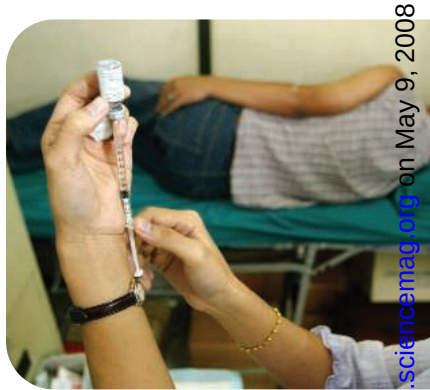
Alan Bernstein is executive director of the Global HIV Vaccine Enterprise, New York, New York.

AIDS and the Next 25 Years

Later this month, researchers will gather at the Institut Pasteur in Paris to mark the quarter century since human immunodeficiency virus (HIV) was discovered as the cause of acquired immunodeficiency syndrome (AIDS). Since then, over 60 million people have been infected with the virus and over 25 million people have died. These numbers make the results of two "proof of concept" vaccine efficacy trials—the STEP and Phambili trials—extremely disappointing. Indeed, these results have raised questions about whether investments in HIV vaccine research are misplaced and whether a vaccine is even achievable. Those views are misguided. The failure of candidate vaccines or drugs is to be expected. More than ever, investigations in humans are essential to explore concepts, test hypotheses, and delineate the human immune response to HIV immunogens.

The STEP and Phambili trials, cosponsored by the pharmaceutical company Merck & Co. and the U.S. National Institutes of Health, were designed to test the efficacy of a recombinant adenovirus vector cocktail expressing three HIV genes. The vaccine candidate failed to limit viral replication in people who became infected with HIV and failed to prevent the acquisition of HIV. Most disconcertingly, a subset of volunteers appeared to show an increased probability of acquiring HIV (see the Perspective by Moore *et al*., p. 753). These results reflect our still-limited knowledge of HIV, its interactions with the human immune system, and the formidable, unprecedented challenges that it poses.



Why has developing an HIV vaccine been so difficult? One reason is that HIV has evolved highly sophisticated ways to evade the immune system. Its extraordinarily high degree of sequence diversity, caused by mutation and recombination, makes it especially challenging to design neutralizing antibodies that recognize the broad range of epitopes needed for effective immune protection. Moreover, HIV wipes out some of the very cells needed to mount an effective immune response. Despite progress in characterizing cellular and humoral immune responses to the virus, we still don't know enough about the magnitude, breadth, or types of immune responses necessary for effective vaccine protection, in part because of the lack of a robust animal model that recapitulates critical features of both HIV and the human immune system.

Indeed, these are major challenges, but evidence of immunological protection in certain experimental models of HIV in nonhuman primates, and the intriguing observation that a small proportion of HIV-infected individuals ("elite controllers") can completely suppress the virus for years, suggest that a vaccine may be achievable (see the Review by Walker and Burton, p. 760). Furthermore, new technologies in structural and computational biology are providing novel approaches for designing immunogens that might elicit broadly reactive neutralizing antibodies, and new insights into innate and mucosal immunity are expanding vaccine design strategies.

At meetings over the past few months, including an international workshop convened last week by the Global HIV Vaccine Enterprise, there was broad agreement on many points, particularly that more, not less, basic and early-stage clinical research is needed. Understanding the human immune response to HIV remains a priority. We need to understand the role of both the innate and adaptive immune responses during HIV infection. Better assays are needed that reflect the functional biology of cellular immune responses and incorporate a systems biology approach—that is, encompass the integrative functioning of gene, protein, and biochemical networks—to monitor the immune system. We need to make it much more attractive for young researchers, including those from other fields, to enter the HIV vaccine field. And the continued engagement of industry is essential if we are ever to have a vaccine.

Laboratory research has led to effective drugs against HIV that have prolonged the lives of infected individuals, and epidemiological studies have shown that interventions such as circumcision (see the Policy Forum by Potts *et al*., page 749) can reduce viral acquisition. However, we know from experience with other pathogens that a vaccine is the best way to stop a virus. The only end for a journey that began 25 years ago should be the development of a safe and effective HIV vaccine.

– Alan Bernstein

10.1126/science.1159797

Published by AAAS