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HIV Vaccine Development: Strategies for Preclinical and Clinical Investigation

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Abstract

This article discusses HIV vaccine discovery and candidate vaccine testing in the context of current realities of funding and clinical trial practice. Lacking perfect animal models for testing candidate HIV vaccines, clinical investigators have proposed a strategy of iterative exploratory clinical trials in the model of cancer chemotherapy development. Problems with the appropriateness of this model to HIV vaccine development are discussed. Also, the future feasibility of this strategy in the context of increasing clinical trial costs and emerging new, efficacious prevention modalities is questioned. Strategies for making better use of animal models are presented as an alternative to iterative exploratory clinical efficacy testing. Some ways in which better data from preclinical studies can refine clinical product development are described. Finally, development of an HIV vaccine under the FDA's "Animal Rule" pathway to licensure when human efficacy studies are not feasible is discussed as a fall-back approach. Not making a preventive vaccine against HIV infection is simply not an option because eradication of AIDS will require a preventive vaccine.

Introduction

The purpose of this article is not to present yet another perspective on the science required to make an efficacious HIV/AIDS vaccine. Rather it is to situate HIV vaccine discovery and candidate vaccine testing in the current reality of funding and the conduct of clinical trials to inform a discussion of our current HIV vaccine product development strategy and suggest an alternate course. Presently, HIV vaccine scientists develop candidate vaccines through preclinical immunogenicity studies and sometimes demonstrate some protection in a nonhuman primate challenge model. Then they apply for the funding to take their vaccines into early stage human clinical testing often without a precise hypothesis for the mechanism of action of their vaccine or a clear understanding of the amount and type of data needed to obtain the major investment required for efficacy testing. Clinical investigators have unintentionally contributed to the confusion by encouraging the field to believe that large-scale clinical trials can easily be used to discover immune correlates of protection against HIV infection to iteratively inform needed improvements in vaccine efficacy. At the same time the costs of clinical testing are increasing, funding sources are under pressure, and manufacturers and funders are increasingly reluctant to make the major commitments required for large-scale clinical testing in the absence of greater certainty of success. Some suggestions for the types of data that will reduce the uncertainty inherent to large efficacy trials and more fruitful approaches and measures that could possibly accelerate HIV vaccine development will be made in this article. But these suggestions are by way of strategies for preclinical studies and tactics for testing in early phase clinical trials rather than insights into the immunology of immunogen design.

Several points will be made. But the first point that must be understood is that HIV vaccine development is occurring in a complex environment of regulatory compliance, clinical trials conduct, and funding limitations that scientists must navigate if their work is to be relevant to the development of a vaccine that can be tested and eventually licensed. I believe that the current approach of iterative, large-scale clinical trials to inform the science of HIV vaccine development is based on a questionable analogy to the paradigm used for cancer chemotherapy development. Furthermore, escalating costs may soon preclude continuing with this approach. While it is true that animal models for HIV vaccine development are not perfect, they must be used more rigorously and more intensely to generate better data to guide clinical vaccine product development. This is not to suggest that demonstrating protection with a vaccine candidate in some preclinical animal model be a gatekeeper for entry into human testing of candidate HIV vaccines. Rather, the gatekeeper should be knowledge of the specific immune responses that

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must be observed in early phase clinical testing to predict vaccine efficacy. Lastly, if large-scale efficacy testing of an HIV vaccine becomes infeasible there is an alternate route to vaccine development but it will also require the same, more detailed preclinical research studies proposed here to facilitate standard vaccine product development.

Challenges with the Present Iterative Exploratory Clinical Trial Approach to HIV Vaccine Development

HIV vaccine developers have long bemoaned the fact that HIV-1 does not replicate in any accessible small animal model and simian immunodeficiency virus (SIV) models do not allow direct testing of HIV vaccines. Furthermore, it is felt that some experimental challenges used in nonhuman primate models might be more stringent than is relevant for typical transmissions of HIV-1 between humans.[1] Inadequacy of animal models has clearly slowed HIV vaccine development. It has also frequently been noted that preclinical animal studies did not predict the lack of efficacy observed in the large-scale HIV vaccine clinical trials of gp120 protein vaccines and the adenovirus-vectored vaccine developed by Merck. Nor did the lack of animal model efficacy data preclude the modest efficacy seen in the USMHRP/Thai trial, RV144. So many clinical investigators argue that the inadequacy of animal models for HIV vaccine design means that such studies must not be "gatekeepers" preventing the large-scale testing of candidate HIV vaccines that have not demonstrated efficacy in animal studies.

Some clinical scientists have proposed that preventive HIV vaccine development follow the iterative exploratory clinical trial pathway successful in cancer chemotherapy development. In this paradigm multiple successive trials are used to refine treatment regimens, producing regimens with greater and greater efficacy. Instead of simply refining vaccine regimens HIV vaccine developers would use iterative trials to inform the discovery of immune responses that correlate with protection to serve as a guide for vaccine improvement. This strategy, while well-motivated and imaginative, ignores some very real differences that make such an approach impractical for HIV vaccine development. Cancer chemotherapy regimens could be tested in small numbers of subjects at serious risk of dying in a short time. Thus the clinical investigators were allowed to test relatively toxic drugs because any benefit to someone dying usually outweighed the risk from the product. This is not the case with preventive HIV vaccines, which are tested in healthy people. Candidate prophylactic vaccine products to be tested in healthy people require much more extensive and expensive preclinical toxicity testing. And because vaccines are biologic products rather than simpler drugs, which can be evaluated postmanufacturing for structural identity and purity, the cost and time involved in setting up GMP[a] manufacture is much greater. Also, while partial efficacy could be seen in cancer chemotherapy trials with as few as 10 to 20 subjects (all of whom had the cancer in question), because of the relatively low transmission rate HIV vaccine studies must be performed in thousands of people in order to see any hint of efficacy. Furthermore, small cancer chemotherapy trials gave results in months to a year allowing multiple regimens to be successively tested in a relatively short time while most large-scale HIV vaccine studies take 4 to 5 years for enrollment, vaccination, and follow-up to determine whether there was any effect. These factors taken together mean that the cost and time frame for the iterative clinical trial approach to HIV vaccine development is daunting.

An Additional Problem with the Present Approach: Increased Clinical Trial Costs to Incorporate Other Preventive Modalities

If the pace and cost of the iterative clinical trial approach were not already problematic, it will be much more of a challenge in the future. HIV/AIDS vaccine developers must consider the recent successes in demonstrating efficacy of other prevention modalities. Male circumcision, female microbicides, treatment-as-prevention, and some regimens of preexposure prophylaxis have all shown some effect in reducing transmission of HIV. As these prevention modalities become approved or licensed and available there will be increasing ethical need to provide them, along with condoms and risk-reduction counseling, to all participants in vaccine trials even in developing country settings where many participants would not normally have access or be able to afford them. This will immediately increase the materials costs for HIV vaccine trials. Also, inclusion of other prevention modalities in vaccine trials will inevitably greatly reduce the HIV transmission rate in cohorts enrolled in the clinical trials, which will necessitate much larger sized clinical trials to demonstrate efficacy if it does not preclude efficacy testing altogether.[b] Already it can cost more than $100 million to perform a phase IIB "proof of concept" clinical trial. Inclusion of new prevention modalities as they come on line can be expected to at least double if not quadruple or quintuple this cost. Yet with the current economic downturn in developed world economies it is unrealistic to expect such a large increase in funding without greater certainty of success. In addition, the incorporation of some of the new prevention modalities (e.g., preexposure prophylaxis) in clinical trials of vaccines may mask potential early vaccine enhancement of transmission and thus complicate the licensure of the vaccines as regulatory agencies may require coadministration with the prevention modalities with which they were tested in order to ensure the efficacy demonstrated in the clinical trials.

Adaptive clinical trial designs have been proposed[2] that may make it somewhat easier to discard ineffective products more quickly. And if multiple products are available for testing in different arms of the same trial then fewer subjects would be needed because the placebo group could be shared. However, delays in manufacturing appear to be routine, so multiple products are rarely available for concurrent testing. Thus these designs are unlikely to significantly reduce the number of subjects needed or substantively address the increased cost issues.

[a] "Good Manufacturing Practice" as defined by the FDA in the Code of Federal Regulations (21 CFR §210, 211), which is necessary to ensure biologic product consistency from lot to lot.

[b] Indeed, some already worry that the efficacy trials planned in Thailand and South Africa in follow-up to the successful RV 144 Thai Trial may not take place if there is too much delay caused by manufacturing difficulties and/or difficulty reaching a consensus on crucial product/dose/regimen questions.

In recognition of the insufficiency of resources to advance every HIV vaccine candidate into efficacy trials, individuals in the Division of AIDS, the Bill & Melinda Gates Foundation, and the Global HIV Vaccine Enterprise are working together on an "Immunological Space Table Project" to help funders and vaccine developers rationally prioritize candidates for testing. By "immune space" is meant the characteristics or quality, quantity, and durability of the immune responses elicited in early human trials by a candidate HIV vaccine. All else being equal (safety profile, preclinical animal model protection data, product production considerations) the approach proposed to decide which candidates advance to efficacy trials is to advance the best candidates that elicit each distinct immunologic profile and, by doing so, enable evaluation of a spectrum of potential immune correlates of protection. While this is a laudable attempt to categorize vaccines for prioritization, all vaccines induce multiple immune responses and some investigators hypothesize the need for vaccines that induce a combination of responses for protection; it is unclear how complex, partially overlapping vaccine responses will be easily categorized in the Immunological Space Table. Nevertheless, this is a needed refinement of the iterative exploratory clinical trial paradigm that may help funders make some of the hard decisions. But it does not address the escalating costs and other difficult issues in HIV vaccine efficacy testing. Also, it would be tragic to discontinue work on a promising vaccine modality if the best in its class simply did not elicit a sufficient quantity or epitopic specificity of what could have been the correct immune response to score as efficacy in an expensive, large clinical trial.

An Alternative Approach to Iterative Exploratory Large Clinical Trials: Make Better Use of Preclinical Models

The way out of this vaccine testing dilemma is to garner greater support for the expensive efficacy trials by developing greater certainty that a vaccine will work before launching the large-scale clinical trials. This can be done with more intensive and rigorous testing in preclinical animal models to inform bridging immunologic assays for early phase clinical testing. This is not to suggest that preclinical animal models be a gatekeeper for entry into human testing of candidate HIV vaccines. Rather, the gatekeeper should be the development of enough knowledge about how a candidate vaccine will actually work, such that clinical investigators know specifically what immune responses to measure in early phase clinical testing (and how much activity is required).

In the past few years nonhuman primate investigators have developed repeat, low-dose mucosal challenge (rectal, vaginal, and penile) models that can better, and more quantitatively, assess protection against the establishment of infection. Recently it was shown that such challenges of rhesus macaques with SIV recapitulate the establishment of infection by a single virus[3–5] frequently observed in human mucosally acquired infections with HIV-1[6]; this significantly contributes validity to these models. Also, there have been recent advances in the development of mouse models with "humanized" immune systems. Some will contend that these models are still not perfect, and thus not a substitute for iterative exploratory clinical trials. However, another view is that past preclinical animal models were not used appropriately, or were not sized to allow for sufficient quantitation of protection to establish quantitative immune correlates or the mechanisms of any protection observed. With the improvements in the nonhuman primate models in the past year and the availability of larger numbers of test animals several investigators have already published analyses of "correlates of immunity" associated with vaccine protection in nonhuman primate challenge studies.[7–9] This is an advance, but these studies have still not been performed with the rigor, as described below, required to obviate the need for iterative exploratory large clinical trials in search of immune correlates of protection.

The animal models should be used before human testing to establish quantitative immunologic "mechanisms" of protection to be assayed for in early phase human trials. As a first step investigators would test their products for immunogenicity. Then challenge of the immunized animals would determine if protection has occurred before determination of the immune correlates of that protection. But this is only the start. If the correlate is actually indicative of a protective immune mechanism then increasing the quantity of that quality and specificity of immune response in the operative location should result in an increased number of animals protected in a follow-up study.[c] Next the immune correlates must be further analyzed to determine not just the quality of immune response needed, but the quantity (titer or level of T cell response), epitopic specificity, and location of response required for protection.[d]

Requiring clear definition of quantity and mechanism of protection is not asking more of HIV vaccine developers than of the developers of other vaccines. HIV vaccine developers frequently remark that most efficacious human vaccines were developed empirically, with at best only a poor understanding of the immune responses needed to be induced for protection.[10,11] However, such remarks indicate a lack of appreciation of the scientific efforts of earlier vaccine developers. The developers of most earlier vaccines relied on antibody responses to evaluate vaccines in early phase clinical trials as they hypothesized that antibodies would be the basis of immune protection. Sometimes these vaccine developers used or attempted to use information from animal protection studies,[12–15] protection by passive transfer of antibodies studies,[16–18] and natural history studies[13,17,19] to estimate target protective antibody titers. They did not proceed "empirically" into large efficacy trials with products that failed to induce sufficient antibody responses. In addition to quantity of immune response, the extreme epitopic diversity of HIV makes it clearly important to define the epitopic specificity of a vaccine response in order to ensure broad

[c]Maximum magnitude of protection is also important to determine. There may be little interest in investing a large amount of resources in the development of a vaccine that, at best, provides only enough protection to require six challenges with virus instead of three challenges before infection of all animals in the study even though that protection is statistically significant.

[d]Note that quality of immune response, epitopic specificity, quantity, and location of the specific immune response required for protection are all listed. An imprecisely defined "correlate" is not a mechanism that can be built upon in the iterative testing scenario proposed. Things such as "avidity of the antibody response for gp120" or "mucosal $CD8^+$ T cells" are an improvement over the old "antibodies vs. cellular immunity" debate but are still insufficiently defined to be useful "mechanisms of protection" in this strategy.

coverage of the vaccine. And knowledge of the location of the operative response is necessary to match the vaccine with populations likely to benefit since HIV is transmitted at different locations by several very different modes of transmission (genitally, rectally, percutaneous, peripartum, and by breast milk).

Some investigators may prefer to work in humanized mice so that the animals can be immunized with the actual HIV vaccine and challenged with HIV, while others may prepare analogous SHIV or SIV vaccine constructs and perform their studies in nonhuman primates. This is the investigators' choice,[e] but the goal should be the same, to determine very specifically a mechanism of protection. Another "proof" of the mechanism of protection would be to generate the same quality, specificity, and quantity of immune response with a different vaccine construct/modality and demonstrate that it was similarly protective in a challenge study. Using animals to dissect out the mechanism(s) of protection by experimental HIV vaccines was the basis for the Gates Foundation-funded Pacific Northwest Correlates Consortium (grant award #41185 entitled "Immune correlates of protection against HIV and SIV infection") and is also the basis for the Consortia for AIDS Vaccine Research in Nonhuman Primates recently funded by NIAID (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-10-004.html).

Much of this suggested preclinical analysis has already been done for one possible mechanism of an HIV vaccine, neutralizing antibodies, in studies performed more than a decade ago by Mascola and co-workers for MPER and glycan specificities.[20,21] It has been confirmed by others with passive transfer of neutralizing monoclonal antibodies directed against the CD4 binding site.[22] Thus, in early phase clinical trials of a candidate neutralizing antibody-inducing HIV vaccine, if investigators determine that a sufficient level and epitopic specificity of neutralizing antibodies were induced this would certainly generate the interest of funders for the investment in further development. All that is being suggested here is that developers of HIV vaccines that are hypothesized to function by other broad neutralizing antibody epitopic specificities or other protective immune mechanisms should work out those protective mechanisms with a similar degree of rigor.

How Additional Preclinical Data Could Be Used to Refine Clinical Product Development

Starting with a "mechanism of protection" hypothesis, phase I clinical trials should then demonstrate that a human vaccine product can induce in people the needed quality, specificity, quantity, and localization of immune response determined to be required for protection in the preclinical studies. In this way the vaccine candidate becomes a well-defined "concept" allowing large phase IIB clinical trials to be truly "proof of CONCEPT" trials (with the "concept" being an immune mechanism of protection) rather than the "proof of product" studies that they are today (where the "concept" is really only that "this product will offer protection"). There can be no justification for proceeding to large-scale clinical trials with a product that does not induce a level and specificity of immunity predetermined to be required for protection. Thus phase I studies could eliminate many products from further consideration, or at least stimulate better designed dose-ranging, regimen optimizing studies in phase II. Furthermore, the path to licensure could possibly be shortened by taking several products designed to induce the same specific immune response(s) into phase I concurrently (these products need not be rigidly analogous to the products tested in nonhuman primates as long as they elicit the same quality, specificity, and location of the functional immune response). All of them that demonstrate adequate immunogenicity in phase I and/or phase II could then compete for position in the phase IIB study based on issues such as scalability,[f] stability, cost of production, availability of a commercial manufacturing partner, etc.

In addition, if enough high-risk subjects were enrolled in each phase IB study[g] (say perhaps as many as 100 for each of 10 products) and they were followed for an extended period of time (say for 5 years instead of for 2 years) with repeated measurement of the quantity of the immune response still in circulation and whether or not the subjects had become infected with HIV-1, enough endpoint data could be obtained to perform a meta-analysis of the multiple trials. This could give both an early read on possible efficacy as well as some indication of the frequency of boosting needed to prolong protection. Such a meta-analysis would never be accepted by regulatory authorities in lieu of formal efficacy testing; however, it could reduce the uncertainty of phase III studies enough to convince funders and manufacturers.

Lastly, the definition of a "mechanism of protection" should contribute to more realistic phase IIB and phase III trial design. While some mechanisms may be protective against multiple modes of transmission others may be more limited,but these limitations could be used to focus clinical trials on the most appropriate populations [e.g., women only, men who have sex with men (MSM) only, etc.] and thus offer savings in reduced trial size.

Moving Beyond Traditional Licensure Trials If Large-Scale HIV Vaccine Efficacy Studies Become Infeasible

Many will complain that the methodical strategy of working out the detailed requirements for protection in preclinical studies may delay HIV vaccine efficacy testing so long that the availability of other preventive measures will ethically or practically preclude efficacy testing of any HIV vaccine. Fortunately, the necessity to protect against agents of bioterrorism has already led the FDA to address the pathway to

[e]Homologous vs. heterologous challenge is not the investigators choice. The diversity of HIV-1 in circulation demands a vaccine that can protect against the heterologous exposure that people will experience.

[f]Scalability of manufacture is a very important issue. It would be tragic, as well as a potential political disaster, to demonstrate that an HIV vaccine worked in a high-risk community desperate for such a vaccine and then not be able to deliver that vaccine to the rest of that community for another 5 to 10 years because not enough attention had been given to manufacturing capability.

[g]Phase IB is the part of phase I clinical testing, after initial testing in 10–20 healthy, low-risk subjects for simple safety, where product testing can be expanded into other populations for an expanded read on safety and preliminary activity (immunogenicity in the case of a vaccine) in those populations. This can be planned for in phase I testing, contingent upon a safety analysis after the initial phase; and it accelerates the collection of phase II-like activity data.

licensure for candidate vaccines that cannot meet the requirements of traditional licensure because human efficacy studies are not possible for ethical reasons or because field studies to assess efficacy are not feasible; this is the "Animal Rule" (21 CFR §314 Subpart I). In this case sponsors demonstrate that the candidate product is likely to clinically benefit humans by (1) selecting appropriate animal models and study endpoints, with concurrence from the FDA on these choices, (2) understanding the pathophysiology of the disease and immune responses involved in protection, (3) conducting studies in the selected animal model(s) using cGMP-produced material, (4) developing and validating assays that are indicators of protection and that link human and animal immune responses, and (5) demonstrating that the appropriate type and level of immune response are induced in humans receiving the candidate vaccine. After licensure postmarketing, phase IV studies that carefully correlate decreasing new HIV infections with vaccine distribution and acceptance would be required to verify the product's efficacy as well as provide additional safety information.[h] Investigators who follow the strategy of more intensive preclinical testing described in this article will be preparing their product for licensure under the "Animal Rule." Please understand that the "Animal Rule" approach is not raised here as a shortcut because as long as it is feasible to perform classical phase III efficacy studies they will be required. Rather this approach is described as a "fail-safe' strategy should the licensure of too many other prevention modalities preclude efficacy testing of an HIV vaccine.

In Conclusion

Some already argue that much of the money devoted to developing an HIV vaccine is wasted because the epidemic can be controlled with the concerted use of the developing multitude of other prevention tools. In his address to the AIDS Vaccine 2012 meeting in Boston, Dr. Anthony Fauci, the Director of the NIAID, acknowledged that it may be possible to control the AIDS epidemic with the developing suite of other prevention modalities. However, he argued that maintenance of control over the long term may require a preventive vaccine, and elimination or eradication of this disease will definitely require a vaccine. This is because of inherent difficulties with continued, large-scale national efforts as well as individual compliance over a long time. Furthermore, the no-vaccine approach to control of the HIV epidemic comes with an extremely large and seldom acknowledged cost. The maintenance of an intensive HIV control effort based on constant adherence to individually directed prevention modalities, with prolonged antiretroviral treatment of prevention failures, will divert enormous resources needed for development in the poorest countries in the world condemning a large portion of the world's population to grinding poverty for decades if not centuries to come. This epidemic may transform some entire societies into HIV-control economies, denying large numbers of people future development of their creative potential. This is unconscionable. HIV/AIDS must be eliminated; this is not a disease that we want to see become an accepted part of human existence. The world cannot be denied an HIV vaccine. But its development will require better and more intensive preclinical research.

[h]This may require a very accurate incidence assay that can be performed on cross-sectional serosurvey samples. Fortunately there has been increased interest in developing such an assay in recent years (see the report of a workshop sponsored by the NIAID in 2011[23]).

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