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where are we in the search for an aids vaccine?

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OVER 20 YEARS after the word "AIDS" entered the global lexicon, a vaccine is still seen as the best hope for curbing, and eventually ending, the epidemic. In fact, no viral disease has ever been controlled without a vaccine. Yet the rosiest scenario is that we won't have even a moderately effective product before the end of the decade. And we're probably still at least a decade away from a more optimal vaccine—that is, more than 30 years after the discovery of HIV as the cause of AIDS. Some scientists see an even longer wait, while a few question whether a highly effective vaccine is possible at all.

For many people, this time frame is hard to understand: After all, we live in an era of unprecedented technological and medical advances. Just in 2004, we've seen remote-controlled robots exploring the surface of Mars, and geneticists scanning all 20–25,000 human genes for the tiny fraction that explains our different individual susceptibilities to diseases, medicines and environmental toxins. Although these trailblazing innovations each resulted from several decades of research, the era of modern vaccines began well over a century ago. So why is it taking so long to make a vaccine against HIV—the best-studied ***pathogen*** on the planet, with a measly nine genes?

The reality is that it almost always takes decades from the discovery of a ***virus*** or bacteria until an effective vaccine is licensed (see table 1.1). That's partly because, even today, there's a lot researchers don't know about how the immune system protects against disease, or how to manipulate it. And despite its diminutive size, HIV is a complicated virus armed with many strategies for evading the immune system—abilities that lie at the heart of the difficulties in making an AIDS vaccine.

Table 1.1 Developing vaccines: how long it takes

Virus or bacteria	Year cause discovered	Year vaccine licensed in US	Years elapsed
Malaria	1893	none	—
Typhoid	1884	1989	105
Haemophilus Influenza	1889	1981	92
Pertussis	1906	1995	89
Polio	1908	1955	47
Measles	1953	1995	42
Hepatitis B	1965	1981	16
HIV	1983	none	—

Source: adapted from references ① ②

Nor has AIDS vaccine development received nearly enough attention or funding since the discovery of HIV, although that's now changing. But the neglect reflects a more general problem: Disease prevention, including vaccines, rarely gets high priority in terms of research dollars, government action or public support. Less than 1% of global spending on health product research and development in 2003 went to AIDS vaccines, according to the International AIDS Vaccine Initiative—about the same as the cost of a few Hollywood blockbuster films.

And scientific uncertainties over what's likely to work, plus doubts about the profitability of an AIDS vaccine, have discouraged the involvement of pharmaceutical companies, which traditionally lead the way in making new vaccines.

But fortunately this lackluster global effort has picked up over the last few years: Funding, political momentum, involvement of more countries and private companies, and numbers of products entering clinical development are all rising steadily.

ramping up: does more activity equal more success?

Can this new activity and money get us a vaccine any faster? People in the field often say that developing an AIDS vaccine is a marathon, not a sprint. It's a useful analogy that captures the need for a long view and lots of endurance. But there's a crucial difference: In a marathon, runners know exactly where, and how far, they must go to reach the finish line—while AIDS vaccine developers can't predict what strategy will work, or even whether they're going in the right direction or heading down a dead end. Instead, they're forced to rely on educated guesses along with trial and error, and to expect definitive answers only from studies in people—ultimately, large-scale, expensive trials. Emilio Emini of the International AIDS Vaccine Initiative likened the situation to Christopher Columbus setting out across the Atlantic Ocean in 1492: "Until the guy up at the top of the ship yelled, 'Land, land!' [Columbus] had no idea where he was"—whether close to shore, or still far out at sea.

Yet most vaccine researchers believe they will eventually succeed. Their optimism comes from evidence (summarized in chapter 8) that a small minority of people *do* develop effective ***immunity*** to HIV. There's also supporting animal data: Monkeys vaccinated with live but weakened ***SIV*** (a virus that's closely related to HIV) are well-protected against simian AIDS. Although this type of vaccine is considered too dangerous for use in humans, these results prove that vaccines *can* induce protection, at least in monkeys.

Grounds for optimism also come from recognizing that researchers haven't yet fully tackled the scientific unknowns that have kept the field guessing for so many years—although a least some of these questions should be solvable with today's tools and knowledge. "Money can't buy a vaccine, but it should be able to buy answers to some of the questions that slow down rational vaccine design," says Emini. "With a vaccine we're trying to get the immune system to clear HIV infection, which it doesn't naturally do. We can't achieve this blindly and empirically. The critical issue is to manipulate the system—and to do this, we need to understand how it works at a fundamental level."

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—Emilio Emini (IAVI)

How can the field accomplish this, if it hasn't managed so far? Actually there's broad agreement on what's needed: A much larger-scale, better-coordinated, better-funded effort, with research groups from different organizations working together on a given problem, each contributing their special expertise. Also needed are standardized laboratory methods and tools (such as virus ***strains*** and ***antibodies***) for measuring ***immune responses*** so that results from different vaccine studies can be easily compared, and the most promising vaccines identified. In other words, the field needs a new way of doing business—albeit one that runs somewhat counter to the culture of US and European academic science, where most of this research is done, and which tends to reward individual achievement.

The major organizations involved in AIDS vaccines are already making strides in coordinating their own research activities. The next level—broad coordination across organizations and countries—is gradually taking shape as an initiative called the "Global Vaccine Enterprise." Spearheaded by the Bill and Melinda Gates Foundation, this alliance of independent partners has set up a Coordinating Committee and a series of expert scientific groups in critical areas, and has received strong political support from leaders of the G8 countries. Its scientific plan, published in January 2005,[3] focuses on the kinds of issues just described and on increasing *clinical trials* capacity in developing countries, and it calls for a doubling of funds for the field (to a level of US$ 1.2 billion per year). In the coming months, the Enterprise will focus on translating these plans into action by fleshing out what form the collaborative activities will take and what money will actually be available.

where are we and what needs to be done?

First and foremost is the need to move the science forward. Over the next few years, this will involve a two-pronged strategy:

- Evaluating and improving the candidates we have, based on our best understanding at the moment, and
- Gathering the knowledge needed to develop new strategies and candidates.

On the first score, there are now about 30 candidates in clinical testing. That sounds like a lot—and it is, compared with even a few years ago. But many of these products are very similar, and nearly all are based on the same underlying premise: that vaccines which stimulate one particular arm of the immune system (called *cellular immunity*) will delay or prevent HIV disease and reduce transmission even if they don't block infection, as many experts predict. We urgently need to know if this is true—information that would be like Christopher Columbus' man on top of the mast suddenly spotting a landmark that tells him whether the ship is approaching land or is lost at sea.

The first hope for an answer rests with two ongoing *efficacy* trials of candidates that target cellular immunity—one a full-scale study, the other a smaller, proof-of-concept trial. (Even if they show promise, both vaccines would probably need to be re-engineered and/or re-tested before licensure; see chapter 8). At the same time, other vaccines that may induce stronger cellular responses are in development, and the most promising ones will surely follow these first two into trials that test whether this approach is valid.

But whatever these trials find, the field needs new candidates based on different approaches—either to replace the present ones if they fail, or to help overcome potential limitations if any of them show partial efficacy. And that's where the need to fill in our knowledge gaps comes in. Some key issues:

- A top priority for the field is figuring out how to design vaccines that stimulate the antibody-producing arm of the immune system—specifically, to generate ***neutralizing antibodies** (NAbs)* which block HIV infection. It's a task that most researchers consider essential for an optimal vaccine but that's proven impossible so far (see chapter 7 on vaccine approaches).

- Vaccine developers don't know for sure what type(s) of immune responses an effective AIDS vaccine needs to induce. If they did, it would be a huge step forward—enabling them to figure out early in clinical development whether a vaccine is likely to work, and even to design vaccines most likely to generate the right responses. Unfortunately, a definitive answer isn't possible until we have a vaccine that shows at least some protection, so that researchers can work backwards to identify the immune responses it generates. In the meantime, the field is looking towards monkey studies for guidance, calling for an all-out effort to learn how live, weakened SIV vaccines—the "gold standard" in the field—protect monkeys so well.

- These monkey studies could also help resolve another big unknown: Whether protection against HIV requires immune responses not only in the blood, but also in the linings of body cavities like the genital tract, anus and gut—ports of entry for HIV during sexual or breast milk transmission. What's more, the gut becomes an important "home" for HIV (and for HIV ***replication***) shortly after infection, since it houses most of the body's ***CD4+ T-cells***, HIV's favorite target. So immune responses that stop HIV in the ***mucosal tissues*** lining these cavities, where many types of immune cells and chemicals are found, might contribute a lot to protection. But little is know about ***mucosal responses*** or how best to induce them.

- HIV comes in a huge variety of strains, and is always generating new ones. So researchers need to find strategies for inducing immunity against the broadest possible range of HIV strains (see discussion of vaccines and HIV ***genetic diversity*** in chapter 10). At the same time, we need to know more about the strains that are actually transmitted (the ones a vaccine must protect against), since new findings suggest that these may be a distinct subset of all circulating strains—perhaps with distinct properties that will be important for vaccines.

Beyond these roadblocks to designing vaccines and identifying the most promising ones lie other difficult, expensive steps on the path to an AIDS vaccine. Much more effort is needed to devise ways for producing mass quantities of the most promising types of vaccines, and to build the manufacturing capacity to achieve this (see chapter 36). Other chapters in this volume discuss the complexities of building infrastructure for clinical trials, working with governments, communities and other stakeholders and advocating for the policies needed to support these efforts.

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from first success to optimal vaccine

Unless we are extraordinarily lucky, an effective AIDS vaccine will probably come step by step, rather than as one spectacular success. Perhaps we'll start with a partially effective vaccine that delays disease. With some improvements, the next version may slow disease more, and last longer. If and when researchers develop a vaccine that blocks infection, the two vaccines can be combined.

Once there is some initial success, effort will also go into refining these products so they're easier to use in massive global vaccination campaigns. The ideal vaccine should give lifelong protection, be inexpensive to produce and stable without refrigeration, be given orally rather than injected, and require only one dose. Although a vaccine is unlikely to have all of these properties, even some of them can make a big difference in how many people will benefit from an AIDS vaccine, and how quickly—as the world has learned from fifty years of experience with polio vaccines and the not-quite-finished effort to eradicate polio from the face of the earth (see chapter 37).

AS WE WATCH the global AIDS epidemic get worse every day, it's hard not to feel a sense of despair that there's still no vaccine, or even a high expectation of getting one within the next few years. Here's where it's important to remember that we're in a marathon, and to stay focused on using the growing political momentum and funding for vaccines, and the growing body of scientific knowledge, to figure out which way to run.

references

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