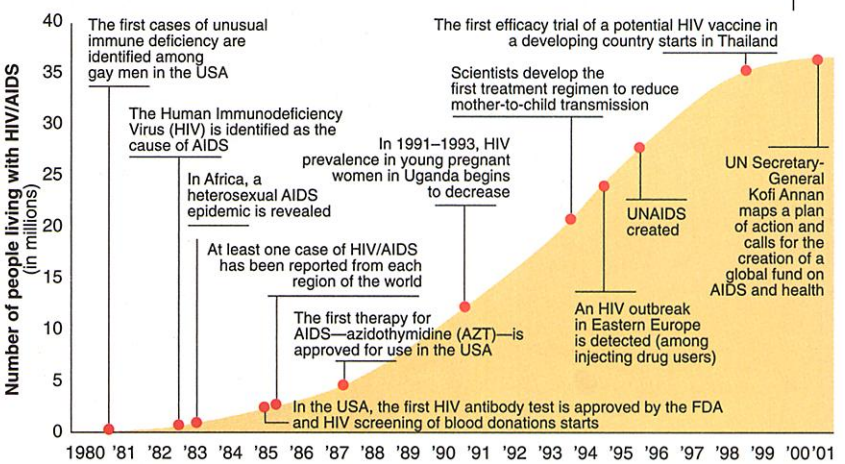
Steering a Course to an AIDS Vaccine

For more than 20 years, AIDS has been progressing relentlessly and predictably while medical technology has been stymied in its effort to provide a fix. We do have effective drugs, but they treat the infection at great expense and with great difficulty. And we know what will do the job: a safe and effective vaccine. After all, vaccines stopped polio and hepatitis B. The difference is that those viruses are highly sensitive to antibody killing, so the vaccines needed only to induce antibodies. But HIV, the unquestionable cause of AIDS, has evolved to elude antibody killing, thwarting our attempts to induce a broadly protective antibody response, even in animals. A test of an antibody-based vaccine is being run by an optimistic company, but few experts give it much chance of success.

Are we powerless? No. A century of study of immunology and protein structure gives us hope that there are ways of designing immunogens that will work. So we examine each detail of the virus's structure, trying to find chinks in its armor where an antibody might penetrate. But the immunologists hold out a different hope: that there is a second type of immunity—the activity of killer T cells—that can clear some viral infections and help antibodies clear others. Maybe we could devise a way to use this arm of our immune systems against HIV. Over 10 years of research has been devoted to this hope, and great progress has been made. But we are still at an early stage; testing of the most extensively evaluated candidate vaccine was recently halted because it is not giving sufficient evidence of immunogenicity.



20 Years of HIV/AIDS

At present, we have a pipeline of potential stimulants of T cell–based immunity feeding into early-stage testing. However, little has been evaluated in humans even for basic safety (Phase I trials). The most promising T cell stimulant is a DNA vaccine followed by a viral vector; it is still in an early phase of testing. Thus, should all go well, we might have a vaccine in 5 years, but things rarely go so well in this difficult business. Few will be surprised if it takes 10 years to get to a licenced vaccine. One big fear now is that we will be able to stimulate T cell immunity, but the virus will quickly elude it by changing its structure a bit. Already in monkeys and humans there is evidence of viral escape from T cell immunity. For reasons that still elude immunologists, even if you stimulate immunity with a complex immunogen, the T cells focus their response on just one simple peptide structure, making it easy for the virus to mutate to resistance. So the T cell route to immunity may yet be a very bumpy road.

Are we appropriately organized to respond to this devastating epidemic? A plus is that the U.S. government is putting more money into AIDS research, and specifically into vaccine development, than the rest of the world combined. But the academic community, while taking the money, is still working on a business-as-usual basis. By contrast, the National Institutes of Health (NIH) itself has set up an integrated unit dedicated to making an HIV vaccine. It combines protein structure determination, immunology, vaccine candidate development, primate testing, and clinical assessment.

Leadership in the vaccine effort at the government level has been diffuse and invisible recently. When Harold Varmus was NIH director, the effort had high-level patronage and constant visibility. There is now new NIH leadership, and we can only hope that the new director will understand that he can have no higher priority than to deal with the AIDS epidemic. It threatens world stability, it kills Americans, and it is the greatest threat to those who can least understand the need to take precautions against infection: the poor, the underserved, and the populations of underdeveloped countries.

Next week, the biannual International AIDS Meeting will take place. There is unlikely to be any exciting news on the vaccine front, because progress is slow. It is important to realize that vaccine research is intrinsically slow because it takes a long time to know whether a trial has been successful. But we ought to make every effort to provide the leadership and vision to ensure that this inevitably protracted process will proceed at the fastest possible pace.

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