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A Proposal to Use Iterative, Small Clinical Trials to Optimize Therapeutic HIV Vaccine Immunogens to Launch Therapeutic HIV Vaccine Development

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Abstract

The HIV cure agenda has rekindled interest in the development of a therapeutic HIV vaccine. An iterative clinical trial strategy that proved successful for the development of effective cancer chemotherapies in the 1960s may be applicable to the development of a CD8 T lymphocyte-based therapeutic HIV vaccine. However, while cancer chemotherapy development could begin with iterative clinical trials to improve the use of active drugs, the first step in therapeutic HIV vaccine design should be discovery of immunogen constructs with potential for activity and their optimization to meet the challenges of HIV-1 sequence diversity and human polymorphism in T cell antigen presentation. A strategy for doing this is discussed in this article. The proposed strategy relies on a major commitment by funding organizations to fund organized and coordinated manufacture and clinical testing of a series of first- and second-generation constructs to test basic concepts in product design. This is presented as an alternative to funding a more traditional competition among private manufacturers and product champions of individual, already designed products.

Introduction

While preventive HIV vaccine development has been a constant goal since the discovery of HIV-1, interest in a therapeutic vaccine for HIV-infected people has fluctuated. Many have felt that a therapeutic vaccine is not possible as until recently there were no examples of such vaccines for other diseases.[a] And with the advent of increasingly effective, simple to take, and relatively nontoxic combination drug therapies there has been less call for immune therapies to substitute for or augment drug therapy. However, the HIV cure agenda has rekindled interest in a therapeutic vaccine to enhance immune-mediated clearance of virus-producing cells and/or assist in the destruction of the reservoir of latently infected cells that drug therapy alone does not seem to be able to eliminate.[1]

Last year a meeting was held in Bethesda, Maryland (September 19–20, 2013) to reinvigorate therapeutic HIV vaccine development.[2] Recent therapeutic HIV vaccine trials were described, and there was a discussion of results of therapeutic vaccine studies in nonhuman primate models. It was clear that therapeutic HIV vaccine development requires addressing several very different issues. These include the following: (1) What type of immune responses can be induced in an already HIV-1-infected person and which will be most effective? (2) Will responses with new specificities be required or will simply boosting the body's initial responses be effective? (3) What vaccine vectors, vehicles, or adjuvants will induce maximal (titer and breadth) responses? (4) Why do initially controlling responses fail with time? and (5) Can adjuvant or adjunct non-antigen-specific immunotherapy contribute to vaccine efficacy by prolonging or reconstituting preexisting responses?

It was readily apparent that therapeutic vaccine development trials and studies are following the standard preventive vaccine development path. After conceptualizing a product, 5 to 10 years of animal model testing are performed before 2 to 5 years of GMP product development to enable another 10 to 15 years of phase I then phase II then phase III clinical trials of a specific candidate vaccine product before licensure and distribution will occur. This path is depressingly slow and may not be an optimal way to deal with the multiple critical issues to be addressed in therapeutic vaccine development. Attempting to design a vaccine to address such a complexity of issues by reasoning out all the multiple aspects of the

[a]The shingles vaccine, Zostavax, could be considered a therapeutic vaccine as it prevents clinical cases of shingles in people already infected with the Varicella zoster virus.

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final product before testing is very risky. There is a strong possibility of total failure at the end of a prolonged period of testing because of failure to include one essential component, or the inclusion of unnecessary components that detract from overall efficacy.

An effective therapy should be built up from components all known to be active. A methodical, iterative development strategy could address the multiple product aspects individually. This article proposes a methodical clinical testing approach to start the development of a cellular immunity-based therapeutic vaccine immunogen (i.e., working out the optimal HIV antigenic content and its sequence refinement as an insert in a vector or vehicle for delivery) as a first step in therapeutic HIV vaccine development. This alternate path may require some changes to the organization of funding and greater collaboration between academic scientists and product developers in the early stages.

The First Decision: Humoral versus Cellular Immunity

The first issue for therapeutic HIV vaccine development is the basic choice between inducing an antibody response or a $CD8^+$ T-lymphocyte response. Many therapeutic vaccine developers have focused on CD8 responses since they are known to contribute to the initial control of viremia.[3,4] Also, the broadly neutralizing antibody responses that some investigators hope will control viremia have been so difficult to induce by active vaccination.

The administration of already identified broadly neutralizing monoclonal antibodies (MAbs) for passive protection is clearly the most direct route to the development of an effective antibody-based therapeutic product. Indeed, several broadly neutralizing MAbs are already in development, and the path for development of a therapeutic monoclonal antibody is well worked out. Some iterative clinical trials may be required to put together the most effective combinations of MAbs after individual monoclonals have been shown to have effect. This may present some challenges in measuring clinical endpoints. However, there will be a strong incentive to work through these challenges because of the demonstrated superior efficacy of combination chemotherapy for cancer, tuberculosis, and AIDS itself. This article will focus on a strategy for the development of a CD8 cell-based therapeutic vaccine because that task is more complex and less certain of success, and thus in greater need of a plan to jump start the process.

Iterative Clinical Trial Strategy for Product Development

In the mid-1960s major breakthroughs in cancer treatment occurred. Several anticancer drugs had previously been shown to selectively kill cancer cells, but their anticancer efficacy in patients was usually only partial and transient, rarely completely eliminating the cancer. It was reasoned that cancer therapy could benefit from the new strategy of combination therapy, developed for tuberculosis, where combinations of drugs with different mechanisms of action eliminated a greater fraction of the pathogen than any single drug alone, leading to complete suppression of disease or even cure of the infection. But the experience of failure in treatment with single drugs convinced clinicians that optimizing these combinations must be done with patients in clinical trials because the ability to kill cancer cells *in vitro* did not accurately predict curing cancer in a patient. Thus multiple clinical trials were performed to enhance the efficacy of cancer chemotherapy by iteratively testing different combinations, doses, and treatment regimens in small scale clinical trials until effective protocols were developed to treat and even cure cancers such as leukemia and Hodgkin's disease.[5]

The complexity of issues to be addressed in therapeutic HIV vaccine development, the absence of a good animal model for AIDS, and the lack of systems to induce cellular immune responses *in vitro* argue that there is a role for iterative clinical trials to play in this field. However, iterative clinical development for a therapeutic HIV vaccine will be more complicated than it was for cancer chemotherapy. This is because the great sequence diversity of HIV-1 and human population diversity in antigen presentation requires first the identification of the most effective target antigens before optimal vectors, vector combinations, dosages, regimens, and adjunct therapies can be determined.

The identification of cancer chemotherapy drugs was facilitated by the ability to test drugs *in vitro* for cancer cell killing potential. Testing the ability of immune responses against specific targets in the virus (the epitopes in the antigens) to kill HIV-infected cells or suppress virus replication will require first inducing those immune responses in people. Natural history studies of acute HIV-1 infection make it clear that not all CD8 cell antiviral immune responses measured in the laboratory are equally effective at killing infected cells or suppressing virus proliferation to control viral load. In some cases peptide epitopes that can be synthesized and used in an *in vitro* ELISpot assay are not efficiently processed or presented *in vivo*. In other cases escape from different responses by mutation of specific target epitopes may have very different fitness costs for the virus,[6] which will be reflected in different apparent levels of control of viremia. In yet other cases what may be effective epitopic targets in some individuals may not be present in the virus that infected other people or may not be presented by the polymorphic antigen-presenting molecules of other individuals.

In very few cases is the initial CD8 response sufficient to efficiently control viremia.[7] It is commonly believed that a therapeutic vaccine must generate more and different epitopic responses than occur upon infection, especially new responses to escape epitopes and difficult to escape from epitopes many of which are subdominant immune responses in an individual exposed to whole virus proteins. The more critical epitopes recognized the more effective a vaccine will be for more people. Thus in an iterative development strategy for a CD8-based therapeutic HIV vaccine the first step should be studies in people to discover the most broadly effective antigen targets and optimize immunogen constructs to meet the challenges of HIV-1 sequence diversity and human MHC polymorphism.

Some may think that this has already been done in the many years that candidate preventive HIV vaccines have been under testing, but this is not the case. Many preventive vaccine developers have simply opted for as much of the virus protein content as possible, hoping the immune system will respond to the best targets; they have not addressed immune dominance or sequence diversity issues. While simply getting a response to a large enough diversity of epitopic targets may be sufficient for protection against

acquisition of infection, therapeutic vaccine developers must pay more attention to the optimization of epitopic targets as the HIV-infected people in need of a therapeutic vaccine have already been exposed to all of the HIV-1 proteins and the immune responses they have made are clearly inadequate.[b]

Competing theories of how to optimize the virus antigen targets have been proposed. These theories are the consensus,[11] mosaic,[12] and conserved[9,13] sequence approaches. The consensus approach proposes to use consensus or ancestor sequences of the virus proteins to minimize the sequence differences between vaccine constructs and the strains of virus in circulation to which people are exposed. In the mosaic approach a small set (two to four) of ''mosaic'' proteins, assembled from fragments of natural sequences via a computational optimization method, is proposed to cover most virus sequence diversity. The conserved sequence approach builds on the observation that greater viremia control in newly infected people was correlated with $CD8^+$ cell recognition of epitopes in protein sequences that showed little variability (suggesting that these immune responses might be more difficult to escape from because the sequence of the protein in that place was more critical to virus replication); thus vaccine designers with this approach have used immunogen constructs that contain only the most conserved regions of the virus protein to focus the immune response on what are often subdominant epitopes.

These are all interesting hypotheses, but no one has systematically compared the effectiveness of all the different possible target virus proteins, designs, and constructs under the conditions of the human immune response.[c] What is proposed here is to perform this systematic analysis in two to three sets of sequential small clinical trials as a way to identify the optimal immunogens to be included in a therapeutic vaccine product.

Clinical Study Design Issues

The choice of the HIV-infected subject population in whom the immunogen constructs will be tested is important in choosing the clinical endpoint assay for these clinical studies. This stage of testing must be performed in subjects with sufficiently high levels of $CD4^+$ T cells (e.g., greater than 350/μl) to have effective immune responses. This is the case even though subjects with more advanced disease are in greater immediate need of a therapeutic vaccine product. The goal at this early stage is not making the final product but rather simply the identification of the most useful targets and the insert immunogen designs that will induce the broadest and best $CD8^+$ responses (responses that are cytotoxic for HIV-infected cells and suppress virus replication). The comparative study of vectors/vehicles that will induce maximal responses and adjuvants or adjunct immunotherapies that could compensate for or bypass the immunosuppression of later stage HIV disease (and thus make a therapeutic vaccine more efficacious for all individuals) will follow. However, those optimizations will clearly be facilitated by first determining the specific, most effective target immunogens and their best design.

In this first stage of development it is important to identify all responses that could contribute to the efficacy of a final, developed product. Therefore HIV-1 proteins should be examined separately to avoid immune competition masking a response to useful epitopes. It is anticipated that multiple studies will be needed. Thus the clinical endpoint assays for this first stage of development should facilitate rapid, multiple trials at the least risk to the subjects. The clinical endpoint assays should also be relevant to the goal of the therapeutic vaccine as well as the stage of testing. Ultimately the goal will be eliminating the latent reservoir. However, since latently infected cells express no or minimal HIV antigens it may not be possible for a cytotoxic or virus suppression immunotherapy on its own to eliminate the latent cell reservoir in an antiretroviral (ARV)-treated patient with no detectable viremia; thus difficult to perform measurements of the latent reservoir at this early stage may not be useful or necessary.

If the goal of a therapeutic HIV vaccine is enhancing immune-mediated clearance of virus-producing cells in patients poorly controlled by ARV therapy this would be reflected in a decrease in circulating viremia. In this case measurement of viremia and/or some quantitative assay of virus-producing cells should be acceptable assays. However, such patients are probably not the most appropriate subjects for early therapeutic vaccine development studies.[d] I propose that the best and safest approach to determining the activity of potential products at this early stage is a combination of a virus suppression assay[15,16] (using multiple viruses to take into account virus sequence diversity) and an ELISpot assay[17] that will allow the determination of the specific epitopes recognized. If these assays are performed before and after vaccination of fully virally suppressed subjects, comparison should indicate the expansion of the CD8 response to new targets.[e]

What is proposed specifically is to break the virus protein complement down into four smaller pieces[f] and prepare separate vectors containing each of these fragments for

[b]Some investigators believe that the specificity or number of epitopes recognized is not as crucial for viral control as is the specific functionality of the $CD8^+$ T cells that recognize the epitopes.[8] Inadequate T cell functioning may contribute to the problem, but in the absence of clear procedures to change T cell functionality and with accumulating evidence of the importance of different types of epitopes[9,10] optimizing the epitopic response is a clear place to begin work on a therapeutic vaccine.

[c]A soon to start clinical trial in uninfected subjects (HVTN 106) will compare the breadth and depth of epitopic responses to a natural isolate envelope sequence with those to consensus and mosaic envelope constructs, but a conserved sequence construct will not be part of the comparison, nor will the other viral proteins.

[d]Increasingly, clinicians in this country are coming to believe that incomplete virologic suppression is either a compliance problem or means that the correct combination of drugs for that patient has not yet been tried.[14] In either case it will be argued that improvement in treatment is called for rather than enrollment in an experimental clinical trial.

[e]Note that it may be necessary to use a cultured ELISpot assay[18] to reveal prevaccination cytotoxic T lymphocyte (CTL) responses in subjects who have been on antiretroviral therapy so long that few effector T cells remain in circulation.

[f]The fragments should probably be (1) gag, (2) pol, (3) tat/rev/nef, (4) vif/vpr/vpu. The HIV-1 envelope protein is not proposed for optimization for a CD8 response-based vaccine for two reasons: (1) it likely contains the most targets for epitopically specific responses that are easy to escape from, which could detract from more useful targets as it is the virus protein with the greatest sequence variability, and (2) cytotoxic responses against epitopes in envelope could impair antigen presentation if a way is found to induce a neutralizing antibody response against envelope in a future vaccine.

testing to avoid extremely immune-dominant epitopes in some HIV antigens masking the presence of useful epitopes in others. To reduce the number of studies it will be best to first test a single HIV antigen in the three competing construct designs (consensus, mosaic, and conserved) so that the best overall construct design can be used for the separate antigens. The best antigen to use for these tests is probably gag as the quality and quantity of cellular responses to gag have already been implicated in viremia control in HIV infection.[19]

The proposed set of clinical studies would test each of the three first-generation gag construct designs in 30 to 40 subjects looking for expansion of CD8 responses to epitopes not previously seen by the HIV-infected trial subjects.[g] After determination of the best construct design for gag the other three sets of HIV antigens should be tested in the optimal construct design determined for gag. These studies can probably be performed in smaller groups of subjects as the determination of the presence of useful epitopes for a majority of subjects will probably not require as many subjects as determining the superiority of a construct design will.[h] HIV antigens not observed to contain any useful epitopes for a majority of subjects should not be included in a therapeutic vaccine as they may only detract from final product efficacy. The HIV proteins with useful epitopes in the best construct design should then be combined into a small number of optimized immunogen constructs; manufacturing considerations probably limit the number of separate constructs in a final vaccine to six or fewer. These constructs will probably then need to be tested in another 20–30 subjects to ensure that immune competition does not compromise the effective antigen presentation of the individual constructs.

At the end of this first stage of testing a single (or small set of) insert construct(s) will have been assembled that will provide the broadest coverage of epitopic targets to give the greatest therapeutic effect. This will provide the reliable, active ingredients for the next stages of iterative clinical testing, which will be more analogous to cancer chemotherapy development. A comprehensive approach to optimal immunogen construction at the start should enhance the possibility of success with later stages of product development.

Other Factors That May Facilitate Clinical Testing for Vaccine Immunogen Optimization

CD8 responses are best generated against immunogen sequences expressed from vaccine vectors that get into host cells. Initiating the early studies will be accelerated by using vectors that have already been in phase I or phase II clinical trials. This is because the insertion of an HIV antigen (some of which have also already been in some clinical trial) into a vector backbone with a well-established safety record will more quickly pass regulatory requirements.

Fortunately there are many such vaccine vectors from which to choose that have already been tested with HIV antigen inserts (e.g., nucleic acid constructs, adenovirus vectors, poxvirus vectors, alphavirus vectors, VSV). As testing will be performed in HIV-1-infected subjects it may even be possible to use the well-established Adeno5 vectors that have been precluded from preventive HIV vaccine trials because of the perceived risk of enhancement of HIV-1 transmission.[20] Also, the magnitude of the immune response is certain to factor into the size of any impact on virus suppression as well as the ability to detect potentially important subdominant responses. Since most vectors/vehicles tested in humans have not induced very strong responses to HIV antigens,[i] heterologous prime/boosts, which enhance immune responses, will probably be necessary.

We could prime with a DNA plasmid construct (possibly delivered by electroporation) and then boost with a viral vector, or prime with the immunogen sequence inserted in one viral vector and boost with the same sequence in a different viral vector.[21] It would also probably be wise in the first stage (of immunogen insert optimization) when testing with single or small sets of antigens (analogous to treatment with single drugs) to avoid using persistent vectors that could stimulate a long-lasting monospecific response more easily escaped from by virus mutation as this might preclude future effective treatment of the early stage test subject with the ultimate combination vaccine.

Next Stages of Iterative Clinical Testing

There are several distinct target populations that need an immunotherapeutic HIV vaccine. Although the optimized immunogen constructs identified in the proposed set of clinical trials should be useful in all the different populations, the same vaccine products (i.e., the immunogen constructs inserted in vectors with or without adjuvants or adjunct immunotherapies) may not be optimal for all. Neither will the same clinical endpoint assays be useful in different clinical populations. So the next stages of development may need to target each population separately.

The different adult target populations for a therapeutic HIV vaccine are (1) HIV-infected adults on ARV therapy with competent immune systems; (2) HIV-infected adults on ARV therapy with few remaining $CD4^+$ T cells; (3) HIV-infected adults not fully suppressed on ARV therapy; or (4) those not on ARV therapy at all.[j] Similar categories exist for newborns infected with HIV-1 but, as the newborn immune system is not exactly like the adult immune system, therapeutic vaccine development for them may need to consider other factors.

[g]This number is not the result of a statistical analysis but simply starts with the number (30) being considered for each group in HVTN 106. A biostatistician must determine the actual group sizes based on factors such as HLA frequencies, preexisting cellular responses, and epitopic density. Such an analysis has been done for HVTN 106, which will be performed in uninfected subjects, but the results may differ when preexisting responses in HIV-infected subjects are factored in.

[h]The actual number of subjects per group should be determined by a biostatistician.

[i]While different combinations of primes and boosts have demonstrated effectiveness in nonhuman primate studies, it must be admitted that the breadth of immune responses (i.e., the number of different epitopes recognized) that can be induced in humans has been more limited. This emphasizes the importance of the exploration of different vectors and vector combinations in the next stage of iterative clinical testing, which will aim to expand/maximize the breadth of the immune response as well as its magnitude.

[j]With treatment guidelines increasingly recommending effective ARV therapy for more categories of HIV-infected individuals it may become difficult, practically and ethically, to perform therapeutic clinical trials in the third and fourth groups.

The second stage of therapeutic HIV vaccine development should probably start with the determination of optimal vectors/vector combinations and immunization regimens for the first adult population. Dosage, regimens, and vectors/vector combinations should be optimized to provide the greatest magnitude of CTL responses to the largest number of different epitopes.

The best clinical endpoint assays for these optimizations early on will again be viral suppression and epitopic-specific ELISpot assays. Once an optimal combination regimen is determined the ultimate test of an HIV immunotherapeutic product will be an analytic treatment interruption. However, this should be done only in subjects in whom there is a realistic expectation of control (i.e., as evidenced by a significant and substantial enhancement in the virus suppression assay and a significant spreading of the immune response to difficult-to-escape-from epitopes, as well as perhaps a measurable reduction in cell-associated RNA).[22]

Treatment interruption runs a significant risk of doing harm to the subjects by allowing expansion of what was a small reservoir in subjects put on ARV therapy very early in infection or in subjects whose reservoirs have decreased in size because of many years of effective viral suppression on ARV therapy. Thus it should not be used as an exploratory assay but only to confirm expected efficacy. Demonstrated efficacy in the first target population will justify a major program to optimize a therapeutic vaccine for the other populations, although preliminary studies to find useful adjuvants and adjunct immunotherapies could proceed in the other populations in parallel.

Lessons for Preventive HIV Vaccine Development

This iterative clinical trial strategy for therapeutic HIV vaccine development could provide the basis for a more constructive interaction between the preventive and therapeutic HIV vaccine development fields. In the past, too many therapeutic vaccine trials have been dual track efforts with vaccines designed initially for prevention. Product developers have thought that by testing in HIV-infected populations the path to testing would be quicker[k] and the positive results generated would help them obtain the support needed for expensive preventive vaccine licensure trials. Also, if the vaccine has some effect in both populations it would expand the market for any eventually licensed product.

These rationales have led investigators to fail to consider the specific requirements of a therapeutic vaccine that may differ from a preventive vaccine. What is proposed here is a methodic and rapid way to sort through the many construct design approaches (consensus, conserved, mosaic) and potential candidate immunogen sequences (the HIV proteins) for overcoming the virus sequence diversity and human HLA polymorphism challenges posed by HIV-1. This work is essential for a therapeutic vaccine where existing responses are inadequate, but the results should truly inform both fields as both are in need of optimized immunogen constructs. Also, any work performed in the later stages on optimization of doses, vectors, and immunization regimens may contribute to preventive vaccine development. The same is the case for any needed adjuvant or adjunct immunotherapy work. And all these results will be quicker to obtain by iterative clinical trials for therapeutic vaccine development.

Organization and Funding

The iterative clinical trial development model successful in cancer chemotherapy is the starting point for a suggested strategy for therapeutic HIV vaccine development. However, it must be emphasized that although cancer investigators could begin with iterative improvements to active drugs, the first step in therapeutic HIV vaccine design must be discovery of immunogen constructs with the potential for activity and their optimization. This necessary very first stage would be most efficiently performed if a single coordinating group or consortium could decide on the insert constructs and their design variations to be tested and coordinate their manufacture with a single vaccine vector or vector combination for the multiple inserts to be tested. Also, a coordinated clinical testing and laboratory effort under the control of a single, dedicated clinical trials group would contribute to the thoroughness of analysis and comparability of results.

These arrangements should allow the series of clinical trials to be performed under the umbrella of a single IND application, which also would accelerate the process. A coordinated effort also requires that funders be prepared to commit substantial resources to an extensive, coordinated series of clinical trials so that all potential candidate antigens, in the several sequence diversity covering concepts (consensus, mosaic, conserved) and combinations, can be methodically examined. Because the first stage is exploratory, rather than product testing, it is hoped that the academic investigators who have hypothesized solutions to the HIV-1 diversity problem will come together to contribute their designs to this effort as scientific tests of concepts. Failure to show effectiveness under the different and probably more stringent conditions of a therapeutic vaccine setting will not preclude the usefulness of any antigens/immunogen designs in a preventive vaccine setting so that may make these comparative studies less worrisome to concept ''champions.''

What is proposed here is clearly different from the standard product development approach in which a product ''champion'' or manufacturer conceptualizes the complete product and then takes it down the well-formulated path of safety, activity, and finally efficacy trials. The standard path has clear advantages for final product development, licensure, and distribution because it engages manufacturers and their resources at an early stage. However, the standard path is not well-suited to the large amount of exploratory work that must be done in humans for the first step described above as necessary for efficacious therapeutic HIV vaccine development.

Conclusions

An iterative clinical trials approach is proposed for therapeutic HIV vaccine development. The first step in such a process for a CD8 response-based vaccine should involve methodical testing of all HIV-1 antigens to determine the optimal inserts to use in vectored vaccines. This process will

[k]They have reasoned that regulators may not be as concerned about potential risks in a population suffering from a life-threatening disease, but this is not true as with proper treatment HIV infection is now viewed as a chronic rather than a life-threatening disease.

require an organized consortium or collaboratory to oversee manufacture and clinical testing as well as judge optimal candidate immunogens based on the clinical assay results. As the cost of manufacturing and clinical testing continues to rise the funding of this consortium may even require a consortium of funders. An advantage of this process being orchestrated by a consortium/collaboratory of investigators funded by a consortium of funding agencies is that such a consortium could also ensure reasonable access by all reputable manufacturers to optimized antigens for further product development. The initial process may take 3 to 5 years. This first step will definitely require the major funders to work together on the organization and control of the effort.

This organization of iterative studies is not proposed as a complete substitute for more standard product development, but rather to better inform the earliest step in product development (antigen and immunogen sequence selection). Once optimal immunogens are determined vector selection and adjuvant and adjunct immunotherapy selection could be performed in the same way (overseen by a consortium) or the process could be opened up to competition by more conventional product champions. Standard phase III efficacy trials will still be required before licensure, and engagement of manufacturers and product champions may be crucial for that. This is not an either/or proposal because while immunogen optimization studies are taking place, it is expected that others will continue to pursue the more standard product development path in parallel efforts. However, if those other efforts fail, then the next set of therapeutic HIV vaccine development studies will proceed with more reliable immunogens if we now commit to the tasks proposed here.

Lastly, an argument has been made for beginning therapeutic HIV vaccine development by methodically determining the best HIV antigens and their optimal construction(s). However, it must be acknowledged that this is not the only place to start, nor is it certain that it is the best place to start. It may be better to start by determining which vectors/vector combinations give the maximal responses; this could facilitate subsequent sorting through problems of epitope immunodominance by enhancing the detection of all epitopic responses.

What is clear though is two things. First, the complexity of issues in therapeutic HIV vaccine design is best addressed one at a time. Second, while some of these issues can be addressed theoretically in animal models, the incredible sequence diversity of HIV-1 with the great polymorphism in antigen presentation in the human population requires that many of these issues be worked out by human clinical studies. This proposal to start with immunogen optimization by a methodical series of small human clinical trials will at least provide a much needed boost to the field of therapeutic HIV vaccine development.

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References

1. IAS Scientific Working Group on HIV Cure: Towards an HIV Cure: A global scientific strategy. Nature Rev Immunol 2012;12:607–614.
2. Fisher K, Voronin Y, and Jeffereys R: Therapeutic HIV vaccines: prior setbacks, current advances, and future prospects. Vaccine 2014;32:5540–5545.
3. Gulzar N and Copeland KFT: CD8+ T-cells: Function and response to HIV infection. Curr HIV Res 2004;2:23–37.
4. Goonetilleke N, Liu MK, Salazar-Gonzalez JF, *et al.:* The first T cell response to transmitted/founder virus contributes to the control of acute viremia in HIV-1 infection. J Exp Med 2009;206:1253–1272.
5. DeVita VT Jr and Chu E: A history of cancer chemotherapy. Cancer Res 2008;68:8643–8653.
6. Ganusov VV, Goonetilleke N, Liu MKP, *et al.:* Fitness costs and diversity of the cytotoxic T lymphocyte (CTL) response determine the rate of CTL escape during acute and chronic phases of HIV infection. J Virol 2011;85:10518–10528.
7. Walker BD: Elite control of HIV infection: Implications for vaccines and treatments. Top HIV Med 2007;15:134–136.
8. Thobakgale CF, Streeck H, Mkhwanazi N, *et al.:* CD8(+) T cell polyfunctionality profiles in progressive and non-progressive pediatric HIV type 1 infection. AIDS Res Hum Retroviruses 2011;27:1005–1012.
9. Kunwar P, Hawkins N, Dinges WL, *et al.:* Superior control of HIV-1 replication by CD8+ T cells targeting conserved epitopes: Implications for HIV vaccine design. PLoS One 2013;8:e64405.
10. Liu MK, Hawkins N, Ritchie AJ, *et al.:* Vertical T cell immunodominance and epitope entropy determine HIV-1 escape. J Clin Invest 2013;123:380–393.
11. Gaschen B, Taylor J, Yusim K, *et al.:* Diversity considerations in HIV-1 vaccine selection. Science 2002;296:2354–2360.
12. Fischer W, Perkins S, Theiler J, *et al.:* Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. Nat Med 2007;13:100–106.
13. Rosario M, Bridgeman A, Quakkelaar ED, *et al.:* Long peptides induce polyfunctional T cells against conserved regions of HIV-1 with superior breadth to single-gene vaccines in macaques. Eur J Immunol 2010;40:1973–1984.
14. Sarmento-Castro R, Vasconcelos C, Aguas MJ, *et al.:* Virologic suppression in treatment-experienced patients after virologic rebound or failure of therapy. Curr Opin HIV and AIDS 2011;6(Suppl):S12–S20.
15. 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.
16. Slichter CK, Friedrich DP, Smith RJ, *et al.:* Measuring inhibition of HIV replication by *ex vivo* CD8+ T cells. J Immunol Methods 2014;404:71–80.
17. Gill DK, Huang Y, Levine GL, *et al.:* Equivalence of ELISpot assays demonstrated between major HIV network laboratories. PLoS One 2010;5:e14330.
18. Pala P, Serwanga J, Watera C, *et al.:* Quantitative and qualitative differences in the T cell response to HIV in uninfected Ugandans exposed or unexposed to HIV-infected partners. J Virol 2013;87:9053–9063.

19. Streeck H, Lu R, Beckwith N, *et al.:* Emergence of individual HIV-specific CD8 T cell responses during primary HIV-1 infection can determine long-term disease outcome. J Virol 2014;88:12793–12801.
20. Duerr A, Huang Y, Buchbinder S, *et al.:* Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (STEP study). J Infect Dis 2012;206:258–266.
21. Sheehy SH, Duncan CJ, Elias SC, *et al.:* Phase Ia clinical evaluation of the safety and immunogenicity of the *Plasmodium falciparum* blood-stage antigen AMA1 in ChAd63 and MVA vaccine vectors. PLoS One 2012;7:e31208.
22. Pasternak AO, Lukashov VV, and Berkhout B: Cell-associated HIV RNA: A dynamic biomarker of viral persistence. Retrovirology 2013;10:41.

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