as for WHO vaccine prequalifications. Also informs manufacturers on regulatory expectations for clinical evaluation of vaccines intended for global use and should be read in conjunction with Guidelines or Recommendations for specific types of vaccines. (Currently subject to revision; updated version will be available at the http://www.who.int/biologicals/)

General guidelines on clinical trials. The Guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities.

Manual provides more details on the indicators for the evaluation of clinical performance through authorized clinical trials. It offers practical suggestions, references to useful publications for NRAs.

Guidance for newly developing NRAs/NCLs that may have limited resources to license and regulate biological products, including vaccines. It describes the responsibilities of such authorities and of manufacturers and provides references to relevant WHO publications related to their structure and activities.

Guidelines intended to contribute to the development of quality and consistency in the ethical review of biomedical research. Targeted for use by national and local bodies, these guidelines define the role and constituents of an ethics committee, and detail the requirements for submitting an application for review. The review procedure, plus details of the decision making process are provided, together with necessary follow-up and documentation procedures.

Guidelines intended to provide trial funders, sponsors and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials. Provides a framework for development of effective stakeholder engagement programmes. Consideration of specific trial and local contexts will dictate how the guidelines are best implemented.

Document for potential trial research participants, investigators, research staff, community members, government representatives, pharmaceutical companies, other industry partners and trial sponsors, and ethical and scientific review committees involved in development of biomedical HIV prevention products and interventions, including HIV preventive vaccines. It suggests standards, as well as processes for arriving at standards and can be used as a frame of reference from which to conduct further discussion at the international, national, and local levels.

HIV related international standards and reference reagents, which may be used in clinical trial assays.

Documents relevant to HIV vaccines research and development.

Meeting reports from the consultations with the experts for research and development of HIV vaccines on:

Efficacy trial endpoints, trial design considerations

Considerations regarding clinical trials of HIV vaccines in the age range likely to be the target of public health campaigns, i.e., adolescents before or around the time they becoming sexually active and thus, at risk of HIV infection.

Documents related to clinical evaluation

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<th>Title, source and reference</th>
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| Guidelines on clinical evaluation of vaccines: regulatory expectations. WHO TRS No. 924, Annex 1 (2004) http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/035-101.pdf | Guiding principles for regulatory review for the purposes of clinical trial approval and licensing, which apply to a broad range of vaccines. Document serves as basis for setting or updating national requirements, as well as for WHO vaccine prequalifications. Also informs manufacturers on regulatory expectations for clinical evaluation of vaccines intended for global use and should be read in conjunction with Guidelines or Recommendations for specific types of vaccines. (Currently subject to revision; updated version will be available at the http://www.who.int/biologicals/)

General guidelines on clinical trials. The Guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities.

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Guidelines intended to provide trial funders, sponsors and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials. Provides a framework for development of effective stakeholder engagement programmes. Consideration of specific trial and local contexts will dictate how the guidelines are best implemented.

Document for potential trial research participants, investigators, research staff, community members, government representatives, pharmaceutical companies, other industry partners and trial sponsors, and ethical and scientific review committees involved in development of biomedical HIV prevention products and interventions, including HIV preventive vaccines. It suggests standards, as well as processes for arriving at standards and can be used as a frame of reference from which to conduct further discussion at the international, national, and local levels.

HIV related international standards and reference reagents, which may be used in clinical trial assays.

Documents relevant to HIV vaccines research and development.

Meeting reports from the consultations with the experts for research and development of HIV vaccines on:

Efficacy trial endpoints, trial design considerations

Considerations regarding clinical trials of HIV vaccines in the age range likely to be the target of public health campaigns, i.e., adolescents before or around the time they becoming sexually active and thus, at risk of HIV infection.

Documents related to clinical evaluation

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</table>
| Good participatory practice guidelines for biomedical HIV prevention trials, second edition, 2010. UNAIDS/10.E/JC1853E (English original, July 2010). http://data.unaids.org/Pub/manual/2010/guidelines_biomedical_hiv_prevention_2010_en.pdf | Guiding principles for regulatory review for the purposes of clinical trial approval and licensing, which apply to a broad range of vaccines. Document serves as basis for setting or updating national requirements, as well as for WHO vaccine prequalifications. Also informs manufacturers on regulatory expectations for clinical evaluation of vaccines intended for global use and should be read in conjunction with Guidelines or Recommendations for specific types of vaccines. (Currently subject to revision; updated version will be available at the http://www.who.int/biologicals/)

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| Operational Guidelines for Ethics Committees that Review Biomedical Research. TDR/PR/ETHICS/2000.1 http://www.fercap-sidcer.org/publications/pdf/201202/FERCAP-16-WHO%20EC%20Operational%20Guidelines.pdf | Guiding principles for regulatory review for the purposes of clinical trial approval and licensing, which apply to a broad range of vaccines. Document serves as basis for setting or updating national requirements, as well as for WHO vaccine prequalifications. Also informs manufacturers on regulatory expectations for clinical evaluation of vaccines intended for global use and should be read in conjunction with Guidelines or Recommendations for specific types of vaccines. (Currently subject to revision; updated version will be available at the http://www.who.int/biologicals/)

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<tr>
<td><strong>Documents related to clinical evaluation</strong></td>
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<tr>
<td>Ethical considerations related to the provision of care and treatment in vaccine trials. Tarantola D, Macklin R, Reed ZH, Kvien MP, Osmanov S, Stobie M, Hanksins C. Vaccine. 2007 Jun 21;26(24):4863-74</td>
<td>Considerations regarding individuals who seek enrollment or are enrolled into HIV vaccine trials and become infected on study through risk behavior – ethics surrounding their care and treatment, outside the objectives of the study itself. Proposal to rapidly advance HIV vaccine clinical trials by conduct of pilot efficacy trials to prove concept of HIV vaccine strategy/regimen.</td>
</tr>
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* WHO, in collaboration with other bodies, are playing an important role in the area of HIV vaccines. This table includes WHO Guidelines and Recommendations published in the Technical Report Series (TRS), as well as meeting reports from WHO and UNAIDS consultations, as examples of the sources where regulators may find useful information.

### Table 2


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<tr>
<td><strong>General or Quality or Safety-related Documents</strong></td>
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<tr>
<td>ICH Validation, Q2(R1) Validation of Analytical Procedures: Testing &amp; Methodology <a href="http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html">http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html</a></td>
<td>Guidance pertains to the concepts and methodology relevant to the analytical validation of methods of analysis, particularly lot release assays and tests. These concepts may also be used in validation of analytical methods used for clinical trial samples, although the document is not written from that perspective.</td>
</tr>
<tr>
<td>ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products <a href="http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html">http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html</a></td>
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<td>ICH Clinical Trial topics, E8 through E11 <a href="http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html">http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html</a></td>
<td>Guidance pertains to how clinical study reports should be prepared for regulatory review. It may be used as a guide to how clinical trials should be planned and conducted.</td>
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<td>FDA GFI: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases 2011 <a href="http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM282995.pdf">http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM282995.pdf</a></td>
<td>Guidance pertains to how the USFDA would support the review and development of vaccines of global relevance, including HIV vaccines.</td>
</tr>
<tr>
<td>FDA GFI: Toxicity Grading Scale for Healthy Adult &amp; Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007 <a href="http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm">http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm</a></td>
<td>Document provides a sample grading scale for adverse events following immunization, including reactogenicity, to be used in clinical trials.</td>
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<tr>
<td>FDA Clinical Trials Guidance Documents <a href="http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm">http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm</a></td>
<td>Documents cover a range of topics pertaining to clinical trials, including ethics review.</td>
</tr>
<tr>
<td>EMA Regulatory Page for Human Medicinal Products <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&amp;mid=/guidelinedocu">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&amp;mid=/guidelinedocu</a>...</td>
<td>Links to documents on a wide range of topics covering the regulatory procedures of EMA, which has responsibility within the EU for evaluating marketing authorization for vaccines made through DNA technology. Second weblink is specific to clinical trials.</td>
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Table 3
Summary of challenges relevant to regulatory evaluation of clinical trial applications for HIV/AIDS vaccines.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Challenge</th>
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| Unknown type and amount of immune response to guide vaccine development | • Due to a lack of human survivors (convalescents), of predictive animal models, & of a validated immune correlate of protection, there is little compelling scientific evidence to guide vaccine developers as to what type or amount of immune response to aim to achieve with a vaccine candidate or regimen  
  • Regulators should consider the type of immune response the applicant claims to be the mode-of-action of the product to be studied & the data provided demonstrating that the product induces such a response; T cells alone are unlikely to achieve efficacy, but some combination of T cells' & antibody-mediated effects may  
  • Protocols for efficacy studies, pilot or pivotal, should include plans to identify a correlate of protection, including collection of appropriate specimens, in order to gain some parameter(s) to use for bridging, consistency lot studies, etc., later in development or post-licensure  
  • Some vaccines will elicit responses that will score as "positive" in HIV test kits (serological); need assays to be able to distinguish infected from vaccinated (DIVA)  
  • May need to rely more on NAT than serological tests for diagnostics  
  • Adolescents will be a prime vaccination target, so clinical trials enrolling adolescents are needed  
  • Regulators need to consider what adult data they will require before allowing adolescent trials to proceed & whether efficacy established in adults will be bridged to adolescents or whether adolescents should have efficacy directly evaluated  
  • Recognizing that it is unethical to withhold standards of prevention &/or care from trial participants, as these standards evolve with increasing availability of suitable methods/products, trials will need to be designed accounting for the impact these standards will have on reduction of clinical trial endpoints, among other trial design & conduct issues  
  • Some methods will reduce HIV acquisition risk indefinitely (e.g., circumcision) & some only transiently (while the prevention methods are in use), further complicating data analysis & ascertaining contribution of vaccine to protection  
  • Regulators reviewing protocol should ensure that applicant has addressed these facets in said protocol  
  • Protocols for efficacy of preventive HIV/AIDS vaccines should include prevention of acquisition of HIV infection as a primary endpoint  
  • Modulation of disease progression in those who become infected despite vaccination may be considered an important secondary endpoint (in efficacy protocols; could be co-primary)  
  • Safety & immunogenicity should be studied in all clinical phases  
  • Clarity in analysis plan on per-protocol, ITT, MITT analyses, sub-group analyses, hierarchy of analyses vis-à-vis claims to be made  
  • Efficacy trials should incorporate a futility analysis, so studies of non-efficacious or enhancing vaccines can be halted as soon as feasible; hence need for DSMB/DMC oversight  
  • Statistical adjustments for multiple looks at data need to be defined in analysis plan  
  • Regulators should consider whether applicant has adequately addressed such issues in protocol & receive analysis plan for review & comment before applicant performs analyses |
Table 3 (continued)

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<tr>
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| **Adaptive Design** | - Adaptations to trial design or conduct can be prospectively planned & engaged depending on contingencies (e.g., change in attack rate within trial due to evolving standards of prevention, changes due to outcomes of other trials likely to be completed during the conduct of trial under review)  
- Regulators need to concur with such adaptations in advance of their execution by applicants, either during initial review or in amendment(s) |
| **Correlates Analysis** | - Regulators should expect applicants to plan for & collect necessary specimens to conduct an analysis for correlates of protection (or risk) in efficacy trials  
- Regulators need to consider how applicants will be expected to bridge efficacy, if correlate of protection is not identified, despite efforts to find one or more  
- Vaccines that act through different modes-of-action may have different correlates of protection  
- Regulators should consider whether applicant has anticipated that by time efficacy study is completed, new assay methods will be available, so specimens should be collected & stored for future analyses |
| **Access Issues & Planning for Success** | - Although access to a successful HIV/AIDS vaccine is not strictly a regulatory issue, regulators should review proposed efficacy protocols with a mind towards how applicant has planned for success, incl. partial success, e.g.:  
- Will placebo recipients be vaccinated at end of trial after successful outcome?  
- Will community from which trial participants were drawn or country in which trial was conducted have affordable & sufficient access to successful vaccine after licensure?  
- Others  
- Regulators may wish to communicate with relevant national agency responsible for public health/access to vaccines/medicines |
| **How Regulators Can Prepare** | - Familiarize themselves with what is and what is not known, in order to have scientifically realistic expectations & requirements of applicants  
- Familiarize themselves with available guidance documents, meeting reports, reviews summarizing scientific challenges & regulatory expectations with eye towards what is or is not known  
- Recognize that there are many scientific unknowns, so relative lack of expertise on HIV/AIDS vaccines by regulator does not mean that regulator has to make decisions in isolation & with greater uncertainty than exists within the field  
- WHO provides various documents, capacity-building efforts, & fora for regulators in different countries to discuss issues among themselves & with experts in HIV/AIDS vaccine field  
- Regulators & applicants are encouraged to avail themselves of the aid WHO provides |

**Appendix 1**

Documents that provide some useful information for development and regulatory evaluation of vaccines in general and HIV vaccines in particular

**References**


