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Is an HIV Vaccine Possible?

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Abstract

Although many new prevention modalities that include the use of antiretroviral drugs (ARVs) show promise, there is no question that a global solution to the HIV epidemic will not be economically or logistically feasible without the development of vaccine that provides durable protection. In the best case scenario, the vaccine has to protect against acquisition of infection, likely mediated by Env-specific B cell responses combined with CD4+ T cell responses to evoke full maturation and maintenance of protective antibodies. But HIV-specific CD8+ T cell responses are also likely to be a key element, particularly for those inevitable situations in which full vaccine-induced protection from acquisition is not achieved, in which case durable control of established infection will be required. Although there is reason to be optimistic that an effective HIV vaccine is possible, one of the major constraints moving forward will likely be constraints on funding to support a diversity of concepts at a time that the correlates of protection from acquisition and disease progression are still unknown. Given the scope of the epidemic and the economic climate, we must strive to do much more with less and seek to access additional resources, both scientific and monetary, from every possible source.

Keywords

Vaccine; Antiretrovirals; Economy

Thirty years into the AIDS epidemic, reflection on medical accomplishments reveals stark contrasts. When HIV was conclusively identified as the causative agent,^{1,2} it was publicly anticipated that a vaccine would be available to prevent infection within a few years. At that time, few antiviral agents existed, and a pharmacologic solution to the epidemic was not even entertained. Now it is male circumcision and antiretroviral therapy that have shown the greatest promise for preventing infections,^{3,4} and an effective vaccine continues to be elusive, to the point that some believe it will not be possible. Some question whether it will be necessary at all. With drug therapy, we have been able to progress to a stage of relative epidemic control in certain parts of the world although there is currently but distant hope that treatment alone will lead to elimination and eradication. In our view, elimination and eradication will happen only with a vaccine, which, necessarily, will markedly reduce the daunting challenges of behavior and logistics of delivery and monitoring. However, achieving effective vaccine-mediated protection will require that we do better than nature. In HIV infection, unlike other vaccine-preventable illnesses, natural eradication of infection

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does not happen; viral integration into the host chromosome makes any infection lifelong, even in the setting of fully suppressive antiretroviral therapy.⁵

The challenges to achieving a protective vaccine are readily apparent given the results of HIV vaccine efficacy studies to date.⁶ In 30 years, only 3 vaccine concepts have been tested—already a paltry number—and all have either failed or shown signals of possible protection far below the level that would be needed to impact the epidemic.^{7,8,9} The correlates of protection remain unknown, and there is yet to be an immunogen available and tested that mimics the natural trimeric form of the HIV envelope on viable virions. New persons needing treatment outpace our ability to place people on therapy globally. Lack of impact of HSV treatment on the HSV epidemic¹⁰ provides a sobering reminder that therapy alone may not provide the required inflection point. The desperate need for an effective vaccine cannot be overstated.

But there are reasons to be optimistic. The recent successful prevention interventions with ARVs indicate that HIV-1 infected persons can reduce HIV transmission¹¹ and HIV-1 uninfected persons can avoid infection upon exposure.¹² These strategies offer attractive alternatives to slow the epidemic, but in a practical sense, they are the opening act for prevention while we await a vaccine that can provide safe, effective, and durable immunity to take the stage. The efficacy observed in the RV144 trial with the immunization of the canarypox/subunit protein gp120 prime-boost regimen in vaccinated Thai adults was at a low level: 26.4% (95% confidence interval [CI], -4.0 to 47.9; P=0.08) in the intention-to-treat analysis; 26.2% (95% CI, -13.3 to 51.9; P=0.16) in the per-protocol analysis; and 31.2% (95% CI, 1.1 to 52.1; P=0.04 by the O'Brien-Fleming method) in the modified intention-to-treat analysis; this result provides the best hope yet that a vaccine may one day be possible.⁹

As the HIV vaccine field seeks to confirm and build on the findings of the RV144 immune correlates analysis, we can increase the chances of future success by sharpening our focus now. We recognize that correlates may be different for different immunization strategies and are reminded of past experiences where it has been challenging to define correlates even when a highly efficacious vaccine regimen has been demonstrated¹³—something that still eludes us in the HIV field. Furthermore, we need to remain cognizant of the fact that the small numbers of end points in trials to date limit the sensitivity for detecting immune correlates. For example, there is a trend suggesting a role for HIV-specific CD4+ T cell responses in the RV144 trial, but the end points are too few to be certain. Yet such cells may be critical to control.¹⁴ The bottom line is that we must expect to move forward without a litmus test for vaccines while taking care that each new efficacy trial advances us beyond what we already have tested.

We must also embrace diversity. Experience over the decades has taught us the folly of an exclusive focus on a single strategy. We need to maintain an open mind, take a balanced and unbiased approach, and explore diverse strategies, moving products into phase 1 testing quickly and preparing for larger-scale testing when potentially relevant immune responses are generated. For example, the RV144 prime-boost regimen did not elicit detectable strong HIV-specific cytotoxic CD8+ T cells, so their impact on potentially improving or reducing efficacy is unknown. Yet it is testable, particularly with future mosaic constructs designed to induce broader epitope specificities.^{15,16,17} Similarly, envelope immunogens designed to induce broadly reactive neutralizing antibodies may increase vaccine efficacy,^{18,19} and their development should be encouraged, even though such neutralizing activities were not apparent with the RV144 regimen. New data on the structure of the HIV envelope trimer should be used to develop immunogens such as scaffolded V1V2 envelope, and together with a broad CD4+ T helper response, perhaps including direct effector function as well,¹⁴

should be taken forward into human trials. The recent advent of monoclonal antibodies that identify neutralizing epitopes and refined analysis of envelope crystal structure may expedite this process. The HIV-specific CD4+ T cells that have been generated to some extent with all prototype vaccine regimens evaluated thus far⁶ need to guide future efforts in this direction. Further, it will be crucial to understand the properties of CD4+ helper T cells that can enhance antibody avidity and durability as well as to optimize methods to detect these responses.

Parallel, coordinated strategies to define vaccine immunogenicity and immune correlates of protection in the SIV/SHIV nonhuman primate model and in humans can accelerate vaccine development. The nonhuman primate studies require careful study designs, including sufficient numbers of animals and relevant challenge inocula and routes that can better inform clinical trials and provide rationale for phase 1 studies. In turn, the need to rapidly move these concepts into humans requires rapid manufacture of clinical-grade products—but there is no efficient pipeline for this because dedicated resources are insufficient. Lack of understanding of immune correlates of HIV protection have made it difficult to formulate criteria to advance products to efficacy trials. Nevertheless, those that do reach that stage can be included as arms in test-of-concept trials using adaptive designs, which can then filter out those less likely to be efficacious.²⁰ Every efficacy trial to date has yielded important information that has been critical to defining the path forward, and this fact alone should endorse extensive testing of candidates in humans. By focusing such studies on places with extremely high incidence of new infections, we will accelerate the entire process.

We must also recognize the current severe economic limitations to moving the vaccine ahead at greatest possible speed. Current major funders in the field—the National Institutes of Health and the Bill and Melinda Gates Foundation—have expressed finite capacity to shift candidates into efficacy trials; already, some candidates for which efficacy testing should be in the active planning stage are being left unfunded. Thus, we must find a way to reduce costs of current trials (through such mechanisms as novel trial design, delaying correlates analysis until outcome is determined, testing in higher incidence areas, and reducing production times and costs). Simultaneously, we must find ways to seek new sources of funding and to engage scientists across all disciplines, to apply the full scientific toolbox to this problem. There will be increasing competing priorities as different prevention mechanisms show efficacy. These economic issues will almost certainly require meaningful increased partnerships with the philanthropic community, much as broad-based donations had a transforming impact on polio vaccine development.

Over 3 decades, medical progress has been truly impressive. Yet it has been insufficient for the problem at hand. The major scientific breakthroughs in HIV prevention and vaccine development have arisen largely out of dedicated affected communities and by partnerships led by scientific teams that include those from areas hit hardest by the epidemic. Undoubtedly, future insights will occur on the front lines of the epidemic, through iterative trials that build upon and think beyond RV144. It behooves the scientific community to embrace this amazing opportunity—to work with an open mind and to unite along all fronts with a goal to fulfill the need for a vaccine. We believe the problem is this is a solvable, and that what we learn from these efforts will have a lasting impact not only on vaccine approaches to infectious diseases in general but also on interventions for cancer, autoimmunity, and beyond. And we believe that the present generation has the ability to do this.

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