Clinical Development of Candidate HIV Vaccines: Different Problems for Different Vaccines

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Abstract

Realization of individual and public health benefit from an HIV vaccine requires clinical testing to demonstrate efficacy. To facilitate clinical testing, preclinical HIV vaccine developers should consider the realities of clinical practice and the conduct of clinical trials in product design. There are several essentially different approaches to prophylactic HIV vaccine design: (1) induce immunity that allows infection but reduces initial peak viremia and viral load set point; (2) induce immunity that allows infection but controls viremia to below the level of detection; (3) induce immunity that allows infection but promotes viral clearance before disease (classic vaccine approach); (4) induce “sterilizing immunity” that prevents acquisition of infection. Each approach presents different challenges for clinical product development. Current clinical trial practices and evolving treatment standards may make it infeasible to perform an efficacy trial of a preventive vaccine that only modestly reduces viremia. A vaccine that promotes control of viremia to below the level of detection is testable but will require extended follow-up to determine how long virus control persists; once control is lost boosting with the same vaccine may not be useful. A vaccine that permits infection but promotes subsequent complete clearance of the virus from the body will require the development and validation of an effective assay for virus clearance. A vaccine that prevents acquisition of infection is the most straightforward to test in the clinic, but escalating costs require more attention by vaccine developers to understanding how the vaccine works and the breadth of protection. All types of vaccine require attention to effect size to ensure adequate powering of efficacy trials.

Introduction

THERE ARE SEVERAL WAYS IN WHICH a prophylactic HIV vaccine could provide individual as well as public health benefit (Fig. 1). An ideal vaccine would prevent acquisition of infection (“sterilizing immunity”); this type of vaccine is the goal of most HIV vaccine developers today. Failing prevention of infection, a vaccine that allowed infection but then promoted virus clearance before disease could be manifested would provide clear benefit as well and would actually be analogous to most licensed vaccines for other pathogens. However, because HIV-1 rapidly integrates into the host genome and establishes a reservoir of latently infected cells such a vaccine was not thought to be possible for HIV until very recently. Slow progress in the development of these two types of vaccines has led some HIV vaccine developers to point out that HIV vaccines that simply reduce initial peak viremia and viral load set point would likely delay progression to AIDS and thus provide individual benefit while at the same time

reducing onward transmission of infection to others. But it is a frustration to many laboratory scientists working on this last vaccine approach that it is increasingly difficult to generate the support needed for the expensive clinical development required for licensure. Some candidate products are regarded as not economically or logistically feasible for delivery in the developing world where they are most needed. In addition, some funders argue that the increased focus on combining newly developed nonvaccine prevention modalities as well as increased access to antiretroviral therapy in the developing world has reduced interest in such vaccines. But also, many vaccine developers have failed to fully consider the dictates of best clinical practices and conduct of clinical trials, which has led them to push vaccine candidates where demonstrating efficacy may not be feasible. This article discusses some of the complicating factors in clinical testing that basic scientists should consider before making a large investment of time, resources, and energy in extensive preclinical laboratory research.

FIG. 1. Course of viremia during HIV-1 infection with potential vaccine effects indicated (modified from Chuen-Yen Lau, NIAID/Division of Clinical Research).

Fundamental Problems with Testing HIV Vaccines That Do Not Prevent Infection

HIV vaccines that do not prevent acquisition of infection face serious complications in efficacy testing. The difficulties in the path to licensure for such vaccines were extensively discussed by an expert consultation organized by the WHO, UNAIDS, ANRS, and the Global HIV Vaccine Enterprise in 2007.¹ A major concern presented was that although the clinical benefit of greater viral load control on delay in disease progression has been seen in analyses of natural history studies, this assumption has not yet been validated for when that control is induced by the different immune mechanisms that may be operating in different candidate vaccines. For example, a vaccine that induced binding antibodies to the HIV-1 envelope could lower plasma viremia and create the appearance of better viral control by promoting enhanced clearance of noninfectious virus from the bloodstream without significantly impacting the spread of infection from cell to cell in the tissues. And while many believe that virus-specific cytotoxic T-lymphocytes (CTL) contribute to early viral load set point, it is also certain that multiple genetic factors [including but not limited to human leukocyte antigen (HLA)] contribute to natural virus control. Thus disease progression may reflect a complex interaction between immune and innate factors that is not simply captured by viral load set point. In the absence of validation of clinical benefit from vaccine reduction in viremia, clinical trials of such vaccines will be complicated by the requirement of extensive, long-term follow-up to measure clinical end points [or surrogate markers for clinical end points such as time to initiation of antiretroviral therapy (ART)]. Recently an assay of the antiviral inhibitory capacity of CD8⁺ T cells at viral load set point was observed to be predictive of the rate of CD4⁺ T cell decline.² If such an assay could be validated then, perhaps in conjunction with the measurement of viral load, it could contribute to greater confidence in the efficacy of viral load set point-lowering vaccines.

Postrandomization selection bias was another concern about the use of viral load set point as an end point in preventive HIV vaccine trials that was raised by statisticians and regulators in the panel consultation.¹ Such bias is a problem that can complicate analysis when only a subset

of the originally randomized clinical trial population is analyzed (in this case, only those who become infected during the course of the trial). The subset of people who become infected after vaccination may be biased toward people with a different inherent/genetic ability to control viral load set point. So an observed difference in viral load set point could be the result of inherent factors rather than vaccine effect.

Another major problem, not discussed by the panel consultation, has arisen more recently because the frequency of testing for HIV infection in vaccine and other preventive clinical trials has increased to as often as every 2 to 3 months. This better ensures the ability to detect enhancement of infection effects and thus enhances subject safety by facilitating early stopping of the clinical trial for harm. Also, frequent testing is necessary to capture the transmitted/founder viruses for enumeration of infecting viruses and sophisticated sieve analyses that could give some indication that a vaccine product whose efficacy did not reach statistical significance was at least partially effective. Such analyses are important because they may also give some clues to the molecular mechanism(s) of that partial protection. However, with such frequency of testing, more infections in clinical trial volunteers are being detected in the very acute phase (the first few months after infection). Increasingly, the recommendation of most clinicians in the developed world to all individuals diagnosed with HIV infection is to start antiretroviral drug treatment immediately; but this is especially a concern for those diagnosed with acute HIV-1 infection.³ Immediate treatment preserves as much as possible their immune system from the massive destruction of CD4 cells that occurs during the first months of infection and reduces the size of the reservoir of latently infected cells.^{4,5} Also, some clinicians believe that acutely infected individuals, with higher viral loads, composed of largely unmutated, recently transmitted viruses, are much more infectious and so may disproportionately fuel the HIV epidemic⁶; this presents another reason for immediate treatment. However, the accurate determination of viral load set point in clinical trial subjects who become infected requires them to delay treatment in order for clinical investigators to obtain several independent measurements of viral load. Some may argue that subjects in developing country settings will not go on early treatment because of harsh economic realities that restrict access to antiretroviral drugs and so such studies may still be performed there. However, we must anticipate that evolving ethical guidelines, in the not too distant future, may include offering the same standard of care to clinical trial subjects in the developing world that is offered to subjects being given the same trial products here in the United States.

These testing realities and treatment complicate the testing of all vaccines that do not prevent acquisition of infection. But they present a much greater problem in the testing of vaccines that propose to only reduce initial peak viremia or viral load set point without lowering viral load profoundly, or to undetectable levels. While inevitably some subjects diagnosed with acute HIV infection will decline immediate treatment, there are unlikely to be enough of such subjects to accurately determine a statistically significant difference between the viral load set points of vaccinated and control subjects. This means that in the absence of other measurements suggesting efficacy, vaccines that only

modestly lower viral load set point may have become infeasible for efficacy testing.

HIV Vaccines That Reduce Viral Load Set Point to Below the Level of Detection Without Clearing Virus Reservoirs May Still Be Testable

Despite the testing problem described above, some HIV vaccines that do not prevent acquisition of infection may still be testable. Vaccines that promote such good control of virus that viremia is reduced to near or below the level of detection without viral clearance would essentially turn infected individuals into what are called "elite suppressors."⁷ Because this level of control is not usually observed until several months after infection, clinical development of such vaccines will still be complicated by the same clinical trial testing realities discussed above for all vaccines that do not prevent infection. Since subjects will be tested for HIV infection more frequently, most new infections will be detected, and the vaccinated group will appear similar to the placebo group with respect to acquisition of infection. However, even if offered, it is unlikely that all subjects diagnosed with acute HIV-1 infection will choose to start immediate treatment. Because fewer than half of 1% of natural infections are controlled to the level of "elite suppression,"⁸ only a small number of subjects declining immediate antiretroviral treatment may be needed to demonstrate a clear difference in the numbers attaining such profound viral control between vaccinated and placebo control groups. This is an example of using an increased "effect size"^a as an alternative to increasing sample size to enhance the statistical power of a clinical trial.^b

While a very large vaccine effect may satisfy the statistical concerns in demonstrating vaccine product effect it may not satisfy regulators concerned about validation of clinical benefit so extensive follow-up and clinical end points (or surrogates for clinical end points) may still be required. In addition, there will be persistence of a reservoir of viable latent virus that could reemerge. The question will arise as to how long the profound degree of viral control will be maintained after initial vaccination. Determining the persistence of viral control will require a substantial extension of the follow-up period in a clinical efficacy trial and add expense that must be considered. Also, since reemergence of viremia suggests virologic escape from immune control by mutation of the epitopic targets of the vaccine-induced

immune response it is unlikely that revaccination with the same vaccine product will be useful, as it would with a completely prophylactic vaccine.

Testing HIV Vaccines That Allow infection and Then Promote Viral Clearance Is Still Clearly Possible

Recently a candidate HIV vaccine based on a persistent viral vector (CMV) was tested in the SIV/nonhuman primate model system. This vaccine, which did not prevent acquisition of infection, demonstrated such profound control of viremia that it is believed a significant number of challenged animals in the study were actually cleared of virus after initial establishment of infection.¹⁰ This is significantly different from a vaccine that "solely" reduces initial peak viremia and viral load set point. Indeed a vaccine that enables the body to clear HIV-1 after acquisition of infection is truly analogous to the many licensed vaccines against other pathogens that do not prevent infection but rather help the body clear the infection more rapidly and thus reduce or prevent disease.¹¹ Such a vaccine against HIV would be of unarguable individual and public health benefit. Nevertheless, clinical development of this type of vaccine to prevent AIDS will be complicated by the same clinical trial testing realities discussed above for vaccines that only reduce viral load. However, as with vaccines that create elite suppressors, vaccines that promote clearance will first reduce viral load below detection; therefore an effect will be observed with the small number of subjects that decline immediate antiretroviral treatment. Nevertheless, a vaccine that promotes clearance of virus will almost certainly require accompanying development and validation of a cost-effective assay to determine that complete virus clearance has occurred.

Because of perceived regulatory constraints on testing vaccines based on persistent viral vectors in normal, healthy individuals, some have proposed testing a CMV-vectored HIV vaccine first as a therapeutic/cure vaccine in HIV-1 infected individuals. This may be a good regulatory strategy. However, used prophylactically, where the latent reservoir should be smaller, this vaccine may be more efficacious than if used to cure individuals who have been infected for prolonged periods of time. So if clinical development as a therapeutic vaccine fails, preventive trials with this category of vaccine should still be pursued.

The General Challenges to Development of Any HIV Vaccine Also Apply to Vaccines That Prevent Acquisition of Infection

Although vaccines that truly induce sterilizing immunity^c will not encounter the diagnosis/treatment complications in testing that vaccines that allow initial infection will have, they still share some serious challenges in clinical development with the other approaches to HIV vaccine design. A previous article,¹² which should be read as a companion to this article, discussed how the need to incorporate new prevention modalities will greatly increase the cost of clinical efficacy trials.

^a"Effect size" is the measure of the strength of a phenomenon. Along with increasing the sample size (i.e., the number of subjects enrolled in the trial) or tinkering with the significance level or type I error (e.g., a priori changing the acceptable *p* value), increasing the effect size (i.e., seeking an outcome that departs more from the null hypothesis) is an accepted way of increasing the statistical power to detect the desired outcome.⁹

^bAdmittedly the development of increasingly sensitive measures of plasma viremia blurs the distinction between an "elite suppressor vaccine" and a vaccine that merely reduces viral load set point. Thus the author allows that some of the vaccines that may be described as reduction in viral load set point vaccines may be licensable if the degree of reduction is profound enough to be observed in a small number of subjects and to overcome the postrandomization statistical bias concerns. Clearly the target reduction must be thoroughly discussed with regulators early in the development process and must factor into the powering of any efficacy trials.

^cThe word "truly" is used here to acknowledge that some vaccines may only appear to provide sterilizing immunity because the frequency of testing was not sufficient to pick up abortive or rapidly cleared infections. This is probably only of academic concern as regulators will not require validation of clearance of infections not detected in the first place.

To cover such increasing costs funders will require greater certainty of success. This can be provided if the developers of such vaccines more clearly determine, in preclinical animal model studies, the immunologic mechanism(s) of protection of their vaccines and the quality, quantity, epitopic specificity, and location of the immune responses required for protection. Then the vaccine products can be assessed for whether they induce predetermined target immunogenicity profiles in earlier, less expensive phases of clinical testing. Those that do not meet target immunogenicity can be refined in small-scale clinical studies or returned to the laboratory for additional optimization before the large expenditure of funds to conduct large-scale clinical efficacy trials. Of course, these considerations also apply to the vaccine approaches that allow initial infection with HIV-1.

It is also critical to assess predicted magnitude of protection for the design and costing of large-scale clinical efficacy trials. The smaller the percent of people protected by a vaccine, the larger the number of subjects that must be enrolled in an efficacy trial in order to detect a significant difference in acquisition between the vaccine and placebo groups. Thus vaccines that are predicted to protect only 40–50% of subjects will require larger efficacy trials, which will make them more expensive to test, than vaccines that are predicted to protect 80–90% of subjects. This is another example of the impact of “effect size” on the statistical power of a clinical trial. Vaccine developers should consider the magnitude of the protective effect in product design and preclinical testing and not spend time and resources on vaccine approaches that cannot be made to offer broad protection in preclinical models.

Discussion and Conclusions

Not all logically beneficial HIV vaccines are practical candidates for clinical development. Several HIV vaccine developers have demonstrated that their candidate HIV vaccines (or SIV analogs) are able to significantly reduce peak viremia and/or viral load set point in nonhuman primate models.^{13–15} Many review articles and presentations at scientific meetings have indicated that an HIV vaccine need not be completely protective against establishment of infection to have some individual and public health benefit.^{8,16–18} If a vaccine simply reduced the viral load set point it would probably delay progression to AIDS and thereby offer some health benefit to the recipient. Also, a vaccine that reduced peak viremia and viral load set point would probably have public health benefit as it would reduce further transmission of infection by the newly infected.⁶ In fact, a group of expert consultants assembled by the WHO, UNAIDS, ANRS, and the Global HIV Vaccine Enterprise has even established recommendations on efficacy end points to be used in testing such vaccines.¹ However, there are many complications in the path to licensure for such vaccines and funding agencies appear to have diminished interest in clinical efficacy trials of vaccines that enhance viral control without prevention of acquisition of infection.

Some have suggested that interest in an HIV vaccine that only reduces viral load set point without preventing acquisition of infection is declining simply because of the increased focus on combining newly developed nonvaccine prevention modalities. But access and adherence to individually targeted prevention measures for everyone at risk of infection remain seriously limited. Without an expensive and difficult to

sustain global effort, large numbers of people will continue to become infected. And incomplete access to testing means that most infections will continue to be diagnosed only years after they were acquired. In this situation a vaccine that would reduce peak viremia and viral load set point continues to offer significant value. Yet evolving clinical practices and clinical trials testing protocols increasingly complicate testing such a vaccine. So while the benefits of reduced viremia would be real, evolving clinical trial and treatment practices may have made it impractical to test for or detect such effects on viremia in the absence of other measures of clinical benefit. When emerging best practices in treatment for the subject and for prevention are at odds with the requirements of clinical trial design, this presents an ethical dilemma. If it is not feasible to measure viral load set point as a primary end point in an efficacy trial, scarce resources should not be used on the development of products that reduce viral load only marginally.

Vaccines that prevent infection are the most straightforward to develop for prevention of HIV/AIDS. But developers of such vaccines must put more effort into determining the mechanism of protection of their candidate vaccine and target immunogenicity to be observed in early phase clinical trials to justify the large expenditure of funds required for efficacy testing. A vaccine that promotes complete clearance of virus after acquisition of infection is also a promising candidate for clinical development. Such a vaccine would provide protection against the disease of AIDS in the same way as the many licensed vaccines against other pathogens that do not prevent infection but rather help the body clear the infection more rapidly to reduce or prevent disease. But investigators interested in developing a vaccine for HIV that promotes viral clearance should work to develop a cost-effective assay for HIV-1 viral clearance. Vaccines that reduce viral load set point substantially, especially to below the level of detection, may also still be testable but will require plans for long-term follow-up to ensure continued efficacy.

Practical challenges in conducting large-scale clinical trials make developing an HIV vaccine about more than elegant science. Laboratory investigators must consider the complications inherent to the clinical testing of their vaccine approaches in product design and sometimes also be prepared to develop additional assays to facilitate clinical trials. Scarce resources should not be consumed on the development of products without a feasible efficacy testing plan. Clinical development time should not be unnecessarily lengthened by inadequate preparation for foreseeable challenges in clinical efficacy trials. With increased thought about the implications of different product designs for clinical testing, HIV vaccine development could be accelerated. Millions of people around the world are depending on the success of our efforts.

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References

1. Fruth U: Considerations regarding efficacy endpoints in HIV vaccine trials: Executive summary and recommendations of an expert consultation jointly organized by WHO, UNAIDS and ANRS in support of the Global HIV Vaccine Enterprise. *Vaccine* 2009;27:1989–1996.
2. Yang H, Wu H, Hancock G, *et al.*: Antiviral inhibitory capacity of CD8+ T cells predicts the rate of CD4+ T-cell decline in HIV-1 infection. *J Infect Dis* 2012;206:552–561.
3. Saag M: When to start: As soon as possible. *J Int AIDS Soc* 2012;15(Suppl 4):18070.
4. Archin NM, Vaidya NK, Kuruc JD, *et al.*: Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infections. *Proc Natl Acad Sci USA* 2012;109:9523–9528.
5. Walker BD and Hirsch MD: Antiretroviral therapy in early HIV infection. *N Engl J Med* 2013;368:279–281.
6. Powers KA, Ghani AC, Miller WC, *et al.*: The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: A modeling study. *Lancet* 2011;378:256–268.
7. Blankson JN: Control of HIV-1 replication in elite suppressors. *Discov Med* 2010;9:261–266.
8. Walker BD: Elite control of HIV infection: Implications for vaccines and treatments. *Top HIV Med* 2007;15:134–136.
9. Sharp DS and Gahlinger PM: Regression analysis in biological research: Sample size and statistical power. *Med Sci Sports Exerc* 1988;20:605–610.
10. Hansen SG, Ford JC, Lewis MS, *et al.*: Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature* 2011;473:523–527.
11. Walker BD and Burton DR: Toward an AIDS vaccine. *Science* 2008;320:760–764.
12. Shapiro SZ: HIV vaccine development: Strategies for pre-clinical and clinical investigations. *AIDS Res Hum Retroviruses* 2013;29:1401–1406.
13. Shiver JW, Fu T-M, Chen L, *et al.*: Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature* 2002;415:331–335.
14. Wilson NA, Reed J, Napoe GS, *et al.*: Vaccine-induced cellular immune responses reduce plasma viral concentrations after repeated low-dose challenge with pathogenic simian immunodeficiency virus SIVmac239. *J Virol* 2006;80:5875–5885.
15. Liu J, O'Brien KL, Lynch DM, *et al.*: Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys. *Nature* 2009;457:87–91.
16. Watkins DI: The hope for an HIV vaccine based on induction of CD8+ T lymphocytes—a review. *Mem Inst Oswaldo Cruz* 2008;103:119–129.
17. Freel SA, Saunders KO, and Tomaras GD: CD8+ T-cell-mediated control of HIV-1 and SIV infection. *Immunol Res* 2011;49:135–146.
18. Katsikis PD, Mueller YM, and Villinger F: The cytokine network of acute HIV infection: A promising target for vaccines and therapy to reduce viral set-point? *PLoS Pathol* 2011;7(8):e1002055.

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