




aids vaccine handbook

2nd edition:
global perspectives

edited by PATRICIA KAHN



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May 2005



www.avac.org

First printing.

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In our effort to promote well-informed and honest dialog about AIDS vaccine research, we are pleased to send out additional bulk copies. Please contact AVAC for pricing information. Contributions will greatly facilitate this book's distribution.

AVAC is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of vaccines against HIV/AIDS.

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—P.K.



contents in brief

the handbook is divided into the following sections:

- 1 OVERVIEW**
The big picture of where we are now and the main challenges we confront.
- 2 AIDS VACCINE SCIENCE**
A primer on vaccine research and development.
- 3 CLINICAL TRIALS**
How AIDS vaccine candidates are tested in people and what issues arise as individuals, communities and countries engage in the process.
- 4 COMMUNITIES AND COHORTS**
Issues specific to certain highly affected and vulnerable communities that are integral to the fight against AIDS.
- 5 GLOBAL ADVOCACY**
Policy issues affecting AIDS vaccine development and eventual access, and why advocacy matters.
- 6 VOICES**
Insights from people, issues, times and places that have helped shape the AIDS vaccine movement.
- 7 APPENDIX**
Detailed listings, including information about the authors, international vaccine trials, participating research agencies and non-governmental organizations (NGOs) involved with AIDS vaccines, and a glossary.

NOTE: Listings of Resources and References to learn more about each subject are located at the end of many chapters. Summaries of the cited references can be found in the PubMed bibliographic database at the US National Library of Medicine: www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed
Terms in *bold italics* are defined in the Glossary (Appendix 5).



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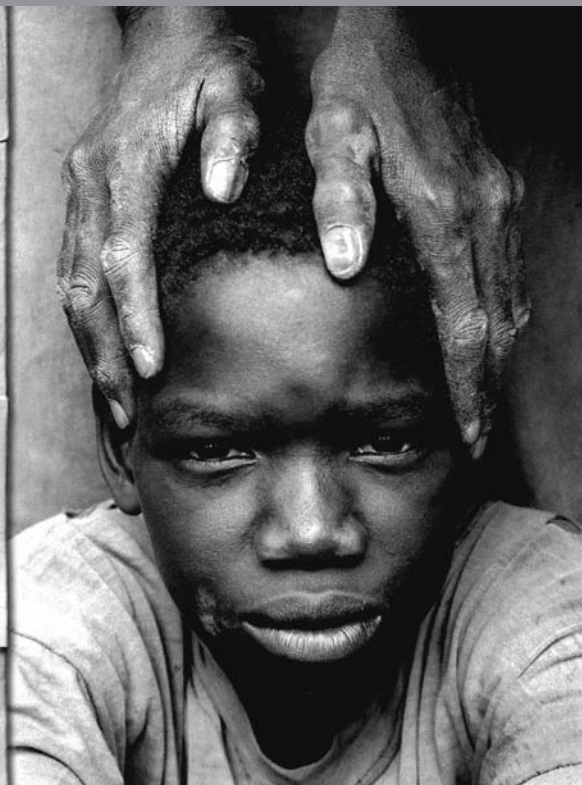
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Superman n'est pas venu.
Ça lui aurait pris dix minutes.
Dix minutes pour apporter des médicaments.

Mais Superman n'est pas venu.
L'Afrique c'était trop loin pour lui.
Peut-être qu'il ne connaît même pas.
Ou qu'il s'en fiche carrément.
Il n'a pas sauvé mon père.
Il est mort du sida.
Superman, tu sais quoi ?
Mon père était bien plus super que toi.

AIDES rappelle aux 60 millions de Français que nous manquons de médicaments, 60 millions d'Africains vont mourir du sida.



AN EPIDEMIC THAT RAGES ON

AVAC forward

Superman n'est pas venu. Superman never came.
Ça lui aurait pris dix minutes. It wouldn't have taken him ten minutes.
Dix minutes pour apporter des médicaments. Ten minutes to bring some medicine.
Mais Superman n'est pas venu. But Superman never came.
L'Afrique c'était trop loin pour lui. Africa was too far for him to go.
Peut-être qu'il ne connaît même pas. Maybe he didn't even know where it was.
Ou qu'il s'en fiche carrément. Or he just flat out didn't care.
Il n'a pas sauvé mon père. He didn't save my father.
Il est mort du sida. My father died of AIDS.
Superman, tu sais quoi? Hey Superman—you know what?
Mon père était bien plus super que toi. My father was so much more super than you.


CAMPAGNE AFRIQUE / previous page

Poster from a national campaign by the French community-based organization AIDES (www.aides.org) to raise public awareness of the epidemic's devastating impact in Africa.

an epidemic that rages on

MITCHELL WARREN

From the Executive Director of the AIDS Vaccine Advocacy Coalition (AVAC)



CONSIDER THIS: Since AVAC published the first edition of this book just six years ago, 25 million more people have become infected with HIV, and almost 15 million have died.

Almost 5 million people became infected in 2004 and more than 3 million were killed by AIDS. Over 20 million people have died since the first cases of AIDS were identified in 1981. The number of people living with HIV continues to grow and is now about 40 million worldwide. Each day 14,000 men, women and children get infected—people in the most productive years of their lives, or with their whole lives still ahead of them.

Shocking, numbing, sobering—the tragic testament to an epidemic that rages on.

Some countries and communities have been living with and fighting this epidemic for decades. Statistics and stories from sub-Saharan Africa get wide coverage in the press. But in other parts of the world—for example, Russia, China and India—the curve of the epidemic is just beginning, and threatens to create

similar crises over the next decade if the world doesn't start responding far more effectively.

No matter where we live, what our HIV status is, with whom (or whether) we have sex, we are all affected by HIV/AIDS—a fact that's often ignored. Not by those who live in communities where AIDS-related funerals are a daily reminder of the scourge. But in places where relatively few people are infected, the epidemic is more easily overlooked. Yet HIV/AIDS continues to change our collective global future by the devastation it wreaks on families, villages, cities and countries.

Besides the immediate crisis it presents, HIV/AIDS also undermines global development, nullifying or even reversing decades of progress—deepening poverty, reducing life expectancy, contributing to political and economic instability, exacerbating food shortages and increasing the divide between rich and poor. In many places, AIDS continues to take its biggest toll on racial and ethnic minorities, the poor and the disenfranchised, leaving the well-off relatively unscathed.

Against this background though, one important statistic is too easily forgotten: Even in the most affected regions of the world, the vast majority of people have *not* acquired HIV. Providing people—especially youth—with access to the information, tools and support to remain HIV-free is an enormous challenge. Today's AIDS prevention efforts, including HIV counseling and testing and behavior change (from promotion of abstinence or mutual fidelity to reducing the number of sex partners, delaying sexual debut and increasing condom use) must be expanded, so they can reach more places and more people.

A massive scale-up of access to treatment for infected people is also critical. First and foremost, it will help tens of millions of people live many more productive years when they can raise their families and contribute to the economy. It's also crucial to increasing people's willingness to learn their HIV status, and to avoid infecting others.

But the unbroken spread of the epidemic and its ever-more dire social, political and developmental consequences are a constant reminder that none of this is enough. We must add new tools to those we already have.

An effective AIDS vaccine remains the world's best chance to reverse this relentless epidemic. But the search for a vaccine must not come at the expense of our immediate response. And it doesn't have to. Testing vaccines requires that we do all the other key things anyway—delivering the best possible risk-reduction counseling and prevention tools; ensuring confidential, voluntary counseling and testing; providing referral to comprehensive treatment. Prevention, testing, treatment, and trials.

We must do more in our quest for a vaccine, and we must do it as part of a truly comprehensive response. It is not “either/or.” It is “all the above.”

The development of vaccines to prevent AIDS is a long-term undertaking, a fact that's clearer now than ever. More than 20 years into the epidemic, the answer to a simple question—“When will we have a vaccine?”—remains unanswered. And the standard response—“in ten years or so”—has not changed, as the time frame keeps getting pushed back.

We are on a long-term quest. We must collectively do everything possible to keep re-defining what needs to be done and make sure we're doing the most important things. Because vaccine development takes so long, we need to set an agenda for sustained and sustainable action that stretches out beyond the decade.

Who are “we?” Advocates, activists, providers, scientists, policy-makers, everyone infected and affected by HIV/AIDS—it is all of us. Men, women, children; national leaders and community leaders; teachers and students; public health and AIDS advocates; scientists and researchers; AIDS-affected individuals and communities—you name it.

Working together, we must build a broader global movement advocating on issues that directly impact progress, including more funding and accelerated vaccine research and testing. While scientific issues remain a great challenge, without an increased sense of urgency and expanded community and public involvement, a vaccine is far less likely to bring the AIDS epidemic under control in our lifetimes.

An effective AIDS vaccine remains the world's best chance to reverse this relentless epidemic. But the search for a vaccine must not come at the expense of our immediate response. And it doesn't have to.

Founded in 1995, the non-profit AIDS Vaccine Advocacy Coalition (AVAC) uses education, policy analysis and advocacy to accelerate the ethical development and global delivery of vaccines against HIV/AIDS. AVAC is committed to translating and communicating this long, complex web of activities to a wider constituency and to ensuring that the rights and interests of trial participants, eventual vaccine users and communities are fully represented and respected in the process.

To marshal and sustain public involvement in global AIDS vaccine efforts, communities need information that not only educates but also suggests how people can play an active role. And this information and mobilization must be provided within the context of a comprehensive response to the epidemic. Hence, our *AIDS Vaccine Handbook*.

This completely revamped and international edition of the original *HIV Vaccine Handbook*, first published in 1999, provides an overview of the key scientific, policy, social, ethical and economic challenges, and of the diverse experience gained around the world over the past two decades. The 43 easy-to-read, lively essays are written by people involved in this work as community educators and advocates, trial staff and volunteers, scientists and researchers, policy-makers and journalists.

We hope that this new Handbook serves well as a resource and reference guide. And we hope that it motivates you to take action.

Table 0.1 Global Estimates of adults and children living with HIV (2004)¹



THE TOLL: 39.4 million people living with HIV as of the end of 2004			
Adults	Women	Children under 15	Total
Adults and children living with HIV in 2004:			
37.2 million	17.6 million	2.2 million	39.4 million
Adults and children newly infected with HIV in 2004:			
4.3 million	—	.64 million	4.9 million
Adults and children who died from AIDS in 2004:			
2.6 million	—	.51 million	3.1 million

¹ The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). WHO/UNAIDS AIDS epidemic update, December 2004: "Adults and Children Estimated to be Living with HIV as of End 2004" and "Global Summary of the AIDS Epidemic December 2004."



overview

- WHY WE NEED VACCINE ACTIVISM, STILL CHAPTER 1
- WHERE ARE WE IN THE SEARCH FOR AN AIDS VACCINE? CHAPTER 2
- HIV IN PICTURES CHAPTER 3

PHOTO ©Treatment Action Campaign (TAC), South Africa

1

SOUTH AFRICA / previous page

Members of Lesotho's Positive Action attend a funeral, wearing T-shirts from the Treatment Action Campaign (TAC).

why we need vaccine activism, still

BILL SNOW

In November 1995 I wrote an article called “Why We Need Vaccine Activism,” which became a mainstay reference for the AIDS Vaccine Advocacy Coalition when it was founded the next month. With this new, more international edition of the *AIDS Vaccine Handbook* nine years later, it seemed time to re-address this question and think about why we still really need activism and what form it should take in the times to come.

WELL, there’s still no vaccine, for one thing, right? So a number of the arguments I made in 1995, when the AIDS Vaccine Advocacy Coalition was just being started, about the need for an AIDS vaccine and AIDS vaccine activism still apply.

If you’re reading this book, chances are you’re already somewhat sympathetic to the notion that even a partially effective vaccine would be an excellent addition to the arsenal of weapons against this amazingly tenacious *virus*.

In the meantime, some of the other activism needs described then have been at least partially addressed:

- › There are now a small but critical number of reasonably well-funded organizations focused on AIDS vaccines, most with public or community input.
- › Funding has increased several-fold for academic research, product development and *clinical trials*.
- › Public and foundation support has also kick-started industry to become more involved.

- › A variety of vaccine concepts are waiting to be tested, all with the aim of inducing cellular *immune responses* that will blunt infection.
- › Many more countries and international organizations are joining in the effort to advocate for, develop and test AIDS vaccines, with particular emphasis on the developing world.

Yet, for better or worse, my conclusion then applies just as well today: “We now believe that it will take a series of candidate vaccines being tested, going well into the 21st century, to develop a truly effective vaccine. Widespread support for this effort would focus attention on the process and could shorten it. We need to be prepared to support this long-haul effort, while looking out for the interests of our communities and ourselves.”

To be somewhat more radical today, here's what makes vaccine activism just as important as ever:

- › The worst of the disease remains imperfectly confined to groups of people who are least equipped to manage it: the poor, the disenfranchised, and the stigmatized. So the world can go about its business as if things weren't really as bad as they are, or will become. Those with money and insurance can get treated and live tolerably well, while everyone else is hoping (and sometimes fighting) for treatment or waiting for death. It's an ugly picture of the human condition; much of the world is a death trap.
- › Anyone who's sexually active, particularly youth, lives with the nightmare of AIDS the way earlier generations lived in fear of nuclear war. HIV colors and even governs the way we grow up, make love, partner, and die. What a dream it would be to get it under control!
- › The future of the planet will be determined by the course of the HIV pandemic as much as by the fate of the environment, global warming, and economic globalization. Whole societies, whole sub-continents are already being affected in immensely destructive ways.

Against a time bomb ticking away, we have science scratching its head, reorganizing itself, contesting turf and how to proceed. This still sounds like a case for activism to me.

The sad truth is that there are still only a few hundred people, mostly people who have a direct problem with AIDS, or specialized scientists, advocates and trial volunteers committing their energies to the quest for a preventive vaccine. The rest of the AIDS-ridden world still needs to be talked or argued or shaken out of its torpor by those of us who “get it.” Got it?

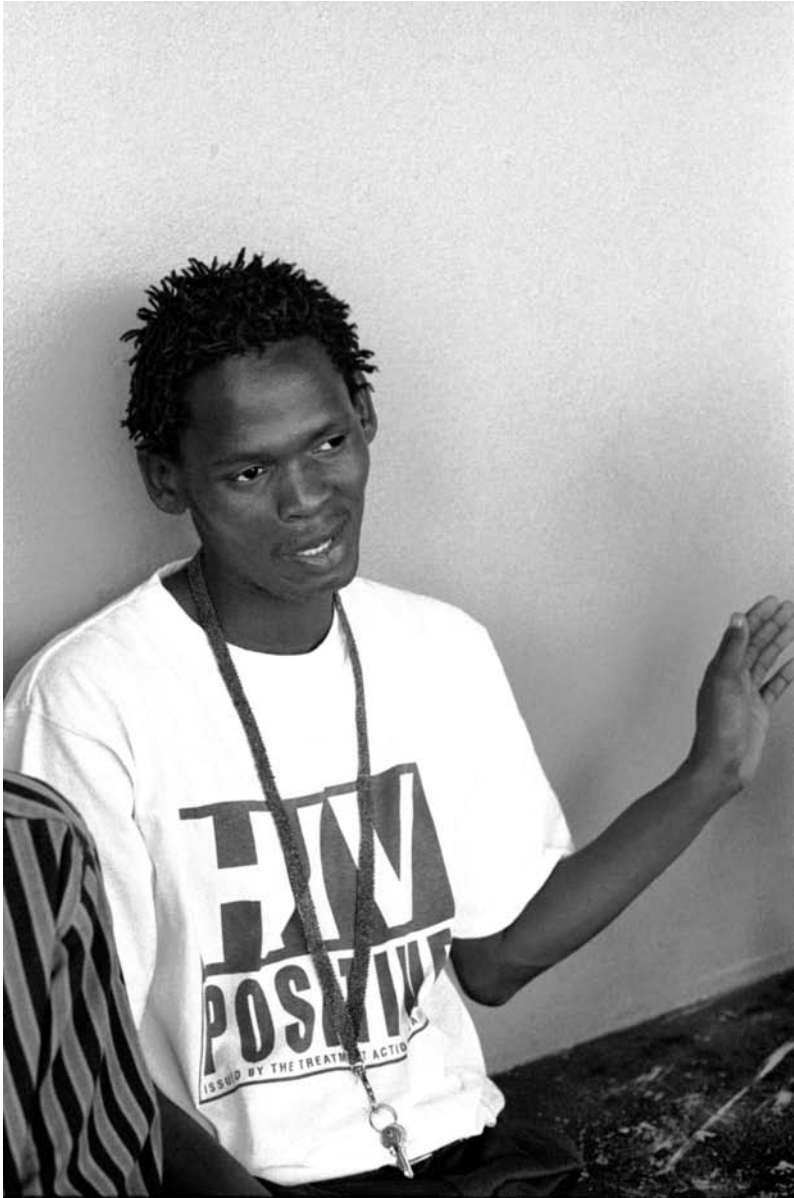
FORTUNATELY the AIDS vaccine agenda is increasingly part of some larger agenda: alleviating poverty and promoting development and economic growth; global health, emerging diseases and health care; social equity, women, children, minorities; AIDS prevention; human rights; bioterror, war and peace. The trick in the years to come will be to make alliances with these movements and—to borrow the cliché—to keep our eyes on the prize.

The science is undeniably hard, and the road will be long. In fact, the completion of two *efficacy* trials in 2003 and the launch of another have reminded us *how* hard and *how* long. Activism is needed and it makes a difference, so hang in there.

There are places to go (for information), people to meet, and things to do everywhere in the world, at every level and with any skills. Many possibilities can be found in this book, but also look around you. The AIDS vaccine effort is newly global and ready to grow.

Welcome to the 21st century, dubbed by many to be the century of biology. Our century.

There are places to go (for information), people to meet, and things to do everywhere in the world, at every level and with any skills. Many possibilities can be found in this book, but also look around you.



©Clive Gray

SOUTH AFRICA

Community counselor at the Nomzamo HIV Clinic in Masephumelele, a township about an hour's drive from Cape Town.

where are we in the search for an aids vaccine?

PATRICIA KAHN

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

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.

—Emilio Emini (IAVI)

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.”

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 known 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.

Unless we are extraordinarily lucky, an effective AIDS vaccine will probably come step by step, rather than as one spectacular success.

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).

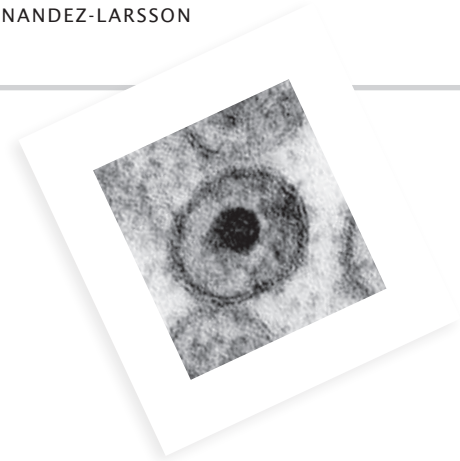
AS WE WATCH the global AIDS epidemic get worse every day, it's hard not to feel a sense of despair that there's still no vaccine, or even a high expectation of getting one within the next few years. Here's where it's important to remember that we're in a marathon, and to stay focused on using the growing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

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hiv in pictures

PATRICIA KAHN and ROBERTO FERNANDEZ-LARSSON

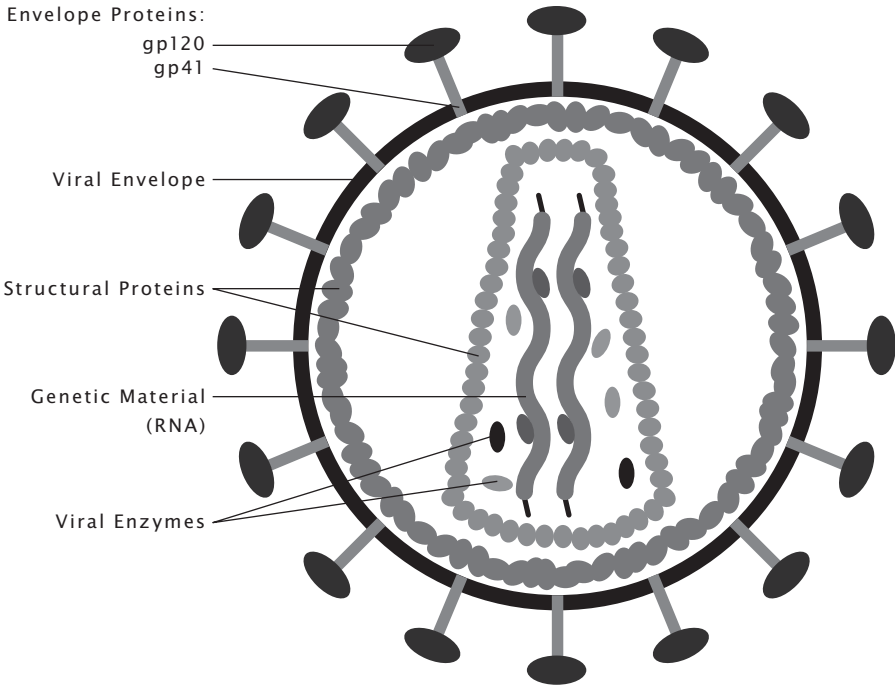


HIV is a deceptively simple creature:

Two strands of genetic material and a few *protein* molecules, with an outer wrapping to hold it together. Each *virus* particle, or *virion*, is shaped like a tiny sphere and measures only 1/10,000th of a millimeter in diameter.

The photographs and diagrams on the following pages will show you what HIV virions look like, what they're made of, and how they infect immune cells. Like all viruses, HIV can reproduce itself only when it's inside cells and can use their "machinery" to make new parts.

Photos were taken with cameras attached to a powerful type of microscope called an electron microscope, which can magnify objects up to several hundred thousand times.

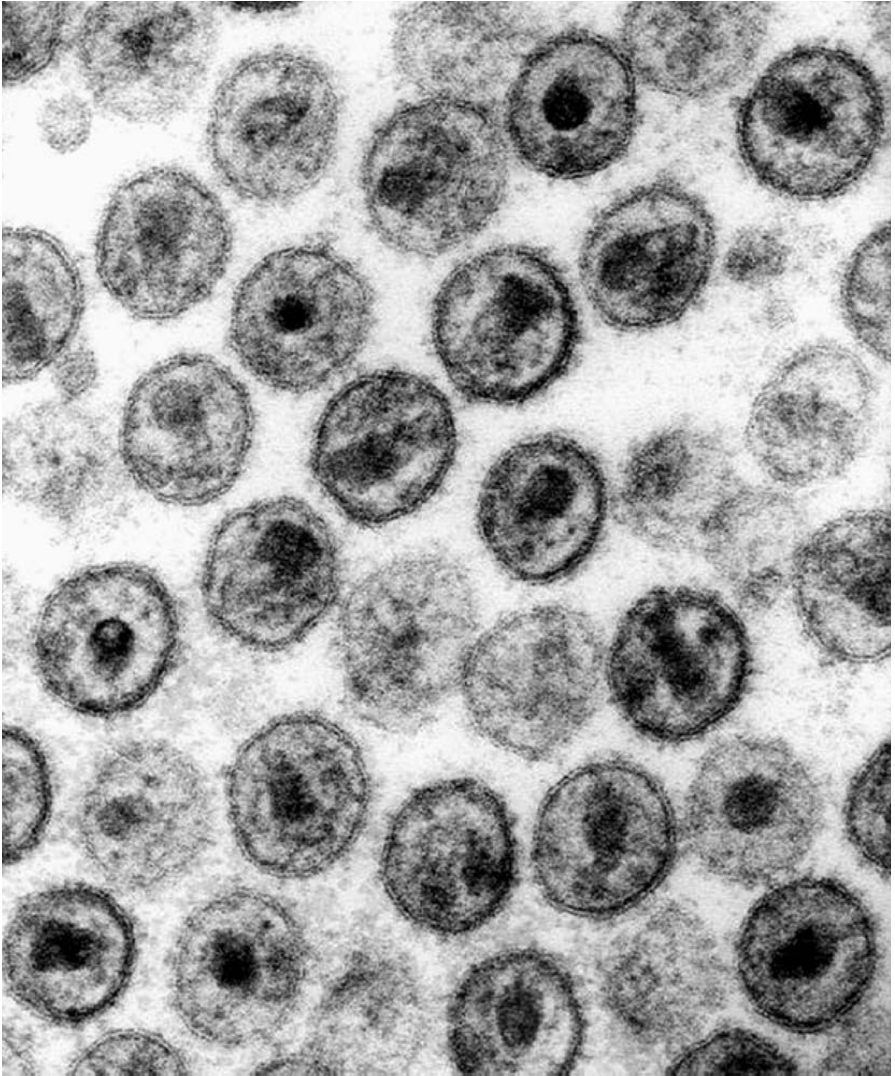


STRUCTURE OF AN HIV VIRION

The **viral core** contains the HIV genetic material (**RNA**) and several proteins called **enzymes**, which help the virus start copying itself inside the human cell it has infected (the host cell).

Structural proteins encoded by the **gag** gene help keep the virion intact.

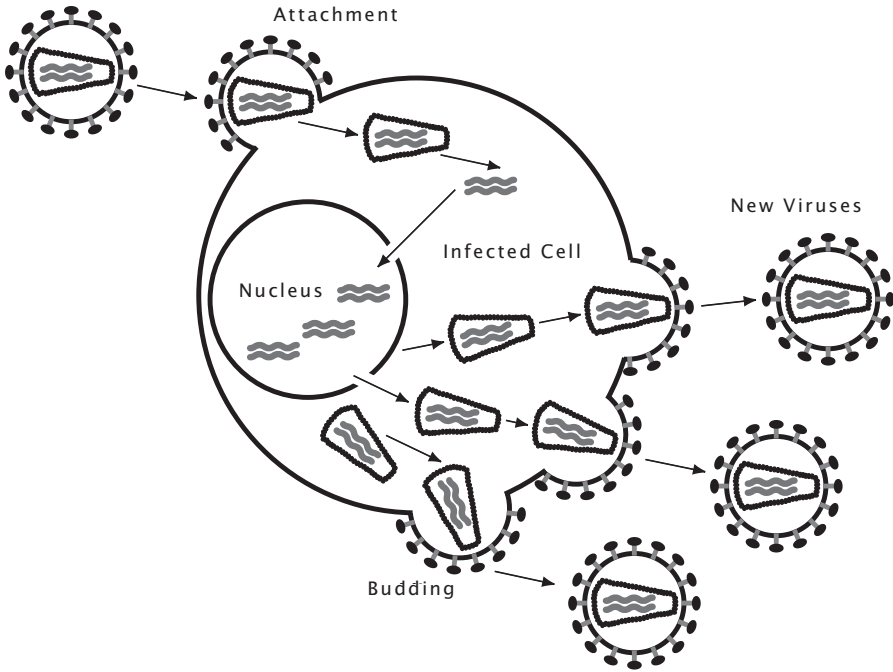
The particle is enclosed by a **membrane** picked up from the host cell, with molecules of the HIV **envelope protein** sticking out from the surface. The envelope protein is made of two parts, called **gp41** and **gp120**.



©US Centers for Disease Control and Prevention (CDC)

HIV PARTICLES

Electron microscopic view of HIV virions.
The dark centers are the viral core (see illustration, facing page).

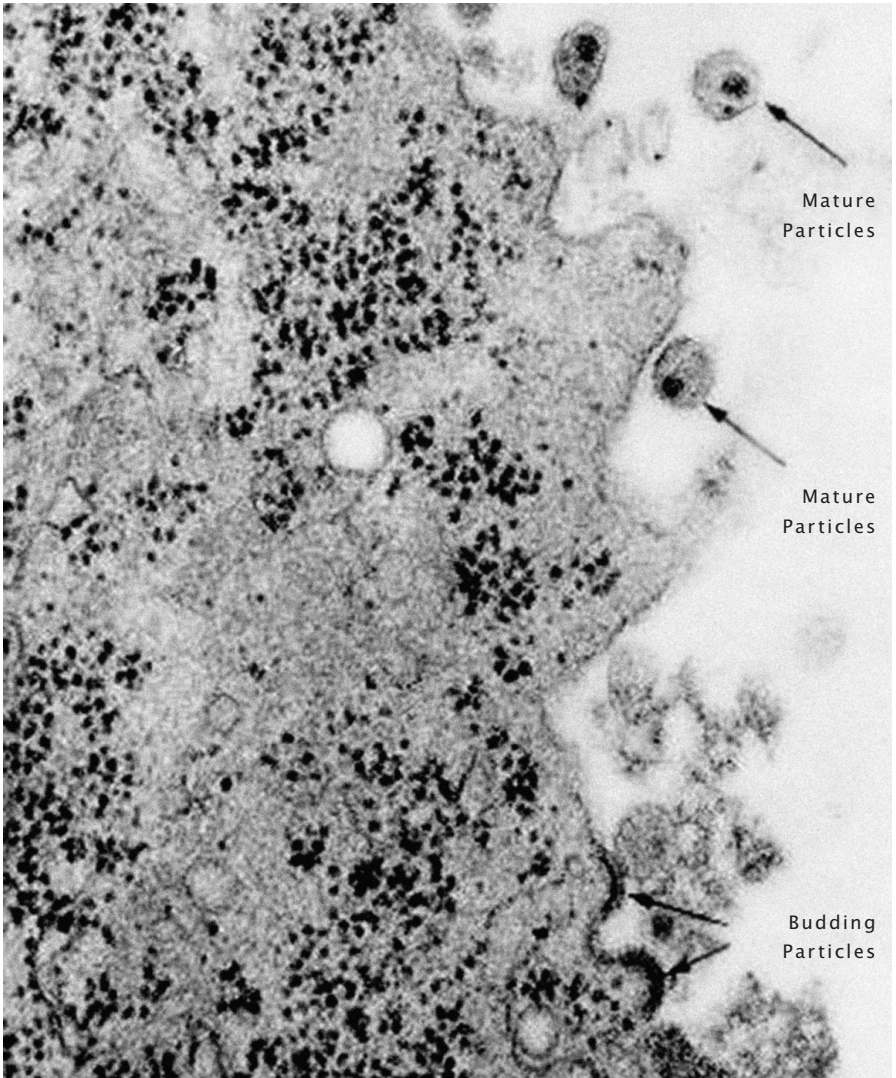


THE HIV LIFE CYCLE

In the first step of infection, HIV attaches to a susceptible host cell (for example, a *helper T-cell*) via gp120. The virus and host cell membranes then fuse, releasing the viral core into the cell.

Once inside, the HIV genetic material copies itself many times (and leaves a copy incorporated into the cell's genetic material), makes the proteins it needs for new particles and then assembles thousands of new virus cores.

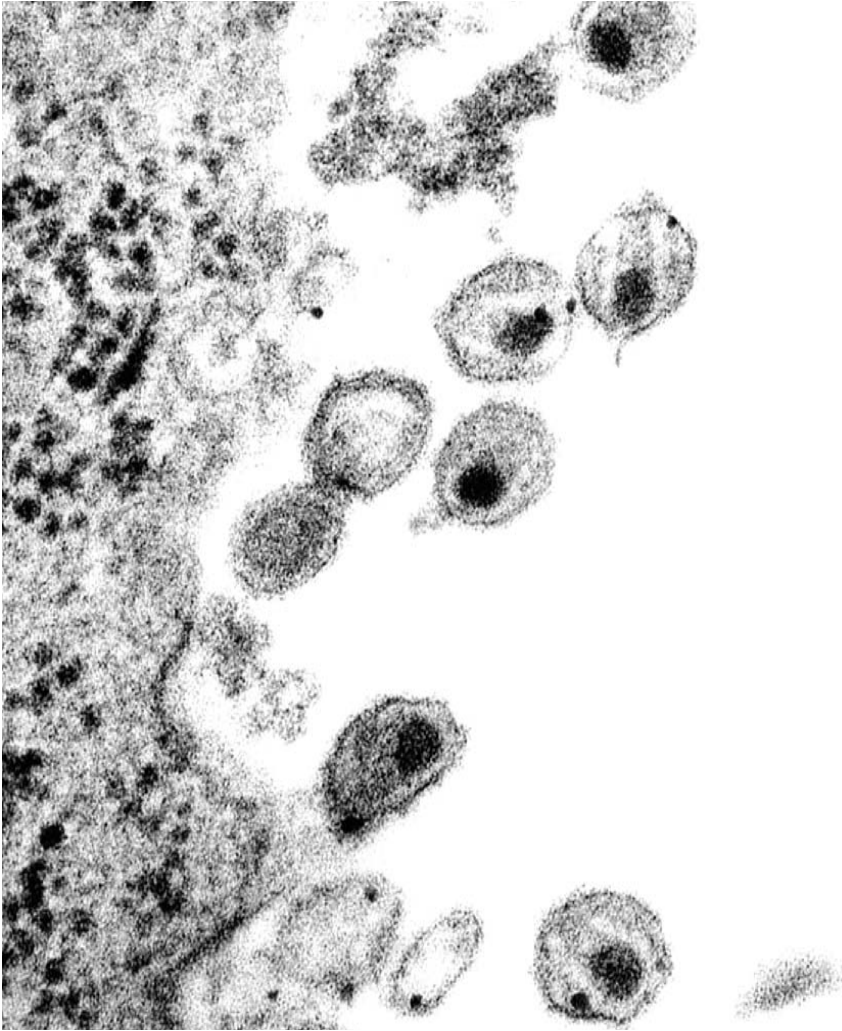
These cores then move to the cell membrane and “bud” outwards through it, wrapping themselves in the host cell membrane and forming new virions with the HIV envelope protein protruding from the membrane.



©CDC

BUDDING AND MATURE HIV PARTICLES

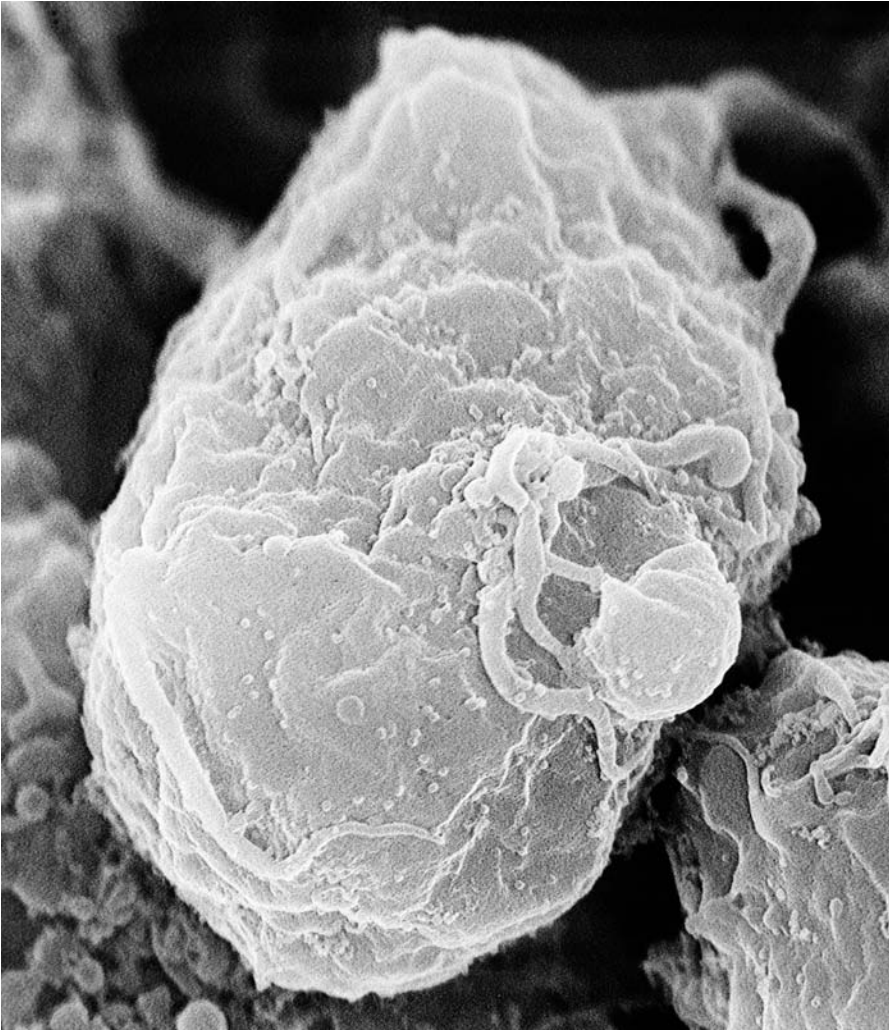
Free HIV particles and particles budding from the surface of a human *T-cell*.



©CDC

MAGNIFIED BUDDING AND MATURE HIV

A more highly-magnified view of budding HIV particles and mature virions.



©C Goldsmith/CDC

3-D HIV

This three-dimensional view, taken with a different type of electron microscope than the other photos, shows a *lymphocyte* with an HIV particle on its surface.

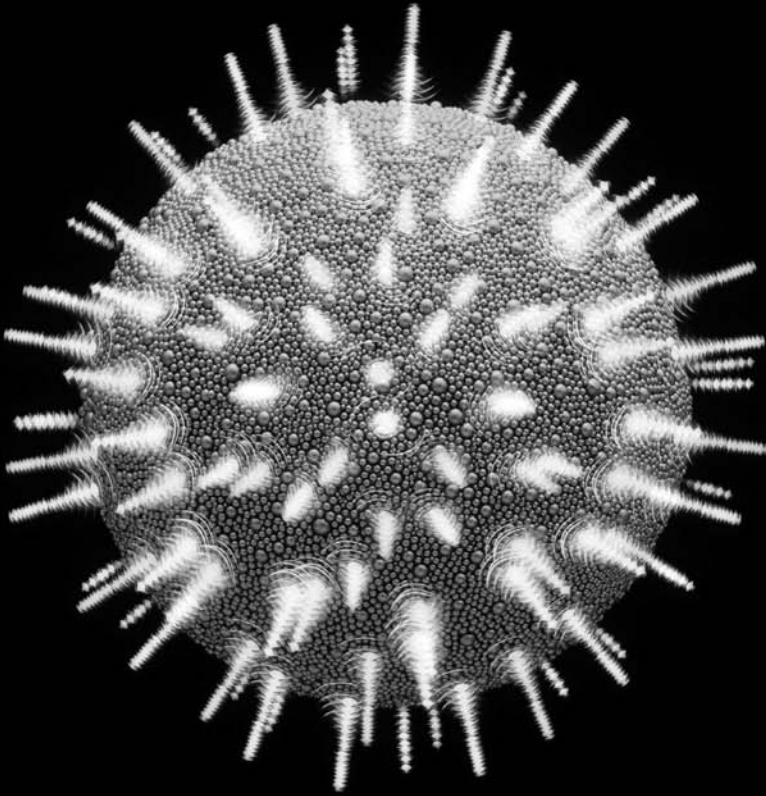
resources

<http://phil.cdc.gov/phil/default.asp>

Public Health Image Library of the US Centers for Disease Control and Prevention (CDC). Offers web-based access to the CDC's photographic images, including a large collection on HIV.

www.thebody.com

The Body has comprehensive information on HIV/AIDS, from the science to prevention, treatment and policy. For information on the HIV life cycle and structure, click on "the basics."



aids vaccine science

VACCINE BASICS	CHAPTER 4
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AIDS VACCINE APPROACHES IN DEVELOPMENT	CHAPTER 7
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PHOTO ©Michael Freeman/CORBIS

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THE NEW YORK TIMES, SUNDAY, NOVEMBER 7, 2004

No Requiem Yet for Vaccines

At a time when experts are wringing their hands over a huge shortage of influenza vaccines and blaming low profit margins and high risks that drive companies from the market, it is a pleasure to note two significant advances in developing other vaccines. An experimental vaccine developed by GlaxoSmithKline to prevent malaria has shown that it can save many children from infection or death, offering the first real hope for containing a disease that kills more than a million people every year. Another experimental vaccine, developed by Merck, has shown that it can provide long-term protection against cervical cancer, which kills some 225,000 women every year, mostly in poor countries where women do not have regular Pap tests. Both Glaxo and Merck have other vaccines in development, suggesting that laments about the withering of the industry are premature.

Glaxo's malaria vaccine got a big assist from

the Bill and Melinda Gates Foundation, which is supporting tests of 15 experimental vaccines. The Glaxo vaccine, now the front-runner, cut malaria infections by 30 percent and severe disease by 58 percent in a test involving 2,000 children in Mozambique. Further tests are needed, but this is the first real proof that a vaccine can work against malaria.

Merck's vaccine against human papillomaviruses, or HPV, the cause of almost all cervical cancer cases, was completely effective in preventing precancerous growths in a test of 1,500 women, half of whom got the vaccine. Glaxo is racing to produce its own HPV vaccine.

Several other companies are also developing vaccines, at least some of which could become blockbuster revenue producers. The challenge will be to find ways to pay for vaccines that are desperately needed in poor countries but have little market potential in wealthy nations.

The New York Times
November 7, 2004

vaccine basics

BILL SNOW

VACCINES ARE AMONG the most effective (and cost-effective) public health measures we have. They've wiped smallpox off the planet and come close to doing the same thing for polio. Every year they save many millions of lives from childhood illnesses like measles, mumps and whooping cough, and from a long list of other diseases—with the crucial caveat that lots of work still needs to be done so these life-saving products reach more people.

Yet familiar as vaccines are, many people don't understand how they work or how they are made. More specifically, even fewer people understand the unique challenges in developing a vaccine against HIV. So we begin this section about AIDS vaccine science with some background on *immunity* and vaccine development.

The immune system is the body's set of defenses for recognizing and eliminating germs that cause disease (called *pathogens*). When functioning properly, the immune system can tell the difference between these invaders and the body's own cells and *proteins*. In many cases, it can marshal an *immune response* that destroys the pathogen. When you get

sick, some of the symptoms you experience—such as fevers and rashes—are actually signs of your immune system on the attack. For many diseases, once you get better you are then protected against that pathogen in the future.

In ancient Greece, it was known that only those who had recovered from the plague could nurse the sick because they would not contract it a second time.

In fact, the field of immunology grew out of the observation that people who had recovered from certain infectious diseases were protected from ever getting the same disease again. In ancient Greece, it was known that only those who had recovered from the plague could nurse the sick because they would not contract it a second time.

With AIDS there is no proven instance of the immune system protecting an individual from infection or from ultimately succumbing to AIDS. But there are intriguing examples which suggest that at least partial natural protection occasionally occurs—for example, among a small percentage of commercial sex workers who are continuously exposed to HIV but remain uninfected, and in those few infected people who remain symptom-free for unusually long periods of time (called *long-term non-progressors*). Scientists are trying to understand the reasons for this protection by studying the immune systems of these people, and then to develop AIDS vaccines that stimulate the same type of immunity.

Although making vaccines is now a high-tech undertaking, the concept of immunity was recognized as far back as 1000 years ago: The Arabo/Islamic medical literature contains accounts of healthy people being inoculated against smallpox by exposure to a small amount of fluid from the skin sores of smallpox sufferers (that is, to a low dose of pathogen). The technique spread to India and Persia, and was apparently also practiced in parts of Africa by the early sixteenth century. Although it was a highly risky procedure that caused some infections and deaths, it nevertheless improved the chance of survival during an epidemic, given the 30% death rate from smallpox.

It wasn't until the end of the eighteenth century that the English country doctor Edward Jenner developed the first true

vaccine. Intrigued by the observation that milkmaids who contracted a mild disease called cowpox never became sick with smallpox, Jenner reasoned that cowpox fluid might be protective—and safe, since it was much weaker than smallpox (especially in humans). To test his idea, he inoculated an eight-year-old boy with the fluid and later intentionally infected him with smallpox. Although the experiment was certainly not safe or ethical by today's standards, his idea proved to be right: The boy remained healthy.

Jenner's technique spread quickly through Europe, but it was almost a hundred years later before French microbiologist Louis Pasteur applied it to other diseases. When Pasteur returned from vacation and injected some chickens with fluid containing the pathogen that causes cholera in chickens, and that had been fatal in earlier experiments, he was surprised to see that the chickens recovered. Aging had weakened the cholera bacteria—and Pasteur quickly discovered that this weakened (*attenuated*) strain protected animals against the fully pathogenic one. This finding led him to develop an attenuated vaccine against rabies, and over the next fifteen years attenuated or killed pathogens were also used to make human vaccines against cholera, typhoid and plague.

Pasteur quickly discovered that this weakened (attenuated) strain protected animals against the fully pathogenic one.

Although Pasteur proved that vaccination worked, he didn't understand the mechanisms involved. He developed his vaccines empirically, that is, by trial and error. Even today, there is debate among AIDS vaccine developers about the right balance between basic studies to work out the mechanisms of protection against HIV, versus a more empirical approach.

Since Pasteur's time, vaccines have been developed for many diseases that were once major afflictions of humankind. Alongside the eradication of smallpox, vaccines have brought about dramatic declines diseases such as polio, diphtheria, tetanus, measles, mumps, whooping cough and German measles (rubella), along with certain types of pneumonia and meningitis. There are even vaccines that prevent selected cancers: *Immunizing* infants against hepatitis B prevents them from getting liver cancer caused by chronic infection acquired

at birth, while a promising experimental vaccine against the *human papilloma virus (HPV)* may protect against cervical and rectal cancer.

Vaccines in use today follow only a few basic designs. Most common are attenuated vaccines (like the smallpox or oral polio vaccines), which contain a live pathogen that has been weakened to reduce or eliminate its potential to cause disease. Also common are vaccines made from pathogens that have been killed or rendered unable to multiply.

New methods for genetic engineering ushered in the possibility of making vaccines from just part of the pathogen rather than the whole thing, eliminating the tiny but real risk that the vaccine could cause the very disease it should prevent.

Until about 25 years ago, these were essentially the only two strategies for making vaccines. That's when new methods for *genetic engineering* ushered in another possibility: Making vaccines from just part of the pathogen rather than the whole thing, eliminating the tiny but real risk that the vaccine could cause the very disease it should prevent (for example, if an attenuated strain reverts to a more infectious one). In 1984—just as HIV was discovered as the cause of AIDS—a hepatitis B vaccine made with this technology was licensed, and hailed as the wave of the future. From that point on,

traditional approaches were quickly put on the back burner, with vaccine developers reluctant to pursue them (in the case of HIV) because of their potential risk.

Clearly vaccination is a powerful and cost-effective weapon against disease, as the conquest of smallpox dramatically demonstrated. But despite this progress, more than 2 million infants worldwide die each year from diseases that are preventable by existing vaccines. Although more than 350 million people are chronically infected with hepatitis B virus, globally the vaccine reaches only about 40% of those who should have it, according to the World Health Organization.

But it is critical to remember that vaccines have not yet tamed some diseases of great importance, including malaria, adult tuberculosis and several sexually transmitted diseases. Malaria and tuberculosis each cause roughly 2 million deaths per year, yet there are still no vaccines against either one.

And despite unprecedented efforts, no effective vaccine has yet been developed against HIV, which killed 3 million people in 2003—more than any other infectious disease—while some 40 million people now live with HIV/AIDS.

SINCE THE FIRST DISCOVERIES of the science called immunology, we have learned a great deal about how the immune system responds to the outside world. One important idea is that there are two kinds of disease-specific immunity:

- › *Humoral immunity*,
in which the immune system makes proteins called *antibodies* that recognize a specific pathogen like HIV in the blood and block (or *neutralize*) its activity before it can infect the body's cells.
- › *Cellular immunity*,
which steps in once the pathogen has infected some of the body's cells. Its role is to recognize and destroy infected cells in a number of ways, so that virus cannot multiply and then spread to other cells.

(See chapter 5 for an illustrated primer on how these immune responses fight infection.)

Many scientists believe that both kinds of immunity will be needed for an AIDS vaccine which prevents infection. But while most AIDS vaccines in the pipeline stimulate at least some cellular immunity, so far they have not induced antibodies that are effective in neutralizing real-world (rather than laboratory-grown) HIV virus.

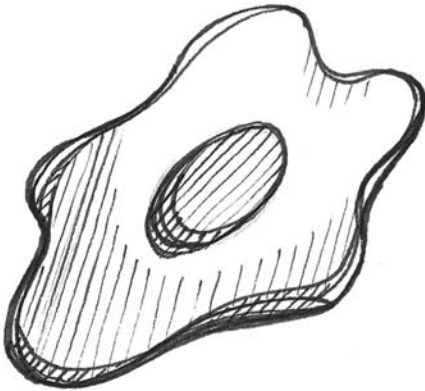
A related issue for vaccine development is the route of infection. Injection drug users become infected when HIV enters their bloodstream directly, while sexual transmission takes place when HIV crosses *mucosal tissues* that line the genital tract and other body cavities. The mucosa have their own immune system, which we know much less about. But a growing number of researchers believe that immunity at the mucosal surfaces may also be crucial for protection against HIV.

Other chapters in this section describe *how* AIDS vaccines are developed and *what types* of vaccines are being made.

the immune system in pictures

text by PATRICIA KAHN / illustrations by LEW LONG

THE IMMUNE SYSTEM is a collection of different types of white blood cells that defend us against disease-causing invaders. Some of the main actors:



Antigen-presenting cells

detect the invader and trigger the immune system to respond.



Helper T-cells

(also called *CD4+ T-cells*) direct the immune system's attack.



B-cells

produce Y-shaped molecules called *antibodies*, which help destroy invaders in the bloodstream.



Killer T-cells

destroy cells that have become infected.

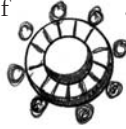
THE BODY has a huge number of white blood cells—a few hundred thousand in just a single drop of blood.

LET'S LOOK AT HOW

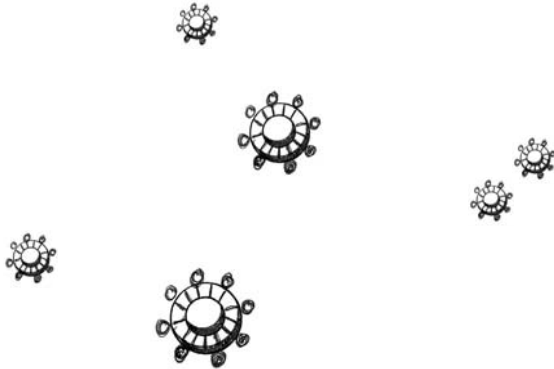
these white blood cells work together to attack invaders.

EVERY GERM THAT INVADES YOUR BODY

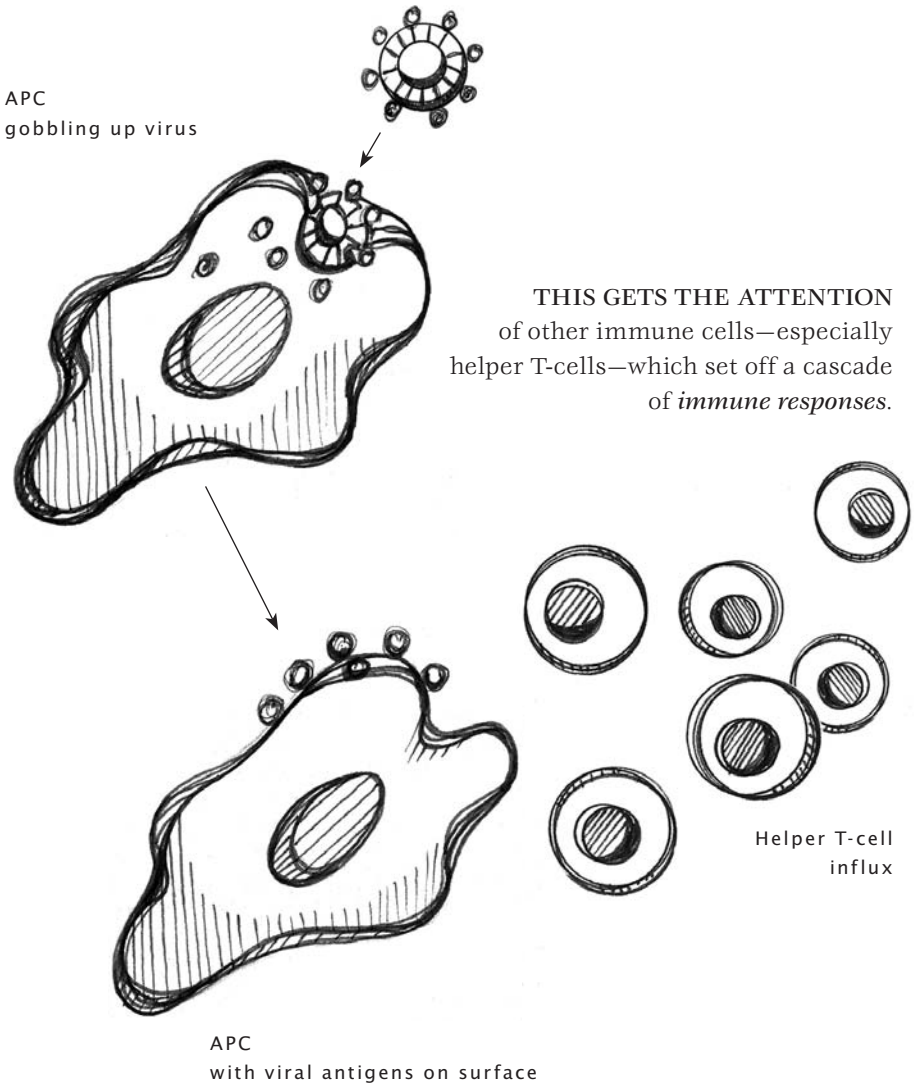
has unique "identification marks" on its surface. These are called *antigens*, and they are what alerts your immune system to the presence of an invader.

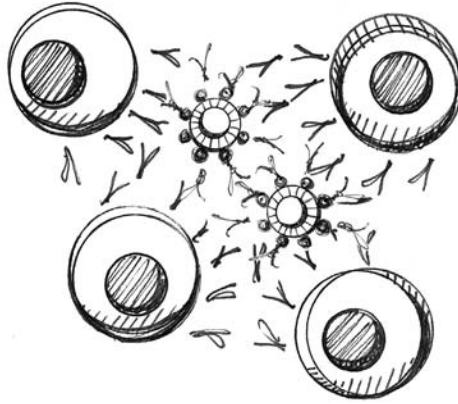


Virus



SOON AFTER INFECTION,
the invader—let's say it's a *virus*—is gobbled up by certain types
of white blood cells, including antigen-presenting cells (APCs).
APCs then take the virus apart and insert pieces of viral
antigens on their surface.



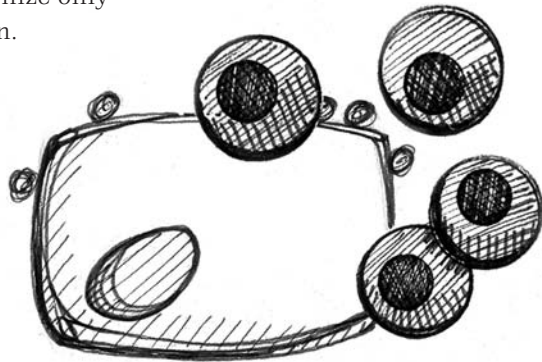


B-cells and antibodies surrounding viruses, with some antibodies binding to virus

ONE SET OF RESPONDERS, called B-cells, multiplies into a powerful squad that makes millions of antibody molecules. Each B-cell makes only one kind of antibody, which recognizes only one type of antigen—fitting it like a key in a lock.

By binding to antigens on the invader, antibodies can often stop it from doing further harm and infecting other cells. Scavenger cells called macrophages roam the body, then come along and clean up by eating the antigen-antibody complex.

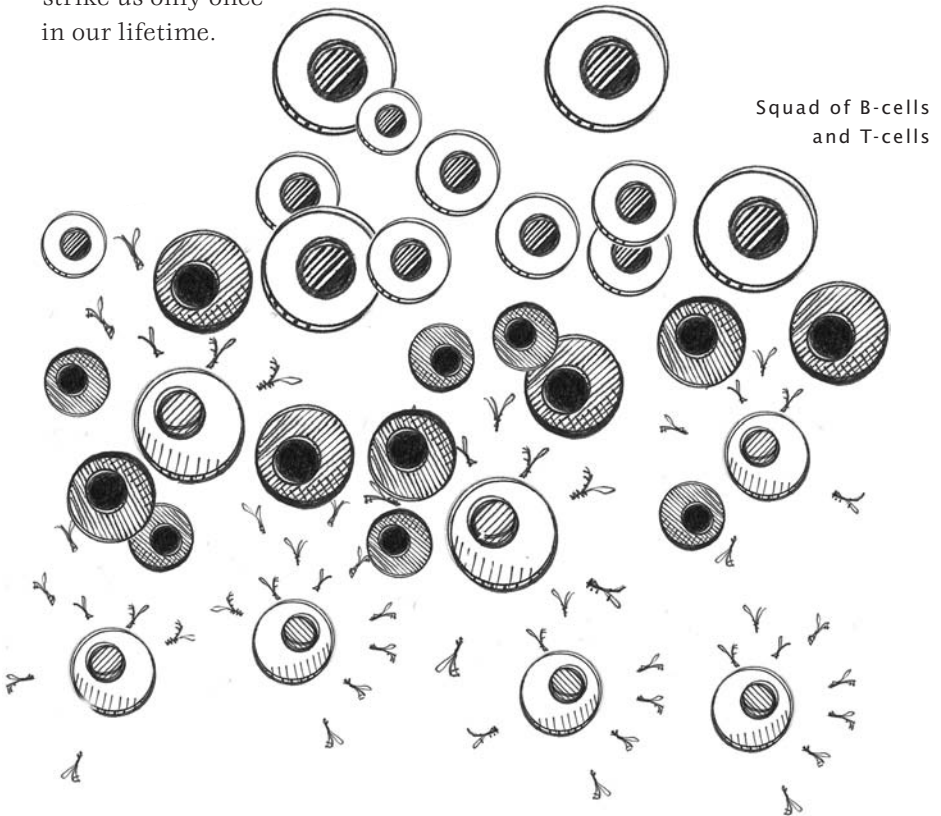
ANOTHER TYPE OF RESPONDER is the killer T-cell. It destroys body cells that display the same viral antigens on their surfaces, which means they've been infected. Like B-cells and antibodies, each killer T-cell is programmed to recognize only a small part of a single antigen.



Infected body cell with killer T-cells attacking it

WHEN THE IMMUNE BATTLE IS OVER AND THE INVADER DESTROYED, the squad of B-cells and T-cells is much bigger and stronger.

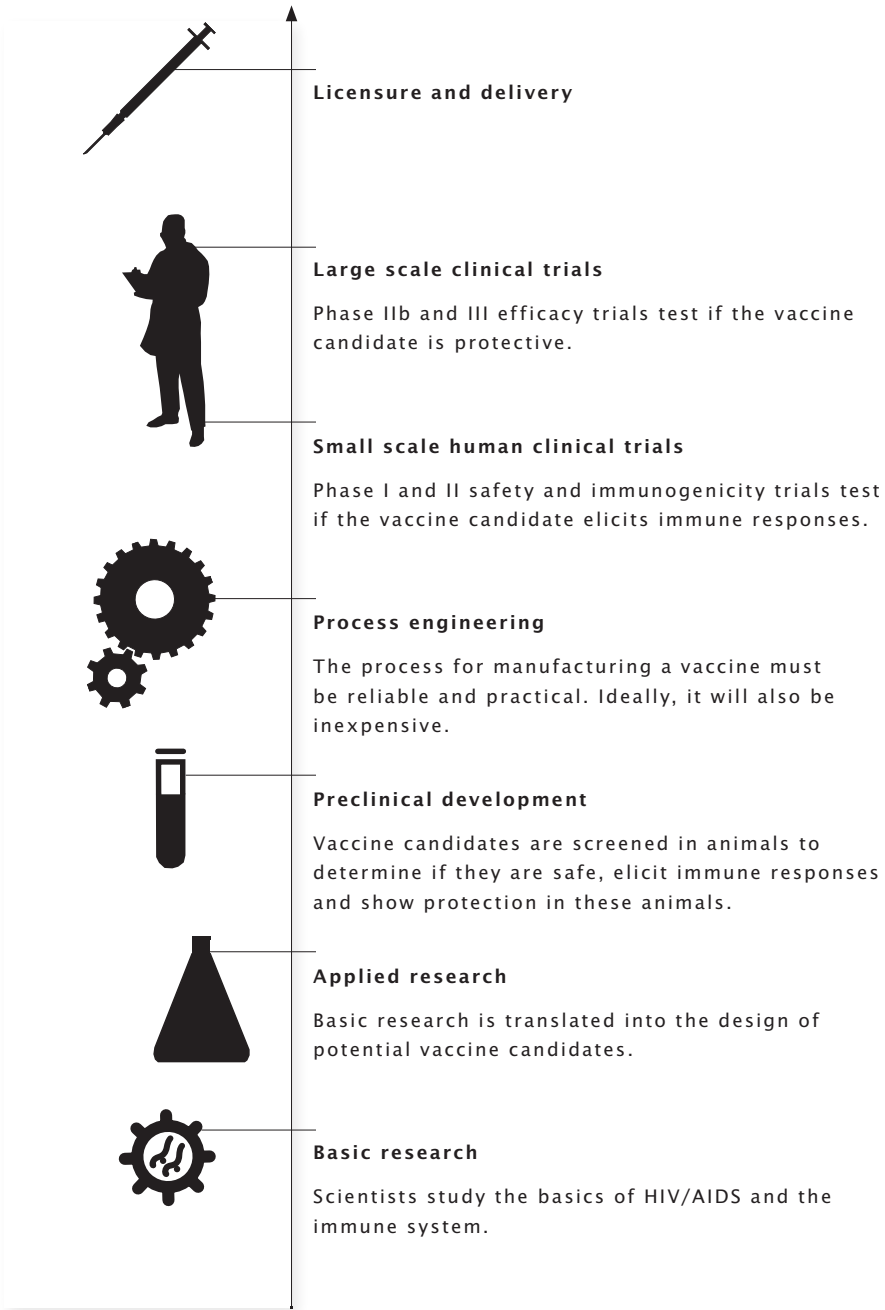
Some of these cells become *memory cells* which remain in the body for many years. If the same virus tries to infect you again, the immune system is ready with a faster, more potent response and can often kill off the invader before it even makes you sick. That's why certain diseases, like measles and mumps, strike us only once in our lifetime.



VACCINES WORK

by setting off these same kinds of immune responses, so the body is trained to recognize the antigens of disease-causing invaders even though it's never been infected with the real thing. But HIV has many tricks for evading the immune system, and is proving to be one of the toughest foes vaccine developers have ever tackled.


Figure 2.1 Pipeline of vaccine research and development



©Ann McDonald-Cacho, adapted from www.iavi.org

vaccine development: from concept to licensed product

HUNTLY COLLINS



DEVELOPING A NEW VACCINE takes a lot more time, effort and scientific expertise than most people realize—rarely less than ten years, and sometimes several decades. While each vaccine is different, the research and development process moves through defined stages that take candidates from a concept to a licensed product. This article gives a quick overview of the whole process. Most of the stages are described in more detail in other chapters.

getting started

Before a vaccine concept can get off the ground, certain basic knowledge is needed. First and foremost, researchers must know what *pathogen* causes the disease and they must be able to grow and isolate it in the laboratory. The more they know about the pathogen, how it works and how the immune system responds to it, the better.

Building on this basic knowledge for HIV, an experimental AIDS vaccine begins with an idea—what scientists call a hypothesis, or an educated guess. Based on their own and others' observations, scientists hypothesize how the human immune system might be stimulated by a vaccine so it can defend the body against HIV infection or disease.

For instance, in the 1990's researchers came to realize that people infected with HIV are able to control the *virus* for a period of years before it begins multiplying more rapidly and destroys their immune system. This temporary control, it turns out, corresponds with a relatively high number of certain immune cells (*T-cells*, or *T-lymphocytes*) that specifically recognize HIV-infected cells. Hence, scientists hypothesized that a vaccine which stimulates these T-cells might not prevent the initial infection but could perhaps control virus *replication*, which in turn might delay or prevent people from getting sick with AIDS. This is the concept behind nearly all the experimental HIV vaccines now being tested.

designing vaccines

Translating a hypothesis into an actual HIV vaccine is a difficult step. A big part of the reason is that we don't understand enough about HIV transmission or our *immune responses* to HIV to know just which parts of the virus to include in a vaccine, and in what form. So vaccine designers have to rely partly on best guesses (the "empirical approach," as it's sometimes called). The next chapter has more information on how vaccines are designed and on the most common designs for HIV vaccines.

Once a candidate has been made in the lab, it is put through a series of tests and gradually improved. If these experiments pan out, the vaccine moves quickly into animals, where its ability to stimulate *immunity* can be tested.

animal experiments

Initial tests are typically conducted in small animals such as mice, guinea pigs or rabbits, and then in monkeys. The aim is to measure the strength and type(s) of immune responses induced by the vaccine. (The stronger these responses are, the more *immunogenic* the vaccine is said to be.) Investigators also look for ways to increase *immunogenicity*, for example, by varying vaccine dosages and *immunization* schedules, or adding certain compounds that may enhance immune responses. Other tests examine the toxicity of the candidate vaccine, including its side effects, to evaluate safety.

Animal testing may also involve so-called “*challenge experiments*” in monkeys to test whether the vaccine actually works. Although monkeys can’t be infected with HIV, they are susceptible to its close relative *SIV (simian immunodeficiency virus)*, which causes the same kind of immune system failure seen in people with HIV, and to a laboratory-made hybrid of HIV and SIV called *SHIV*. In these experiments, small numbers of monkeys are vaccinated and then challenged (that is, deliberately infected) with SIV or SHIV. Scientists then monitor whether vaccinated animals show lower rates of infection or disease, or lower amounts of virus in the blood (called *viral load*), compared with unvaccinated ones. If they do, it is a good sign—although it doesn’t guarantee that the same type of vaccine will protect humans.

Why not? Because animal models are useful, but only up to a certain point. Despite the similarities, monkeys are also biologically different from people. And SIV or SHIV is not HIV. In other words, there is no exact animal model for HIV—a big obstacle in developing an HIV vaccine. So ultimately, the only way to know whether a promising experimental vaccine is safe and effective for humans is to test it in uninfected people, through a lengthy sequence of *clinical trials*.

Ultimately, the only way to know whether a promising experimental vaccine is safe and effective for humans is to test it in uninfected people, through a lengthy sequence of clinical trials.

big decisions

Only relatively few vaccines make the huge jump from the lab into clinical trials. Although there are no strict criteria for choosing which ones to move forward (except for an excellent safety record), decisions may depend a lot on whether animal data are promising enough to justify the enormous time, expense and use of human volunteers these trials demand. Along with good scientific evidence from the lab (although scientists may disagree about what is “good”), the vaccine should have a strong chance of being acceptable to regulatory agencies and to the general public. There should also be a feasible (and ideally inexpensive) way to manufacture it, although in practice this requirement is sometimes factored in only later for decisions on which candidates should go into large-scale human trials.

clinical trials

Clinical trials are conducted in three sequential phases, each enrolling larger numbers of volunteers and answering somewhat different questions. (For more on the later-stage trials, see chapter 11.)

- › *Phase I trials*
typically involve several dozen volunteers at low risk for HIV infection and focus on safety issues, but usually also look at whether the vaccine is immunogenic. Often several Phase I studies will be done in succession, to test different vaccine doses or immunization schedules.
- › *Phase II trials*
involve several hundred volunteers, often including some with a high infection risk, and gather both safety and immunogenicity data.
- › *Phase III (efficacy) trials*
enroll several thousand volunteers or even more, and to *statistically* determine whether the vaccine works—that

is, does it protect some vaccinees from either infection or HIV/AIDS disease? Very few of the vaccines tested in Phase I will go all the way to Phase III testing. So far there have been dozens of different HIV vaccines in Phase I trials, but only three types have made it into Phase III.)

Alongside these traditional categories, HIV vaccine developers are adding a fourth one to the process: so-called *Phase IIb* trials, also called “proof of concept” trials. The idea is to look for preliminary evidence of efficacy in smaller, shorter and much less expensive trials before launching a full-fledged Phase III study.

For HIV vaccines, it's highly likely that *Phase IV* studies will also be done. These are studies conducted after a vaccine has been licensed, to determine its true effectiveness outside the *controlled* conditions of a clinical trial, to measure how long protection lasts and to look for any late-emerging or very rare side effects. A Phase IV study can involve up to many thousands of people.

Since vaccine trials involve giving a new substance to healthy people, scientists need advance approval from various regulatory bodies in the country where the vaccine is produced and the countries where it is to be tested. (For more information on regulatory review and safety, see chapter 14.)

licensing

Before a vaccine can be distributed and used by the public, it has to be licensed by the regulatory body that monitored the clinical trials and by those in countries where it will be used. Licensing decisions involve careful review of Phase III trial data by the regulators, who look closely to make sure the vaccine is safe and that it offers a clinical benefit. There's no fixed standard for how much of a benefit is necessary for licensing an HIV vaccine. In practice it could even end up that countries might make different decisions, depending on factors such as the severity of their epidemic.

Obviously, a vaccine that is safe and highly successful in preventing HIV infection or disease would be licensed. But HIV vaccines may raise some difficult issues for regulators. One is how to recognize, let alone license, vaccines that delay disease without blocking infection—an outcome that can't be fully measured in the 3–4 year time span of an efficacy trial. Another type of dilemma would arise if the first HIV vaccines work in only a relatively small proportion of people—say, 30%. Is this enough to merit licensure? (For a discussion of partially effective vaccines, see chapter 9.) Complicating the decision-making process even more, differences in regulatory procedures from country to country could lead to a bureaucratic mess over licensure, especially since some developing countries are short of capacity and expertise in this area.

manufacturing

At first glance, manufacturing a vaccine may seem straightforward, but in practice it's usually difficult, expensive and time-intensive.

At first glance, manufacturing a vaccine may seem straightforward, but in practice it's usually difficult, expensive and time-intensive. Vaccine makers therefore have to start their planning as early as possible in a product's development. Yet making a major investment in manufacturing capacity before efficacy trials have shown that the vaccine works is a very expensive gamble. (This dilemma is discussed further in chapter 36.)

Problems making a new vaccine can arise even with the (relatively) small amounts needed for clinical trials. But the bigger problems come later, in finding ways to produce hundreds of millions of doses (if the vaccine proves to be effective)—methods that usually take time and practice to work out. It also takes years to build and equip the high-tech factories that can make such huge amounts of vaccine, and to have them approved by regulators. Ideally, construction should begin while a vaccine is still in clinical trials so there is no delay in having enough available if it gets licensed.

Vaccine manufacture must meet strict standards set by governmental regulatory agencies. These standards ensure, for example, that each vaccine lot is identical to the others, that the vaccine doesn't have impurities and that its chemical composition remains stable over time. The plants themselves must follow what is called *GMP (Good Manufacturing Practice)*, which controls everything from the cleanliness of the facility to the source of the raw materials and the production, packaging and storage of the final product.

access for all

HAVING A LICENSED HIV VACCINE in hand is still a long way from getting it quickly to people who need it, especially those in poor regions of the world (see chapter 36 on vaccine access.) Typically, new vaccines are available only in wealthy countries for a decade or more (and at high prices) before they are slowly introduced into poor countries. Making sure this doesn't happen for an HIV vaccine will be a huge challenge, to say the least, and will take money, greatly expanded health care infrastructure, public education campaigns, and above all, strong global advocacy and political will.

aids vaccine approaches in development

PATRICIA KAHN

WHEN TODAY'S common viral vaccines were first developed, their makers didn't have many choices about how to get the job done. They usually didn't know a lot about how the *virus* caused disease, nor (by today's standards) much about the virus or its life cycle. The technologies they had to draw on were also very limited. So most vaccines were made either by killing virus or by weakening it so it couldn't cause disease, then using the resulting particles to *immunize*.

For HIV, these traditional approaches are essentially off the table. Using live virus, even if it's weakened, is too risky, while killed vaccines haven't shown much promise so far. Luckily, AIDS vaccine designers now have a treasure chest of *genetic engineering* tools that allow them to pluck out any portion of the virus—so they can make vaccines that use only parts of HIV, which is a safer strategy. And they can join their selected pieces of HIV genes to gene segments from other sources that might contribute useful properties to a vaccine.

getting started

So where do researchers begin when they set out to make an AIDS vaccine?

One of the first questions they ask is which arm of the immune system it should target, since the answer determines what types of designs to consider.

To make a vaccine that targets *humoral immunity* (the best hope for blocking HIV infection), the basic idea is to use the HIV *envelope protein (Env)*, which protrudes from the surface of free virus particles. There it is “seen” by the immune system and recognized as foreign, triggering specialized white blood cells called *B-cells* to make *antibodies* against specific regions of Env. Some of these antibodies (depending on exactly which regions they recognize) will be *neutralizing antibodies (NAb)s*, and these are the ones vaccine developers especially want to induce. That’s because if NAb)s encounter HIV from a real infection later on and can recognize its particular Env, they would (in theory) lock onto the virus particles and prevent them from infecting cells.

Neutralizing antibodies offer the best hope for blocking infection with HIV.

But so far, there’s been only failure, since HIV has evolved sophisticated ways of evading the NAb response (more on this below). So researchers are now working on new strategies to make forms of the envelope that can outsmart the immune system.

Cellular immunity kicks in once HIV succeeds in infecting host cells. HIV *proteins* are then made inside the cell and incorporated into the *membrane* surrounding the cell, where they are recognized as *antigens* (that is, as foreign) by the immune system—alerting the *killer T-cells* to the presence of infected cells. In other words, for vaccines to induce cellular responses, it’s not enough to expose the immune system to free-floating HIV particles or antigens; instead, the antigens need to be “displayed” on the cell surface.

Although making vaccines that target cellular responses is a relatively new idea, nearly all the AIDS vaccine candidates now in *clinical trials* fall into this category. And a number of them are turning out to have at least some ability to do

the job—although we don't yet know if this will translate into protection. Most researchers think that the effect of this type of vaccine (if it works at all) won't be to block HIV infection but to control *viral replication*, which in turn could slow or prevent the onset of AIDS. (See chapter 8 for more discussion of how these vaccines may work.)

Both humoral and cellular responses also contribute to *mucosal immunity*—immune defenses in tissues that line the body cavities, including the genital tract, anus and gut. How much of a role they play in protection against HIV, and how to best induce them, are areas that still get very little attention in the field.

Let's now take a closer look at some of the vaccine designs in the pipeline.

approaches targeting cellular immunity

THE CRUX of any strategy for stimulating T-cell responses is how it delivers the HIV genetic material (or in some cases small protein fragments called *peptides*) into the cells of a vaccinated person. The main strategies being tested are:

› *Naked DNA vaccines*

These vaccines contain pieces of HIV genetic material (*DNA*) joined to pieces of harmless bacterial DNA (called *plasmids*). When this type of vaccine was first developed around 1989, many researchers thought it would revolutionize vaccine development: Not only did DNA vaccines induce strong *immune responses* in mice, but they are simple and inexpensive to produce, and could eventually be stable without refrigeration—a great advantage for getting vaccines to remote settings. But candidates developed for many diseases (including HIV)

Table 2.2
Types of vaccines in clinical trials (February 2005)¹

Vaccine Type	Number in trials
Viral vector	16
DNA	9
Protein	5
Peptides	4

¹ Sources: International AIDS Vaccine Initiative (IAVI) trials database; the Pipeline Project (see resources and appendix 3).

haven't yet lived up to this promise in humans, since they usually stimulate only weak responses.

Because of their potential advantages, the HIV field hasn't given up on DNA vaccines, but is looking for ways to augment them. One possibility is to pair them with a second vaccine, an approach that's being tested in several clinical trials—most of them using a DNA vaccine to “*prime*” the immune system,

The prime-boost approach—pairing 2 vaccines—may be more potent than either vaccine alone.

followed by a “*boost*” with a second vaccine (usually a *viral vector*-based product; see below) a few weeks later. In monkeys, these combinations are often more potent than either vaccine alone, although in humans, several *Phase I* trials have given disappointing results. Other trials are testing whether DNA

vaccines are more *immunogenic* when given together with substances that boost the immune system (one of the body's natural boosters, called *cytokines* or other immune-stimulating compounds called *adjuvants*).

› *Live vector vaccines*

Most *live vector vaccines* use harmless viruses engineered to ferry foreign genes (like HIV genes) into cells. Each viral vector has its advantages and disadvantages, based on properties such as how much foreign DNA it can carry, the types of host cells it infects best, how long it persists in the host and how easy or difficult it is to grow in large amounts.

One of the more promising vaccines in the pipeline uses a vector made from a weakened cold virus called *adenovirus*; this candidate is now being tested for *efficacy* in a “proof-of-concept” trial (see chapter 8). Another vector, based on a bird virus called *canarypox*, is used in several veterinary vaccines and was made into a series of AIDS vaccines that have been in clinical testing since 1994; one of them is now in a *Phase III* efficacy trial in southern Thailand, in a *prime-boost* combination with an envelope-based vaccine (see chapters 8 and 22). Yet another is based on a weakened virus called *MVA*, a relative of the virus used to make smallpox vaccine. Of the newer vectors, one of them (called *VEE*) infects important

"antigen-presenting" immune cells, while another (AAV) persists in the host for long times, which may lead to better immune responses.

Other types of vaccine vectors are in the pre-clinical stage of research. Several laboratories are developing weakened bacteria as vectors, and an AIDS vaccine made in yeast is also in the works. Scientists in South Africa are even working on plant vectors, which might be usable as oral vaccines.

› *Peptide (or lipopeptide) vaccines*

Peptide vaccines contain small fragments of HIV proteins, which are simpler and less expensive to make than whole proteins. There are almost endless numbers of possible variations. For example, peptide vaccines can include the most immunogenic snippets of any HIV protein, and/or peptides from different *strains* of HIV. Although earlier peptide-based candidates were dropped because they induced only weak responses, research groups in France have been developing candidates with peptides linked to fat molecules, or lipids (the hybrid is called a lipopeptide), which seem to enhance the peptides' *immunogenicity*. One lipopeptide vaccine is now in *Phase II* studies, and another is being tested as a boost for a canarypox-based vaccine prime. The pharmaceutical company Wyeth is also developing a peptide-based HIV vaccine.

Besides deciding what type of vaccine to make, researchers also need to choose which parts of HIV to include. It's a difficult decision, because they don't yet know which antigens matter most for protection. So for now, the choice is just an educated guess. Alongside the question of *which* genes or proteins (or parts of them) is the issue of *how many* to include. On one hand, it seems logical that more is better, since this avoids eliminating potentially useful antigens. But fewer antigens mean a simpler vaccine to make. And certain viral vectors are limited in how much foreign DNA they can incorporate.

Besides deciding what type of vaccine to make, researchers also need to choose which parts of HIV to include. It's a difficult decision because they don't yet know which antigens matter most for protection.

approaches that target neutralizing antibodies

Vaccines aimed at neutralizing HIV all start with the HIV envelope protein, which sticks off the surface of viral particles in spikes made of three individual envelope molecules (see illustrations in chapter 3). But HIV has evolved masterful strategies to hide parts of the envelope that could induce neutralizing antibodies, and to evade detection by those which are nevertheless made. That's turned the problem of how to design vaccines which induce effective NABs into one of the most important scientific hurdles facing the field—one that's only now starting to get the intense attention it needs, after years of frustration over the impasse.

In the early years of AIDS vaccine research, antibody-based vaccines were all anyone worked on—buoyed by the (then-recent) success of a hepatitis B vaccine made from its viral envelope. The strategy was to engineer cells in the laboratory so they produce a *subunit* of the envelope, then purify the subunit and use it as a vaccine. Unfortunately, it emerged that, although these subunits induced NABs to HIV strains grown in the lab, they couldn't neutralize viruses isolated directly from infected people. Still, one of these products went all the way through Phase III trials, but proved not to be protective (see chapters 22 and 23).

Despite all these difficulties, there's good reason to believe that this problem can be solved. In the late 1990's, researchers studying the blood of HIV-infected people found a few examples of just the kind of NABs needed—those which can neutralize a wide range of HIV strains, despite differences in their Env proteins. That led to an approach based on working backwards: analyzing the precise three-dimensional structure of these unusual antibodies, down to the position of individual atoms, to see exactly what part of the envelope protein they recognize. From there, the hope is that researchers can engineer envelope proteins which mimic these key structures. In the meantime, similar kinds of fine-structure studies are helping other researchers pursue different strategies—such as altering the envelope protein to unmask its critical neutralizing regions so

they are exposed to the immune system. Once candidates based on these “rational” approaches progress into clinical trials, Phase I studies will show whether they induce the broadly neutralizing antibodies vaccine designers hope they will—the property that most researchers think will give an HIV vaccine the best chance of preventing infection in the first place.

where are we headed

AS NEW CANDIDATES are finally being tested in Phase I trials, researchers are learning which ones induce the best immune responses and using this information to improve the design of the next candidates. As these precious clinical data accumulate, some of the guesswork in vaccine design will hopefully be eliminated. And with two efficacy trials in the works, finding a vaccine that works even a little would be a major advance, since it would give researchers a handle on finding out just what immune responses a vaccine needs to induce. But for now, the working assumption is that the ultimate AIDS vaccine will probably need to stimulate both humoral and cellular immunity, and possibly also mucosal responses—which will probably require a combination of different vaccines.

The ultimate AIDS vaccine will probably need to stimulate both neutralizing antibodies and cellular immunity.

resources

www.iavireport.org/trialsdb

Database of AIDS vaccine trials. Compiled by the *IAVI Report* (the newsletter of the International AIDS Vaccine Initiative), this is a searchable database of all preventive AIDS vaccine trials (ongoing and completed).

<http://chi.ucsf.edu/vaccines>

The Pipeline Project, a collaboration of the University of California San Francisco (UCSF) Center for HIV Information and the US HIV Vaccine Trials Network (HVTN). This website lists ongoing, planned and completed trials sponsored by the HVTN.

<http://clinicaltrials.gov>

More complete information on federally and privately supported trials from the US government’s clinical trials database.

vaccines that trigger cellular immunity: what can we hope for?

RICHARD JEFFERYS

THE SEARCH FOR an effective HIV vaccine relies heavily on the scientific lessons learned from other vaccines—for example, those that prevent polio and hepatitis B. Until recently, the conventional wisdom was that most vaccines work by triggering the body to produce *antibodies* against the infection. Antibodies are tiny Y-shaped molecules made by immune system cells called *B-cells*. Their main task is to search out invaders, or *pathogens* (like *viruses* or bacteria) floating free in the bloodstream, and then to stick onto them. Once a pathogen is coated with antibodies, it can't infect new cells and is quickly destroyed.

But antibodies are at a big disadvantage when it comes to HIV, because the virus has developed very effective strategies for evading them. The result is that scientists haven't yet found a way of triggering the immune system to make antibodies that block HIV infection (see chapter 7 on the different approaches to designing HIV vaccines). Overcoming this problem is a top priority for the field, but in the meantime, researchers have come to recognize that another arm of the immune system—called *cellular immunity*—is also important in vaccine protection.

HIV vaccines targeting cellular *immune responses* also turn out to be easier to make, and as a result, nearly all the candidates now in *clinical trials* fall into this category. And with a few dozen such candidates in development, it's crucial for the field to figure out whether this approach can induce even partial protection—which, in turn, will tell us whether or not we're on the right track. Here we'll describe what's known about the role of cellular immunity in protection, and discuss how these vaccines might work and how they're being tested.

beyond antibodies: the role of cellular immunity

Cellular responses come mostly from two types of immune cells. First are the “*killer*” *T-cells*, also called by the more technical names of *cytotoxic T-lymphocytes (CTLs)* or *CD8+ T-cells*; their role is to seek out and destroy cells in the body that have already become infected. Second are “*helper*” *T-cells*, or *CD4+ T-cells*, which help both CD8+ T-cells and B-cells do their jobs by acting as overall coordinators of the immune response.

“Killer” T-cells, or CD8+ T-cells, seek out and destroy cells in the body that have already become infected. “Helper” T-cells, or CD4+ T-cells, do their jobs by acting as overall coordinators of the immune response.

There haven't yet been many studies directly proving the role of T-cells in protection by the common vaccines. But antibody expert Dennis Burton (of the Scripps Institute in San Diego, California) says that most vaccines don't induce high enough levels of antibodies to completely block infection, and that cellular immunity must therefore also be playing a role.

In a way it's surprising that this should be discovered only now, since most of the common vaccines have been around for decades. The main reason is a practical one: antibody responses are far easier to measure, and tests to do this have been in use for many years. But until a few years ago, methods for looking at cellular responses were much cruder (and more labor-intensive). Fortunately, new, improved methods are now allowing researchers to tackle the question of what role cellular immune responses play in preventing HIV infection or delaying the long progression to AIDS once a person becomes infected.

So far, research findings suggest that cellular immune responses can play an important role in fighting HIV. Much of this research focuses on two unusual groups of people.

First, there are individuals who remain HIV-negative even though they're repeatedly exposed to the virus. These people are called "*exposed seronegatives*" or ESNs. Researchers have studied different types of ESNs, including uninfected partners of HIV-infected individuals, commercial sex workers and infants who are exposed to HIV via breastfeeding. Many of these studies have found that ESNs show cellular immune responses targeting HIV (that is, HIV-specific CD4+ T-cells and CTLs), but no antibody responses. For example, one study in infants exposed to HIV via breastfeeding found that the presence of HIV-specific CTLs at birth strongly increased the baby's chances of staying uninfected.

Second is the group of rare individuals known as *long-term non-progressors* (LTNPs). LTNPs are HIV-positive people who show no signs of *immune deficiency* although they've been infected for long enough that this is very unusual. (Some have been monitored by researchers for more than 20 years and still show no evidence of disease progression.) They also have very low levels of virus in the blood (*viral load*). At the same time, LTNPs have strong cellular immune responses specific for HIV.

Studies in rhesus monkeys add to the evidence that cellular immunity plays a role in controlling virus *replication*. These animals can be infected with a virus called SIV (*simian immunodeficiency virus*), which is closely related to HIV. Researchers have found that removing CD8+ T-cells from SIV-infected macaques leads to a dramatic increase in viral load, which then gradually declines as the body replenishes its lost CD8+ T-cells. More detailed studies with several vaccine candidates have also shown that the level of vaccine-induced SIV-specific T-cell responses determines how well the animals control SIV replication after infection.

So far, research findings suggest that cellular immune responses can play an important role in fighting HIV. Much of this research focuses on two unusual groups of people.

These findings don't prove that cellular immune responses protect against HIV infection or prevent disease progression. But they provide a good scientific justification for developing vaccines targeting HIV-specific cellular immunity.

the importance of memory

One issue which has plagued the pursuit of this approach is that scientists haven't been able to define just what particular CD4+ and CD8+ T-cells are needed for protection—these cells exist in many varieties, each with different levels and types of biological activity. So when researchers test vaccines in either animal models or people, they don't know precisely which responses best identify the most promising candidates.

Immunological memory is key to our ability to fight off pathogens we've been exposed to before.

But as they hone in on this problem, researchers are starting to pay more attention to the *memory* CD4+ and CD8+ T-cells.

Immunological memory is the key to our ability to fight off infection by a pathogen we've been exposed to before, either from an earlier infection or from a vaccine. But until recently, scientists didn't know much about how immune memory is formed. Fortunately, that's now starting to change, opening up new opportunities for making vaccines that do a better job at inducing memory—for example, by smarter dosing of the vaccine and more optimal frequency and spacing of *immunizations*. And this, in turn, could give the immune system a crucial “head start” against HIV.

Another new finding is that CD4+ T-cells are needed to make fully functional memory CTL; without them, memory CTLs don't kill infected cells as effectively. This gives HIV vaccine makers the crucial piece of information that their vaccines must induce CD4+ responses along with the CD8+'s, information that is now getting incorporated into vaccine design and testing.

potential problems with cellular immunity

On the down side, there are some reasons to worry that vaccines that target *only* cellular immunity may have serious limitations.

One big concern is the potential for “*immune escape*.” HIV has a breathtaking ability to mutate (change its genetic material)—which it does continuously, as it copies itself thousands of times in each infected cell. Some of these *mutations*, in turn, change the structure of the viral *proteins*, or more specifically, of the small regions within them (called *epitopes*) recognized by T-cells. Even if a vaccine suppresses HIV multiplication almost completely, over time it's still possible that mutation will generate *strains* which are no longer recognized by the vaccine-induced T-cells—effectively making an end-run around vaccine protection. A somewhat related worry is that an immune system weakened by age, or by a disease unrelated to HIV, could lose its ability to control virus.

This enormous *variation* in HIV proteins (and epitopes) presents another potentially serious challenge for vaccines: will a single vaccine be able to protect against *all* HIV strains, or will it protect only against strains closely related to the one used in making the vaccine? This issue is discussed at length elsewhere in this volume (see chapter 10); at present, the answer is that we just don't know. But the hope is that, even if the match is poor, those T-cells which recognize the *unchanged* (or minimally changed) epitopes might still be enough for protection. And even if they hold a new infection at bay only temporarily, it might give the immune system enough time to generate new memory responses that lead to more lasting protection.

testing cellular immunity-based vaccines

MOST OF THIS DISCUSSION so far is about what these vaccines *might* do, or what something *could* mean. But we need to know for sure: can vaccines that induce cellular immune responses to HIV (in particular, memory CD4+ and CTLs) either protect against HIV infection or control virus replication

in vaccinated people who become infected? Another very important question is whether, if they do hold viral load to low levels, this will also reduce the frequency of HIV transmission.

The usual assumption in the field is that these vaccines won't give much protection against HIV infection, but that they may slow or prevent progression to AIDS. But the fact that ESNs have T-cell responses without any signs of infection argues that the potential for complete protection shouldn't yet be ruled out.

After years of testing candidates in *Phase I* and *II* trials (and finding out that many of them induce at least modest T-cell responses), the first trial to give some real answers is getting underway. The 1,500-person "proof-of-concept" study started at the end of 2004 at several international sites and is testing a vaccine (designed by Merck & Co.) that uses a weakened cold virus (called *adenovirus*) to carry HIV genes into the body. The trial—a so-called *Phase IIb* study (see chapter 11)—should give some indication about whether these vaccine-induced cellular responses are effective at either preventing HIV infection or reducing viral load in vaccinees who become infected. If all goes as planned, results will be available around 2007/2008. However, if it works, this vaccine will need to be modified and re-tested before an application for licensure. That's because a high percentage of people already have *immunity* to the type of adenovirus used to make the vaccine, which means that they don't respond nearly as well as people without this pre-existing immunity. (Such individuals will be excluded from the Phase IIb trial).

More information about the role of T-cell responses could also come from an ongoing vaccine *efficacy* trial in Thailand. This trial is evaluating a combination of two vaccines (one based on a harmless bird virus called *canarypox*; and *AIDSVAX*, the VaxGen product described in chapter 22). The canarypox-based vaccine induces HIV-specific T-cell responses in about 10–20% of vaccinated people.

As these and other crucial trials get underway, work on vaccines that stimulate antibodies is continuing (and intensifying). And many scientists think that, in the end, the best HIV vaccines will need to stimulate both cellular immunity and antibody responses.

partially effective vaccines

EMILY BASS

MOST PEOPLE HAVE HEARD of vaccines. And most of them are taught that getting vaccinated against a particular disease-causing germ (*pathogen*) means they're protected from ever getting that disease.

There's plenty of truth in this simple equation *vaccine = protection*: Many vaccines do provide high levels of long-lasting protection to most people who get *immunized*. But in practice there is no such thing as a vaccine that provides 100% protection, 100% of the time. In this sense *all* vaccines are only "partially effective." Although that may sound worrisome, in practice vaccines are powerful tools for preventing disease, and they bring enormous benefits to individuals and communities.

Still, when it comes to AIDS vaccines, the concept of partial protection can be especially confusing. That's because there are two different ways of defining what we mean by this term.

In practice there is no such thing as a vaccine that provides 100% protection, 100% of the time. In this sense *all* vaccines are only "partially effective."

what could a partially effective AIDS vaccine do?

The first, more easily understood definition of a partially effective vaccine is one that protects some people in a population, but not others. This is possible because many factors affect our immune systems and, by extension, our ability to respond to vaccines. It's in this sense that most licensed vaccines are partially effective. Many of them protect as many as 80 or 90% of individuals in a population. Others, like oral cholera vaccine, give lower levels of protection but still have a positive effect on health in communities where they are widely used. A textbook example is the original Salk polio vaccine, which is only about 60% effective. This may seem low, but within a few years of its introduction in the US—and even though many people didn't get vaccinated—it caused a dramatic drop in the number of new polio infections.

Vaccines that induce cellular immunity may not block infection but could help the body fight HIV after infection.

The second definition of partial protection describes a vaccine which doesn't completely prevent infection by a pathogen but helps reduce the severity of the disease it causes. An AIDS vaccine of this type would reduce the severity of HIV disease in vaccinated people who later became infected through blood or sexual exposure.

While either (or both) of these definitions could apply to an AIDS vaccine, the second, less well-understood one is now getting most of the attention. That's because most of the vaccine candidates being tested in *clinical trials* are designed to induce *cellular immune* defenses, which act against HIV only after it has entered the body and infected its target cells. So instead of preventing infection in the first place, these vaccines are more likely to improve the immune system's ability to fight the *virus after* infection. They would do this by slowing viral activity and protecting the immune cells (especially *CD4+ T-cells*) which HIV infects and destroys. These defenses could also help to control the amount of virus circulating in the body (*viral load*).

A vaccine that lowers viral load and helps people preserve their CD4+ T-cells could benefit them in several ways. It could allow them to live with HIV for longer periods of time without

getting sick. It could also prolong the time until they needed to start *antiretroviral therapy* (ARV). Each person reaches this point at a different time after infection, and an AIDS vaccine could help extend this period.

It could also have important benefits at the community level. People with low viral loads are less likely to transmit HIV to their partners during unprotected sex or to their infants during pregnancy and childbirth. If enough people in a community or country were vaccinated, these effects could help slow the spread of the epidemic in the region.

how can we test for partially effective vaccines?

Even without a vaccine, people usually don't get sick for five years or more after HIV infection. So clinical trials that directly measure whether an AIDS vaccine extends this healthy phase would have to go on for ten years or even longer. To get faster answers, the less-than-perfect alternative is for trials to look at indirect measures of HIV's effects, especially viral load and CD4+ T-cell count, in volunteers who become infected through high-risk contact. Based on past history with natural infection and with patients on ARVs, these data should give an earlier indication of whether or not the vaccine will affect disease progression or infectiousness.

A vaccine that improved health for people who became HIV-infected would be a major breakthrough, and would probably get licensed for general use. But even after licensure, researchers would continue studies to answer crucial questions: How long does vaccine-induced protection last? How much of a reduction in viral load is needed to translate into long-term health benefits for the individual? How much of a reduction will reduce the risk of transmitting to another person?

preparing for partial efficacy

Although imperfect, partially effective vaccines that reduce the severity of disease but don't prevent infection could be

powerful tools for fighting HIV. Their success depends on establishing realistic expectations and broad understanding of their benefits and limitations. At least two key messages will have to be conveyed:

- › Since these vaccines won't protect against HIV infection, they cannot be considered a replacement for other methods of prevention, including male and female condoms and a *microbicide* (if one is developed). It will be very important to convey this message so that people don't assume they are protected and increase their risk behaviors after being vaccinated.
- › This type of vaccine will not replace or even reduce the need for comprehensive HIV prevention and treatment programs. In fact, it will be most effective when it's promoted as one of several strategies for fighting the epidemic.

MANY GROUPS are already working on ways to convey these messages to different audiences, including governments, public health agencies, and people thinking about how an AIDS vaccine will be used. This involves thinking about ways to explain the concept—for instance, drawing a comparison between partially effective vaccines and family planning methods like condoms, hormonal contraceptives and diaphragms. No single method is 100% effective, but used in combination, these methods can provide very high levels of protection.

Clear understanding of these vaccines also involves studies designed to figure out where a partially effective vaccine would be most useful. For example, some statisticians and public health experts are working out different scenarios to model the impact of a partially effective vaccine in countries with well-established versus emerging epidemics, and in people with different types of risk factors for HIV.

A good, partially effective vaccine would be a huge advance towards controlling the epidemic and making an improved or combination vaccine that could do even better.

do clades matter for aids vaccines?

PATRICIA KAHN

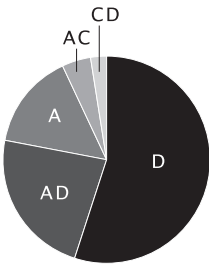
ALTHOUGH WE TALK ABOUT (and treat) HIV as one *virus*, this doesn't mean that everyone is infected with an identical version of HIV. In fact, analyzing its genetic makeup reveals that there are many, many different versions—a phenomenon called *genetic diversity* (or *genetic variation*). And this diversity is continually increasing, since HIV is always changing at the genetic level and creating new versions of itself.

The notion of viral genetic diversity is nothing new: Most viruses which cause disease in humans exist as distinct *strains*. But the amount of diversity with HIV dwarfs that seen for any other virus. To describe this variation, researchers classify HIV strains into one of three groups, based on their degree of genetic similarity: group M, the main one behind the global epidemic, group N and group O. The M viruses are further divided into *subtypes* (or *clades*), named by the letters A through K.

Another key point about HIV diversity is that the various clades aren't distributed uniformly around the world; instead, different clades predominate in particular regions. For example, the epidemic in southern Africa is essentially all clade C viruses

(which are also common in India and China), while North America, Europe and Australia have mostly clade B strains. Other regions have several clades in circulation (see figures 2.3–2.5), with the most extreme examples found in western and central Africa—where just about every known clade is seen. (For a map of global distribution patterns, see resources at the end of this chapter.)

Figure 2.3 UGANDA



Proportion of different HIV clades and recombinants in circulation, based on analyzing 47 HIV genomes from infected people in the Rakai district. Over half were infected with clade D viruses; the second most common strains are recombinants between A and D.

Source: Francine McCutchan

What does any of this have to do with vaccines? This enormous diversity potentially presents a huge problem: Can a single, “universal” vaccine protect against the full range of HIV strains? Or will we need different vaccines, each tailored to the most common strains in a given region? Even worse, with new HIV variants continuously being generated, is it possible that new vaccine formulations might be needed every few years, as they are for influenza?

The answers to these questions will have a big impact on how fast, and at what cost, a successful AIDS vaccine can be developed and distributed globally. Manufacturing even one vaccine formulation and getting it to people quickly once it's licensed will be far more complicated and expensive than anything the public health field has ever attempted. Doing this with several vaccines, or having to repeat it every few years, would make the task even harder. And for regions with more than one HIV clade, the problem goes deeper: Unless an AIDS vaccine protects against all (or most) clades in circulation, it may simply shift the

local epidemic over time towards whatever strains the vaccine can't protect against. For these regions, success in curbing AIDS through vaccination will be especially dependent on having products that induce the broadest possible protection.

That's the bad news. Yet there is room for some optimism. Over 90% of all HIV infections worldwide are caused by four clades (A through D) plus two “mosaic” viruses (see below) that

both contain about 70% clade A sequences—a more manageable focus for vaccine developers.

generating diversity

Before describing how the field is tackling HIV diversity, let's start with a primer on how diversity and clades arise, and what they do (and don't) mean.

The bottom line is that diversity stems from the tendency of HIV to make mistakes when it copies its genetic material while multiplying inside an infected cell, and from the fact that it can produce billions of new virus particles a day. That's a lot of mistakes, hence a lot of new variation.

Let's look closer at how this works. The genetic material, or *genome*, of HIV is made from four different building blocks linked together like beads in a chain, about 10,000 units long. As with all living things, the genetic information is contained in the precise sequence of these four units—information which tells the cell how to build *proteins* that each carry out a specific job. When HIV copies its genome, it sometimes incorporates the wrong unit somewhere in the sequence. The result: a genetic change, or *mutation*.

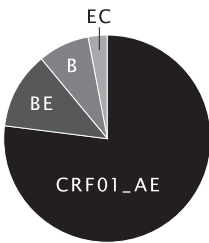
HIV genes vary in how often they mutate. The champion is the *envelope* gene (*env*), which encodes the main surface protein of the virus: *env* genes in viruses taken from a single infected person vary by as much as 10%, and among different clades they vary by up to 35%. (This gives the virus an advantage during infection, since it's difficult for the immune system to keep up with constant change—so some new variants *escape immune* recognition.) Other HIV proteins, like the *Gag* protein that forms part of the virus' internal core, show less than 10% variation from one clade to another; these are said to be more genetically *conserved*.

Beyond mutation, HIV undergoes another level of change: if a person is infected with two different strains, these can exchange whole segments of their genomes—creating a “mosaic” virus called a *recombinant*. Sometimes recombinants spread to other people and become common circulating strains (called

circulating recombinant forms, or *CRFs*). For example, nearly 80% of infections in Thailand, and 50% in Cameroon, involve CRFs (see figures 2.4 and 2.5).

Now comes the rub in terms of figuring out if and how all this diversity will affect vaccine protection: clades don't correspond to what the immune system recognizes. Some genetic mutations are "silent," in that they don't cause any change in the protein they encode. Others *do* cause changes in the protein, but not all changes are noticed by the immune system. (The immune system doesn't recognize entire proteins but only certain portions, called *epitopes*—and only certain changes within epitopes.) In other words, some mutations stay under the radar screen of the immune system, while others wipe out its ability to recognize particular epitopes—which is what matters for vaccines.

Figure 2.4 THAILAND



Proportion of different HIV clades and recombinants in circulation, based on analyzing 70 complete HIV genomes from newly-infected people in northern and southern provinces. The vast majority of strains in both regions were recombinants, although the regions had different proportions of the types shown. Over 75% of all infections involved a group of recombinants called Circulating Recombinant Form (CRF)01_AE.

Source: Francine McCutchan

immunity and cross-clade recognition

So where do vaccine developers start? Beyond the challenge of making a vaccine that induces *any* protection, tackling HIV diversity involves working from two different angles. One is to figure out whether *immune responses* to one strain of HIV recognize a wide range of other strains (that is, whether they *cross-react*) or only very closely related ones. Second is to find vaccine designs that induce responses to the broadest possible range of strains.

To measure the degree of cross-reaction among HIV clades, researchers are studying immune responses both in HIV-infected people and in uninfected people given an HIV vaccine. For example, these studies might test how well blood cells from people *immunized* with a vaccine made from pieces of a clade B virus

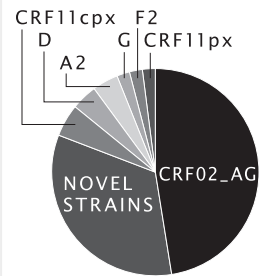
recognize very similar strains compared with more divergent ones. (This type of laboratory test is illustrated in chapter 12.)

So far, the results are reasonably encouraging for vaccines that induce *cellular immunity*: *T-cell* responses often cross-react to HIV strains within and across clades, although they may recognize fewer epitopes, or respond less strongly, than to the original strain. (It's important to note that responses don't fall into neat categories based on clade. There's also some variation from person to person, since people's genetic makeup helps determine what epitopes their immune system can recognize.)

But cross-reaction in a laboratory test doesn't tell us for sure that protection will work across clades, since we don't know if these tests measure the immune responses (or epitopes) that matter most for protection. So answers about cross-protection will need to come from *clinical trials* that compare how well a vaccine protects people against closely related HIV strains versus more distant ones.

For *neutralizing antibodies (NABs)*, the picture looks bleaker: no vaccine tested in people so far generates NABs to anything beyond the strain that induced them and a few closely related strains. Yet studies of NABs in HIV-infected people show that broadly cross-neutralizing antibodies *do* exist—findings that have re-kindled efforts to devise strategies for generating them by vaccination (see below and chapter 7 on vaccine approaches).

Figure 2.5 CAMEROON



Proportion of different HIV clades and recombinants in circulation, based on 30 complete HIV genomes. Samples were drawn from HIV-infected people in rural villages, blood banks, hospitalized adults and STD clinics.

Source: Francine McCutchan

designing for diversity

Until recently, few vaccine candidates were designed to test specific approaches to HIV diversity, since researchers were focused on finding strategies for inducing *any* strong responses. But as more products are developed, several approaches are emerging.

Among the T-cell-based vaccines in clinical trials, a common strategy is to use the most conserved regions of HIV, usually Gag, followed by *Pol* and sometimes *Nef*. In a variation on this theme, two companies are developing candidates containing highly conserved, widely recognized epitopes (rather than whole genes or proteins) from different parts of HIV.

Vaccines aimed at the NAb response are a harder problem, since the protein they target (Env) is so variable. One approach is to make vaccines with Env from several clades—often called *cocktail vaccines*. This strategy was first used by VaxGen to make the vaccines tested in its already-completed *Phase III* trials; for example, the study in Thailand mixed Env proteins from the two most common clades circulating in the country. Several newer candidates are also taking this route; for example, the Vaccine Research Center in the US has made cocktails with *env* genes from clades A, B and C.

Another approach (not yet in the clinic) uses hypothetical HIV sequences rather than real ones, and designs them to recognize the broadest possible set of Env proteins (at least in theory). These vaccines are made by first comparing the sequences of many HIV genomes from different clades using computers and then creating the sequence that best matches the most strains. Researchers are also analyzing the structure of the Env protein down to the finest level of detail—which may help them manipulate it in ways that unmask broadly neutralizing epitopes tucked inside the protein, or perhaps to engineer epitopes that “fit” the few broad NABs which have been isolated from infected people. (These approaches are described in chapter 7.)

testing for vaccine protection across clades

Having a wider range of vaccine designs, along with data on cross-reactivity, puts the field in a better position to address questions of cross-clade protection in *efficacy* studies.

So does the growing number of candidates based on different clades. Until a few years ago, vaccine developers

focused almost exclusively on clade B, which dominates the epidemic in industrialized countries but causes only about 12% of infections globally. (Two important exceptions are the products used in both Phase III trials conducted in Thailand.) But products from other clades account for most of the newer products, including several based on clade C—which is behind over half of all infections worldwide—and on A and D, both common in Africa.

How does all this help study cross-protection? There is broad agreement in the field that vaccine efficacy studies should start in a population where “matching” HIV strains are common, since this will measure whether the vaccine has any ability to protect, while minimizing any possible effects of strain diversity. Figuring out whether it also protects against strains from mismatched clades could be done either in parallel or after initial proof of efficacy, either by adding trial sites in regions where other clades predominate or by doing a single trial where several clades (the matched one plus some mismatches) are in circulation. Having candidates of different clades means that these trials can take place in diverse settings throughout highly affected developing countries.

Cross-reaction data also comes in here. Knowing what clades have at least some strains recognized by the vaccine strain gives clinical trial planners a rational basis for choosing mismatched populations—that is, populations with cross-reacting strains in circulation.

These developments have also helped reduce the political dimension that sometimes attached to the clade issue, rooted in the years when most candidates were based on clade B. This left some countries reluctant to carry out even safety trials of non-matched clades, and created demand for country-level “tailoring” of candidates for *Phase I* studies.

But attitudes have shifted, and there is wide recognition that broader, not narrower, vaccines are desperately needed. For example, in 2003 the African AIDS Vaccine Programme came out strongly in favor of planning efficacy trials to give clear answers about cross-protection. And it endorsed the

Attitudes have shifted, and there is wide recognition that broader, not narrower, vaccines are desperately needed.

notion of unmatched trials in Phases I and *II*, and in efficacy studies as long as there is evidence for cross-reactivity between the vaccine strain and local ones. With several Phase I trials of unmatched vaccines now going on in different parts of the world, hopefully the ground is getting prepared for the day when we have promising vaccines ready to be put to this test.

resources

www.iavireport.org/specials/specials.asp

Map showing “Global distribution of HIV-1 subtypes and recombinants,” which summarizes current understanding of the global distribution of HIV-1 strains (August 2003). Available from the International AIDS Vaccine Initiative, *IAVI Report* online special features.

<http://hiv-web.lanl.gov/content/hiv-db/mainpage.html>

Los Alamos National Laboratory. Databases of HIV and SIV sequences, and defined HIV epitopes, with software tools for analyzing and comparing them, plus research and review articles.

testing aids vaccines in people

EMILY BASS and PATRICIA KAHN

MOST AIDS VACCINE TRIALS so far have been *Phase I* studies that enroll small numbers of volunteers and test a vaccine candidate's safety, along with its ability to induce *immune responses (immunogenicity)*. But studies with small numbers of volunteers can't tell us whether or not a vaccine prevents HIV infection or disease. For this we need to carry out large-scale *clinical studies* called *efficacy* trials, or (in their traditional form) *Phase III* trials.

So far there have been only two completed Phase III trials of an AIDS vaccine, and a third is ongoing—altogether involving nearly 24,000 volunteers and costing hundreds of millions of dollars. But with many vaccine candidates now in early phases of clinical testing, there will hopefully be several promising ones ready for efficacy trials within a few years.

Yet the huge commitment of people and funds required for a single Phase III trial has led many AIDS vaccine developers to consider testing some candidates in smaller, shorter “proof of concept” (*Phase IIb*) trials, which give preliminary information about a vaccine's efficacy. The first IIb study of an HIV vaccine started in late 2004 (see chapter 8).

As complicated as these studies are to carry out, the idea behind them is simple: Compare the rate of HIV infection (or some sign of disease) in people given the real vaccine with those who got only an inactive substance called a *placebo*. If the vaccine is effective, the vaccinated group should have significantly fewer infections or disease markers than the group that got placebo. Statisticians then analyze the data to make sure that the difference isn't just a fluke, but is due to the vaccine.

This approach works only if some of the volunteers expose themselves to HIV (for example, through unprotected sex) over the course of the study—even though the trial staff provide risk-reduction counseling at every study visit. (No study ever deliberately exposes volunteers to HIV.) High quality prevention services during efficacy trials are crucial (as well as morally and ethically necessary), since the vaccine may not work, and because some people get only a placebo. But counseling is rarely 100% effective. If there are few or no infections in the placebo group, it's impossible to tell whether the vaccine is working. And the converse is also true: the higher the rate of new infections, or *incidence*, in the study population, the easier it is to detect a vaccine effect, which means that the trial will need fewer volunteers and/or a shorter follow-up period.

AIDS vaccine efficacy trials need to be done in high-risk populations—which, in turn, is a big part of what makes these trials complicated.

This is why AIDS vaccine efficacy trials need to be done in high-risk populations—which, in turn, is a big part of what makes these trials complicated. High-risk populations are concentrated mostly in countries hit hardest by the epidemic (nearly all in the developing world) and among groups that are often marginalized and discriminated against—such as gay men, injecting drug users and racial/ethnic minorities.

Doing clinical research that involves vulnerable participants—especially when it also involves a stigmatized disease like AIDS—raises lots of sensitive issues, which are the subjects of many chapters in this book. On the other hand, these highly affected populations are among those who stand to benefit most from a successful vaccine.

Besides a high incidence, it's also important that the study population (or *cohort*) in Phase III trials reflects a diversity of people who will use the future vaccine. That's because it's possible that one particular subgroup in the cohort (for example, a certain racial group, or women only) might respond differently to the vaccine—and if there are too few volunteers in this subgroup, such trends can't be detected, as the first Phase III trial by VaxGen vividly showed (see chapter 22). Although a single trial can't analyze the vaccine separately in all possible subgroups of a cohort, it can spot trends in one or two key subgroups if the trial is designed to do so.

preparing for efficacy trials

Before vaccine developers can design an efficacy trial in a given population, they need to have some key information in hand—such as HIV incidence, and a good sense of what other diseases and health issues are common in the community. Often these data are gathered in a “vaccine preparatory” study that enrolls healthy HIV-negative volunteers and follows them for one or a few years. These studies may also look at peoples' knowledge about vaccines, their willingness to participate in vaccine trials, and at practical matters such as how to best recruit and retain participants. They can also help cement referral networks for care of people who become infected during the trial (or are found to be positive at screening) and can deepen the working relationship with a community.

conducting efficacy trials

Volunteers who have gone through screening and *informed consent* and then enroll in the trial are *randomly assigned* to either the vaccine or placebo group. Neither the trial staff nor the volunteers know who received vaccine or placebo until the study is over. Throughout the trial, volunteers receive regular HIV tests and risk-reduction counseling, which reinforces the message that they should not consider themselves to

be protected. Those who nevertheless become infected are monitored for at least the rest of the trial period to see whether the vaccine affects their *viral load* (the amount of HIV in the blood) or their *CD4+ T-cell* counts, both of which indicate how the disease is progressing.

Once completed, the study is “*unblinded*” and scientists look for differences in infection rates between the vaccine and placebo groups and, in infected participants, in viral load and CD4+ T-cell counts. If differences are detected, *statistical* tests can determine whether they are due to the vaccine or to coincidence.

hedging your bets: phase IIb trials

Phase III trials are the gold standard for testing efficacy and, if the vaccine shows some efficacy, for generating data that can be used in applying to national regulatory authorities for licensing the vaccine. Depending on a trial's size and design, it could also reveal trends (of higher or lower efficacy) in one or two subgroups within the overall cohort.

Phase III trials are the gold standard for testing efficacy. Phase IIb trials are best suited to weeding out ineffective candidates and identifying relatively high-efficacy ones.

Phase IIb trials, on the other hand, are best suited to weeding out ineffective candidates and identifying relatively high-efficacy ones. But they can't estimate efficacy with nearly the same accuracy as a Phase III study, nor would they yield licensable results in most cases (except perhaps for a blockbuster vaccine with very high efficacy). So candidates identified as promising in a IIb trial will probably still need to undergo Phase III testing.

multiple trials in multiple populations

Rather than conducting one large trial to see if an AIDS vaccine is protective, vaccine developers may plan multiple trials of the same (or closely related) vaccine(s). One reason for this strategy is that there are several different ways that

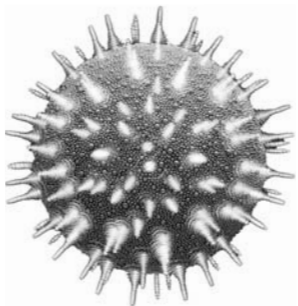
people can become infected with HIV: through unprotected sex, breastfeeding from an HIV-infected woman or use of a needle that has been contaminated with HIV-infected blood, for example through needle-sharing among people who inject heroin.

The ultimate goal is to develop an HIV vaccine that protects people no matter how they are exposed. But since the different infection routes bring HIV up against a different set of immune defenses, we can't assume that vaccines which work against one route will work equally well against the others. The only way to find out is to test vaccines in populations of HIV-negative people exposed to HIV through different routes—for example, gay men exposed through anal sex, and injecting drug users through sharing needles. This strategy was used in VaxGen's two large-scale Phase III trials (see chapters 22 and 23).

Another reason for carrying out HIV vaccine trials in multiple populations is to test the vaccine against the *diverse* HIV *strains* (called *clades*) circulating in different regions of the world. No one knows whether a vaccine based on one HIV clade will protect against infection with others (see chapter 10). Last but not least, the efficacy of a vaccine might be influenced by differences among populations, such as other *pathogens* they are exposed to, the diseases they live with, and genetic differences, which are known to influence how well the immune system responds to particular *antigens*.

trial success and failure

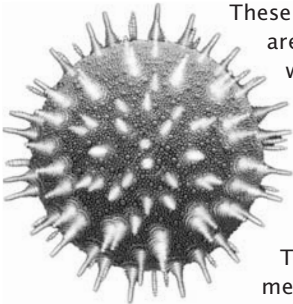
A TRIAL THAT FINDS solid evidence of vaccine efficacy is obviously a clear success. But even if it doesn't, the trial shouldn't be viewed as a failure—if it clearly resolves that the vaccine doesn't work (thus settling an important question) and if it advances our understanding of what's needed to make a vaccine that's more likely to protect.



testing for immune responses to hiv: the science in pictures

PATRICIA KAHN and MICHAEL HOELSCHER

Of the roughly two dozen vaccine trials now going on, all but two of them are early-stage studies looking at the safety of candidates and at their ability to induce *immune responses*.



These studies help vaccine developers identify which vaccines are the most promising and which are not worth pursuing, which parts of HIV stimulate the best immune responses, and whether *booster* doses are needed (and at what time intervals). They also yield important information on how to improve vaccine designs. Even trials of candidates that show poor responses contribute to our knowledge of what should—and shouldn't—be included in a vaccine.

These insights are based on the results of laboratory tests that measure immune responses in the blood samples drawn from volunteers at each clinic visit. On the following pages we show what happens to a blood sample after it leaves a volunteer's arm and is used in one important test, which measures *cellular immune responses*. (Not shown here: part of each blood sample is also sent for clinical analysis to monitor the health of the volunteers.)

This sequence was photographed at the site of a vaccine preparedness study by the Mbeya Medical Research Program (MMRP) in Mbeya, Tanzania and at the Uganda Virus Research Institute (UVRI) in Entebbe, Uganda.



©Michael Hoelscher/MMRP

A nurse collects blood from a trial volunteer.

LAB SETUP

In the meantime, technicians in the lab prepare everything they will need to process blood samples from all the volunteers who visit the clinic that day.

The setup shown is for blood samples from 30 people.



©Michael Hoelscher/MMRP



©UVRI/IAVI

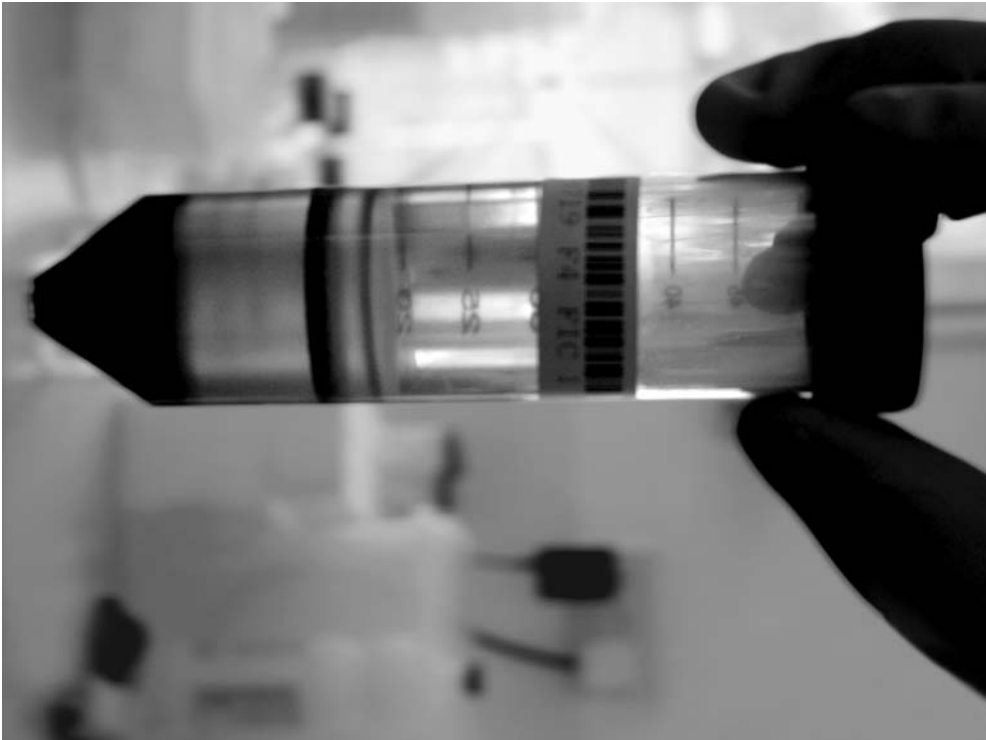
SEPARATING CELLS FROM PLASMA

When test tubes with the samples arrive in the lab, the first step is to separate the blood cells from the liquid part of the blood, called plasma. The cells will be tested for their ability to recognize HIV, while the plasma is used for HIV tests and measuring *antibody* responses, or for *viral load* measurement in the case of an infected person.

The separation is done by spinning the cells at high speed in a machine called a centrifuge. This causes the cells to form a pellet at the bottom of the test tube, with the liquid on top.

ISOLATING LYMPHOCYTES

The next step is to separate *lymphocytes* (the cells relevant for *immunity*) from the rest of the blood cells. This is done by putting the cells from the pellet on top of a very thick liquid (called *ficoll*) in a test tube and spinning them again. The lymphocytes stay on top of the liquid, while other cells move through it and settle at the bottom of the tube.



©Christoph Geldmacher/MMRP



©Michael Hoelscher/MMRP

PREPARING LYMPHOCYTES FOR STUDY

Lymphocytes are “washed” by suspending them in a washing solution and spinning them down again, pouring off the liquid and repeating this cycle a few times. Then they are processed for freezing and placed at -196°C in liquid nitrogen. They can be thawed at a later time for immune analysis, or alternatively, immune tests can be done right away on a portion of the cells.



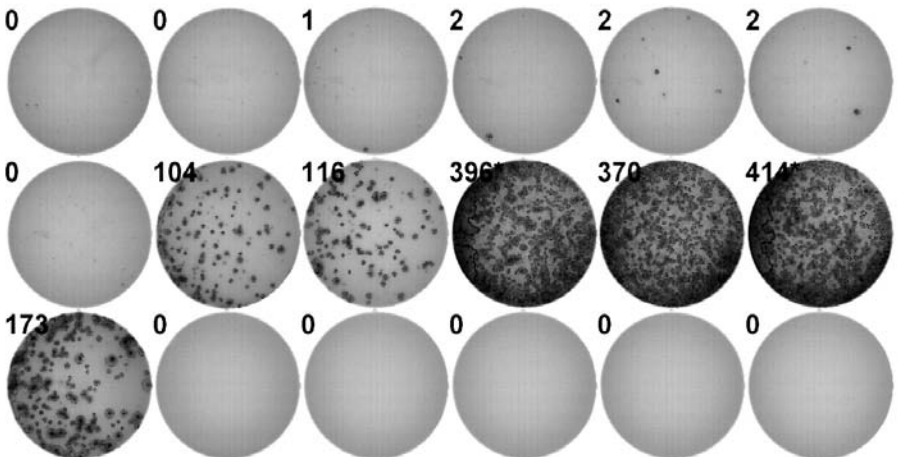
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TESTING FOR T-CELL RESPONSES

To analyze *T-cell* responses using a test called ELISPOT, a technician then counts cells under the microscope and takes a pre-determined number for the immune measurements.

COUNTING "SPOTS"

A fixed number of cells is added to each well in a cell culture plate containing fragments from one or more HIV *proteins*. Cells that recognize the HIV fragment begin producing chemicals called *cytokines*. Then a second ingredient is added, which stains cytokine-producing cells blue. The number of blue spots in each well indicates how many cells recognize the fragment—in other words, how strong the immune response is.



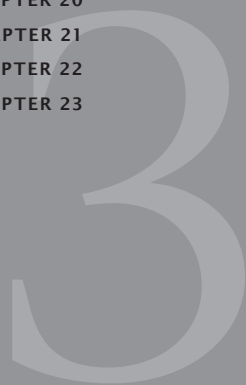
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clinical trials

- BEING A TRIAL VOLUNTEER: WHAT HAPPENS? CHAPTER 13
IS IT SAFE? CHAPTER 14
RESEARCH ETHICS: RECIPE FOR SUCCESS CHAPTER 15
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PHOTO ©Glenda Gray/International AIDS Vaccine Initiative (IAVI)




SOUTH AFRICA / previous page

Dr. Glenda Gray watches as Dr. Mampedi Bogoshi immunizes a vaccine trial volunteer at the Perinatal HIV Research Unit of the Chris Hani Baragwanath Hospital in Soweto.

being a trial volunteer: what happens?

SCOTT CARROLL and PATRICIA KAHN



MAKING THE DECISION to participate in an AIDS vaccine study can be difficult. So can the participation itself. Being a trial participant takes a serious commitment—of everything from time to letting yourself be stuck with needles. You may also find yourself confronting or talking about things that are deeply personal. For some of the same reasons, volunteering can also be tremendously empowering and uplifting.

If you're thinking about volunteering for a trial, you'll probably start out with lots of questions. Other chapters in this book deal with some of the most common ones, from the safety of experimental vaccines to worries about being stigmatized as “high risk” for HIV. Here we offer a nuts-and-bolts description of what actually happens during a trial: What you will do, and what medical procedures and people are involved.

HIV VACCINE RESEARCH. REAL PEOPLE. REAL PROGRESS.

"I'm volunteering to stop a killer."

HIV is a killer. Four of my five close friends died of it. I volunteered to honor them. As someone who is HIV negative, volunteering in an HIV vaccine trial was a way to make a real contribution. My hope is that we will have an effective, preventive HIV vaccine someday. It's the best way to stop HIV from spreading.

Mark McLaurin
Volunteer, HIV Vaccine Research

HIV VACCINE RESEARCH. REAL PEOPLE. REAL PROGRESS.



Join me on Tuesday, May 18th
down to form a "V" — as a sign you share my vision for an HIV preventive vaccine. Showing your support for HIV vaccine research shows you appreciate all the people working to make progress to stop this killer, HIV.

"I'm fighting to stop a killer."

HIV is a killer. I'm a witness. I have buried babies. I have buried old people and young people. People like me, people like you. HIV is serious, so my life's work is helping others learn about it and prevent it.

Today, thousands of researchers, medical professionals and volunteers are committed to discovering a vaccine that prevents HIV and stopping this epidemic. To them, I say, 'Thank you, I'm with you.'

Mark Del Monte
Community Worker



Join me on Tuesday, May 18th for HIV Vaccine Awareness Day. Wear your red AIDS ribbon upside down to form a "V" — as a sign you share my vision for an HIV preventive vaccine. Showing your support for HIV vaccine research shows you appreciate all the people working to make progress to stop this killer, HIV.

USA

From a series of posters by the US National Institutes of Health (NIH) announcing AIDS Vaccine Awareness Day, an education campaign about AIDS vaccine research and clinical trials.

what will happen, who you'll meet

YOUR EXPERIENCE as a trial participant will most likely follow a routine similar to this:

- 1 -

Your first encounter with people connected to the trial might be an information session in your neighborhood or village where community educators talk about AIDS vaccine research, describe how *clinical trials* are done, discuss any trials that may happen at the local site and respond to any questions and concerns. Or you might start out by visiting the clinic for information after learning about an upcoming trial through an advertisement, or from another volunteer.

Once at the clinic, the first person you'll interact with will probably be an outreach worker. His or her job is to find the type of people needed for the trial and inform them about the study. While it's easy to think of outreach workers primarily as salespeople for the study, in practice many of them took their jobs because they are part of the community the trial is targeting and believe that the work they are doing is important for the community as a whole. After you get the information you need, the final decision is yours to make. No one at the trial site should pressure you one way or the other.

- 2 -

The next step is a screening appointment. There you will meet with a person trained to do interviews and draw blood in a research setting. He or she should be able to describe the study in detail and answer all your questions. If not, you should have access to a project coordinator or clinical investigator. You, in turn, will be asked questions about your medical history, health and life (including personal stuff about sex and drugs, etc.) You'll have a physical exam performed by a nurse practitioner or physician, and blood will be drawn for routine clinical lab tests, to make sure your overall health is good. The blood sample will also be used for an HIV *antibody* test.



©GHESKIO/Cornell clinical trial/Port-au-Prince

HAITI

Poster seeking volunteers for an AIDS vaccine trial in Port-au-Prince, Haiti. Text in speech bubble reads: "If you are between 18 and 60, and were negative for HIV when you had your last AIDS test, you can help develop a vaccine against the virus that causes AIDS." Translation from the Creole by Stephenson Jolicœur.

(Before you can participate in a vaccine study, researchers must be sure that you aren't already infected with HIV.) If you're female, you'll also be tested for pregnancy, and asked about your pregnancy plans. Being (or planning to become) pregnant disqualifies you as a volunteer, since investigators avoid intentionally exposing a fetus to an experimental product. For the same reason, women who are breastfeeding an infant are also disqualified.

At this point you might be told that you're not eligible to participate, based on the criteria for *inclusion* or *exclusion*—for example, certain medications you're taking, your medical history, your ability to return for follow-up appointments or your risk activities. Some of these criteria depend on the type of study: For example, early (*Phase I*) safety studies of a product look for volunteers with very low risk of HIV infection, while large-scale (*Phase III*) trials need people with a higher level of behavioral risk. (These different types of studies are described in chapter 11).

- 3 -

One or two weeks later, you'll return for your results from the screening tests, meet with a counselor for your HIV test results and counseling, and either be accepted into the trial or told that you are ineligible. If you are eligible and still want to go forward, you will review and sign *informed consent* material with a screener or clinician and have your pre-vaccine blood drawn for lab tests, including another HIV test (to make sure you haven't become infected since the initial screening), and for storage. You might also receive your first injection, which will contain either the experimental vaccine or a *placebo* (a "blank" given to a group of participants as a basis for comparing to the *immune responses* or infection rates in people who get the real vaccine). Most trials are *blinded*, which means that neither participants nor the clinic personnel know who gets which. Women will be given a pregnancy test just before each vaccination, and are ineligible to continue if they are pregnant.

A research doctor or nurse will give the injection, and you will be asked to stay at the clinic for up to an hour for observation in case of an *adverse reaction*.

- 4 -

Subsequent visits will be much the same. You will return at fixed intervals for blood draws, interviews, counseling and sometimes more injections. The number of visits is predetermined and stated in the consent form.

- 5 -

Once you have completed your visits, your responsibilities as a trial participant are over. When all the other volunteers complete theirs, the study will be “unblinded,” which means that the investigators will get a list of which participants received the vaccine and which ones got placebo. From there a team of scientists will analyze the data, which can take up to several months. When they are finished they will usually communicate with you again, letting you know which group you were in (vaccine or placebo) and explaining the results of the trial.

the site study team

Your site will have its own principal investigator (PI), and you should have access to yours if you request it. Each PI is in charge of one or more trial sites. At each site the PI will have a group of scientists and staff working with them who you will get to know as you return for visits. Most PI's have a medical and/or public health background. You probably won't interact with him or her during your regular study visits, although some PI's look for opportunities to interact with the volunteers.

In addition to the PI, most sites also have a coordinator who is responsible for the day-to-day running of the trial. The whole process at a site is often colored by the PI and site coordinator, so you may want to get a sense about them before agreeing to participate.

The person you will interact with most will be your counselor or study nurse. He or she is usually chosen in part for their good people skills. Often these relationships can grow to

be warm and supportive. You will also get to know the study's lead physician, whose job is to monitor the clinical results and overall health of the participants and to follow up and provide care if needed in the case of adverse events.

what next?

THE END OF A TRIAL means one less obligation on your schedule. But some volunteers also describe it as a letdown; a loss of the sense that you're "doing something" about the epidemic.

It's important to realize that volunteers, past and present, are a fast-growing and potentially potent group of advocates for AIDS vaccines. Worldwide, there are over 20,000 of us.

If you're in a trial that is about to end, you might want to find other ways to stay involved—for example, by serving on a *Community Advisory Board (CAB)*, or doing advocacy work (see chapter 34 for a discussion of this by one former volunteer). Your trial site may know about some others, and perhaps this book and some of the resources it lists will also give you ideas.

is it safe?

PAT FAST

IS IT SAFE? This is the question all of us want answered before we enter a *clinical trial*. The level of risk varies from trial to trial, but as long as a vaccine is investigational (which means that it is being studied to see if it should be licensed), the only honest answer to this question is “we aren’t sure it will be safe for you.” This is a hard answer to hear, but no one should enter a clinical trial until he or she has understood and accepted it. The degree of risk can be estimated from previous experience with the vaccine (and similar ones) in humans, and from the results of tests in animals. But no one knows for sure what will happen to you.

We expect a lot from vaccines. As children, we got vaccines and Mom said they were good for us. She was right. And almost no one suffers serious harm from childhood vaccines. For example: The rates of serious *adverse events* related to two childhood vaccines—Measles, Mumps and Rubella (called MMR), and Diphtheria Toxin, Pertussis (or DTP)—are about one per million or less. These events are so rare that sometimes it’s not really clear if the vaccine causes them or not. And diseases that killed, maimed or paralyzed earlier generations

have been virtually eliminated by these vaccines.

But investigational vaccines could be different. In vaccine clinical trials, one of the goals is to estimate the risk. This means investigators are trying to see how people respond to the vaccine. They ask questions such as: Do people get a fever after getting vaccinated? Do they get a sore arm? Confidence that a vaccine is safe increases as more and more people receive it without harm.

regulation and review of vaccine trials

Before a single person is given an experimental vaccine, it has gone through rigorous laboratory and animal tests to show that it is safe and induces *immune responses*. These data, along with information on the process used to manufacture the vaccine and the procedures being proposed for the clinical trial (called the trial *protocol*), have also been extensively reviewed by a series of expert committees. These include:

National Regulatory Authorities

The US Food and Drug Administration (FDA), the South African Medicines Control Council or the Drugs Controller General of India are examples. Sometimes other national bodies (such as an ethics review committee) or international group (e.g., the HIV Vaccine Advisory Committee of the World Health Organization/UNAIDS) also conduct reviews.

Institutional Review Boards (IRBs) and ethics committees

Every group or institution that enrolls volunteers in clinical trials must have an independent committee that reviews the trial protocol, *informed consent* documents and any advertisements or other recruitment materials, to be sure that they contain the appropriate information, are not misleading, and do not promise things that would make individuals enroll without regard to any risks they may be taking. Although not strictly required, community advisory groups often review specific studies as well.

“no evidence of harm”—what does that mean?

When an investigational vaccine enters *Phase I* testing, you might be only the fifth person to receive it. So alongside animal safety tests, the data could be something like this: “We gave this vaccine to four people last week and so far they are okay.” Later, in *Phase III*, the data might be: “We have given this vaccine and very similar ones to 600 people over 10 years, and there is no evidence that it is harmful.” When a vaccine is finally licensed, the evidence is more like: “We have given the vaccine to over 10,000 people, and FDA scientists plus an advisory panel of medical experts consider it safe and effective.” Even with licensed vaccines, there remains a very small uncertainty about whether they will be safe for every single recipient, but the benefit to individuals and to society as a whole is usually judged to outweigh an extremely low risk.

But evaluating risk is often not simple. People in vaccine trials get hurt, get sick and die from the same things as people who are not in trials. In large trials there may be accidental deaths, murders, suicides, heart attacks or cancer in both the *immunized* group and the *controls* (those who got the *placebo*, or “blank”). Each serious event is evaluated immediately, and later all serious and non-serious events are re-evaluated to look for a pattern that suggests harm. Common sense tells us that murder is not a vaccine effect, but most decisions are not so obvious. Let’s go through this process in detail.

Bad things that happen after vaccination are called adverse events. The official definition of an adverse event is any unfavorable change in the body or worsening of a pre-existing problem shortly after being given the vaccine, whether or not the investigator thinks it is caused by the vaccine. As mentioned above, many of these are unrelated to vaccination. Sometimes a list of predicted adverse events (such as a sore arm after an injection) is included in the trial protocol and informed consent documents, so that trial participants understand what might happen and explicitly agree to take the chance of putting up with these side effects. The protocol should say how severe these events are likely to be (if it is known). Two days

of tenderness in the arm might be considered okay, whereas severe swelling which prevents the use of the arm might not. Still, a few very sore arms might be accepted if the vaccine prevents a fatal disease.

Mild adverse reactions like a few very sore arms might be accepted if the vaccine prevents a fatal disease.

Adverse events can also include symptoms such as a body-wide rash or sore joints, although these may turn out to be unrelated to the vaccination. But to be on the safe side, *everything* bad is reported, even automobile accidents. This is to prevent human error in overlooking events that don't seem related but actually might be.

The numbers and types of adverse events in the placebo and immunized groups are then compared, to see if there is a pattern suggesting that the vaccine is to blame.

To see how this works in practice, let's take an example of an HIV vaccine trial that starts in the winter, with several participants reporting high fever, muscle aches and coughs. These symptoms might be an effect of the vaccine, or they could reflect a seasonal influenza outbreak. Comparing the numbers of immunized people and placebo recipients who showed these symptoms will help: if only immunized people have them, the investigator will suspect that the vaccine is at least partly responsible. But if the symptoms occur equally in vaccine and placebo recipients, they will be judged unrelated. If the investigator detects influenza *virus* on throat swabs from the volunteers who are sick, this provides even better evidence that the vaccine is not the culprit.

Of course, one small trial can't prove that a vaccine won't have rare, serious side effects later on. A "serious adverse event" (SAE) is defined as one which is life-threatening or leads to death, permanent disability or hospitalization, or to a congenital anomaly in an infant of a treated person (usually a woman). SAEs must be reported and analyzed for a possible relationship to the vaccine, although careful investigations have generally shown that most are unrelated.

Other factors can help decide about cause and effect. If five immunized people in a large trial get a rash—one right after vaccination, another two weeks later, and the others after 6 to 12 months—it is much less suspicious than if all five rashes

occurred within a week of vaccination. Most trials have an initial period (usually 4–6 weeks) during which *all* events are captured, while SAE's are recorded throughout the entire study.

The job of deciding whether an adverse event is related to the vaccine falls first to the physicians running the trial, since they have firsthand knowledge of the events and the participants. Physicians who work for the trial sponsors (usually the vaccine manufacturer and/or government) then review these decisions. All initial decisions are made *before* the doctors know whether the person received vaccine or placebo. The sponsor cannot take away the primary physician's judgment that an event is vaccine related, but might see a pattern across several trials, or several centers conducting one trial, that suggests a relationship not recognized by the doctor at a single study site. Usually there is a grading scale: definitely related, probably, possibly, probably not, and definitely not.

The scale reflects how hard it is to be certain. SAEs that are judged "related" (even "possibly related") must be reported to the FDA (or other national regulatory authority) within a few days and to the trial site's institutional review board or ethics committee for review.

Finally, the international standard on *Good Clinical Practice* (a set of guidelines on how best to conduct clinical research) requires that trial participants be given any information that might affect their decision to remain in the study. This applies primarily to trials in which the drug or vaccine is given repeatedly over time. If a vaccine is only given once or twice at the beginning of the trial, then "remaining in the study" after this point means only returning for checkups and blood tests; withdrawal from the trial will not affect risk once no further vaccinations are involved. The requirement to inform volunteers still applies, though, so if a vaccine is shown to be harmful, all trial participants will be notified. This would not apply to sore arms or other minor problems described in the informed consent document, because participants already know about those risks.

The system is a bit confusing, because lots of events that have nothing to do with vaccination are reported and listed. Why make it so hard? The reason is simple. The system of

checks and balances is designed to avoid a natural human tendency to see what we want to believe. Vaccine companies have a motivation to want adverse events to be unrelated. (On the other hand, it is bad business to sell a dangerous product. So if their vaccine really is harmful, they want to find this out and avoid future losses.) Investigators in charge of trials at academic centers won't have investments riding on these decisions, but they do have their sense of expectation, achievement and professionalism. These people do not want to harm anyone.

The system of checks and balances is designed to avoid a natural human tendency to see what we want to believe.

Therefore, all the data are collected and reviewed not only by the trial physicians and company scientists, but also by statisticians (often part of an independent group), the university IRB and the FDA. Many large trials also have a specially appointed “data and

safety monitoring board” of independent statisticians, scientist physicians, and ethics specialists, who review the data on a regular basis. It is their job to decide if a trial should stop early because of safety problems. They also might halt a trial either because it has already succeeded in proving that the vaccine works or because, due to changed circumstances (such as slow recruitment or a very small effect of the vaccine), the trial will be unable to clearly prove whether the vaccine works.

Once a vaccine is licensed and marketed, a different adverse event reporting system comes into play in the US. This system relies on physicians who suspect a link between vaccination and adverse events to submit a report, so it invariably misses some events that should be captured. Because there is no control group, it is especially difficult to assess cause and effect, and many events can be listed that have no relationship to the vaccine.

These data are sometimes misunderstood. A recent article by an opponent of childhood vaccination simply quoted the number of “adverse events” in the database. Without further analysis, such as determining how many people were vaccinated and attempting to relate specific events to specific vaccines, this number is meaningless.

A more sophisticated system for monitoring post-marketing safety is Vaccine DataLink (www.vaers.org). Here, four large US health maintenance organization databases are checked to see how frequently certain events occur without vaccination compared to the period just after vaccination.

LET'S HOPE that someday we will have an HIV vaccine and epidemiologists will be trying to determine how many side effects occur per million vaccinations—while we all watch the epidemic dwindle to nothing.

research ethics: recipe for success

BILL SNOW

THE SOMEWHAT IRONIC title of Spike Lee's 1989 movie, "Do the Right Thing," is emblematic of how difficult it can often be to *actually do* the right thing. This is particularly true in the face of urgent, often conflicting needs, and unknown outcomes, even with the best of intentions.

With that in mind, the purpose of this short article is not to serve as a primer on biomedical ethics—a complicated field with a history of cases like the law, and a fair amount of dispute among it practitioners. My primary purpose is to share some basics of research ethics debates and to issue two warnings, learned the hard way:

1. Beware of self-righteousness—your own and that of others—in the realm of clinical research. Others have probably wrestled with the same problems.
2. Beware of ever letting the end overshadow the means. This is particularly difficult because an AIDS vaccine is so desperately needed that there's a risk of moving forward too slowly as well as too fast, or not moving at all until everyone has confidence what the answer should be, even prior to conducting a definitive *clinical trial*.

Warning #1 will help you stay in the debate and be willing to listen to alternative points of view. Warning #2 will help you think about research from the perspective of participants and communities, which is always a good thing when faced with the demands of science, researchers and the epidemic. Perhaps the most important principle, which sounds obvious but has deep meaning, is this: Only good scientific research is ethical (because some risk may be justified); and only ethical research (based on important and objective questions) is good science.

If you're going to engage in any ethical discussion or debate about AIDS vaccines, it is important to know something about the accepted international ethical standards that apply, listed here in historical order:

The Nuremberg Code

Developed by an international tribunal after World War II to prevent abusive research.^① It specifies that only qualified researchers may conduct human research using appropriate research designs, with a potential benefit greater than the risks taken. It codifies that *informed consent* is absolutely essential and that participants must be free to withdraw from the research at any time. It is less than a page long.

The Declaration of Helsinki

Written and revised by the World Medical Association (WMA), an organization still in existence.^② A declaration for the medical profession, it focuses on protecting research subjects. Its broad and general principles are the underpinning of all subsequent, more specific standards. It was adopted in 1964 and contains 32 content-rich paragraphs.

In the last few years, efforts have been made to update the Declaration to remove some of its original paternalistic language (on "protecting" research subjects) and to emphasize instead the empowerment of volunteers and their communities in determining the course and limits of clinical research. WMA has amended the Declaration five times, with a recent and much-disputed note of clarification (on the use of *placebos* and *controls*) in 2002.

The Belmont Report

An internationally cited US government document, published in 1979, that codified the overarching principles of autonomy, beneficence (doing good) and justice as the primary and equally important ethical principles of medical research.^③ In fact, it is the difficulty of living up to these three principles simultaneously that often creates the complications and conflicts about ethical decision-making. Its fourth principle, nonmaleficence, derives from the ancient medical oath to “first, do no harm.” This can be distinguished from beneficence because there are unlimited degrees of doing good, and because there is always the option of not doing the research at all. Furthermore, it is widely believed to be unethical to do harm to individuals in the interests of some higher or greater good. *The Belmont Report* is 11 pages long. (For more on these principles, see chapter 16 on informed consent.)

The Council of International Organizations for Medical Sciences (CIOMS) International Ethical Guidelines for Research Involving Human Subjects

It consists of 21 guidelines, each with an introduction and sometimes detailed commentaries.^④ The CIOMS guidelines were written in 1982 and revised in 2002 for similar reasons as the Helsinki Declaration.

Ethical Considerations in HIV Preventive Vaccine Research

UNAIDS published its very focused ethical considerations in May 2000 after a series of international consultations that extended over almost two years.^⑤ It consists of 18 guidance points and is 48 pages long.

AS THIS SHOWS, the more specific and contemporary these documents become, the longer, more precise, complex and confusing they also become. It's a little like the US Declaration of Independence, which led to the need for the Constitution, and ultimately the many volumes of the Federal Register,

with ongoing case law and commentary from several levels of federal courts to interpret all of this.

For these reasons, the scientists who design and run research are subject to at least one but usually several boards of review at the scientific, ethical, governmental and local levels. These boards are supposed to be independent of the researchers and generally include an ethicist and a non-scientific member. They are the official forum for discussing the value and protections of the research, and they are usually held in private but with the list of members and decisions made public, so the public has some reassurance that they are legitimate and representative bodies. This review process itself can take many months (or longer) and require multiple rounds of revisions to *protocols* and procedures.

The key thing to remember, however, is that these review boards ultimately have to make *a decision* about whether, and how, to conduct a proposed trial. This need for a yes-or-no answer means that some people outside the process are likely to disagree about some of the outcomes, especially when they involved grappling with difficult problems.

Because AIDS research is so urgent and AIDS vaccine trials test unproven products in healthy volunteers (as opposed to testing products for treating sick people), the review process often raises a lot of internal and public debate about the study design, including the ethics of working with people at high risk for HIV infection and people who become infected during a trial through risky behavior. Reaching consensus is also complicated by the fact that knowledge of how to prevent and treat HIV is continually improving and changing, and that solutions vary in different places where this research is done.

If you read some of these guidelines and find that your head is spinning, wait until you meet a couple of professional ethicists. One at a time, they usually make perfect sense; it's just that they often don't agree with one another. And if this looks like a recipe for criticism, delay and inaction, you've got it right. As a discipline, ethics is a very mixed bag. Venture in at your own risk. It can be quite stimulating, but remember that generally no one has The Perfect Answer in this messy and very important activity.

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What do we mean by informed consent?



A person has the right to all information about the trial.



A person also has the right to choose whether he or she wants to take part.



People should not make a choice until they are free of all pressure, and have all the information they need to choose intelligently.



It is your duty as a CAB to make sure these rights are protected, and that people get the right information.



When is informed consent important?

There are a number of stages in which informed consent is necessary. At each stage, counsellors should provide participants with all the information they need and make sure they understand all the consequences of their choices. Participants are free to leave at any stage they wish. These stages are:

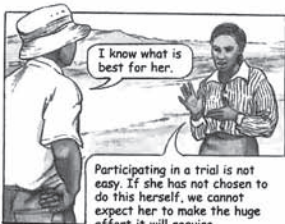
- When participants are tested for HIV antibodies to see if they can be admitted to the trial. This involves pre- and post-test counselling.
- When participants are enrolling for the trial.
- All through the trial, counsellors will do ongoing evaluation of a participant's understanding and consent.
- Any tests during the trial should include pre- and post-test counselling.

I want my wife to try your vaccine.



I'm sorry, Sir, your wife has to give her own consent.

I know what is best for her.



Participating in a trial is not easy. If she has not chosen to do this herself, we cannot expect her to make the huge effort it will require.

What makes a trial ethical?

Before any trial can begin, an ethics committee must approve the protocol, and make sure that it is in the interests of the people involved in the trial. An ethical trial will insist on the following things in its protocol:

- All participants must give their informed consent.
- The community must be involved at all levels of decision making, from the early phases of planning a trial, right through to the final phases of delivering the vaccine.
- Counselling needs to be provided for all trial participants.
- Information about prevention and prevention methods needs to be provided for all trial participants.
- Participants have the right to leave the trial at any time.
- Participants have the right of access to all important information about the trial (except who has received real vaccines and who has received placebos).
- Participants have the right to access the best treatment available for any HIV-related condition that arises as a result of the trial.
- A supportive environment must be created for all those involved in the trial.
- A truly representative Community Advisory Board should be established to represent and protect the interests of the community.

An ethics committee should be independent of the company running the trial, and should have no financial interest in the trial.

What is a protocol?

The detailed plan for a trial is called a 'protocol'. This is the official trial guideline – an outline of all the procedures involved in the trial. For example, how the vaccine will be given, who can take part, what the timetable is for tests and visits to the clinic by participants, how long the study will last, how results will be assessed, etc. A protocol should also include the rules and standards, or 'ethics', guiding the behaviour of scientists and the community.

What are ethics?

Ethics are a set of guidelines for the moral choices people have to make. When it comes to a trial, ethics concern the moral decisions that face scientists and the community.

©South African HIV Vaccine Action Campaign (SA HIVAC)

SOUTH AFRICA

Excerpt from the comic book *Finding the Way*, explaining how HIV vaccines are developed and how communities and individuals can participate. Developed by the Centre for the Study of AIDS at the University of Pretoria as part of their work on the South African HIV Vaccine Action Campaign, a project financed by the European Community (EC) and the South African AIDS Vaccine Initiative (SAVI).

informed consent in hiv vaccine trials

GRAHAM LINDEGGER / south africa

INFORMED CONSENT is an essential part of any ethical research study involving human volunteers. When the horrific “experiments” conducted by Nazi doctors on concentration camp inmates came to light after World War II, doctors, ethicists and other concerned people worked to establish international standards for protecting the rights of people in *clinical studies*, while allowing research aimed at improving human health. Their efforts led to the *Nuremberg Code*, and since then, to other widely recognized international ethical regulations (see chapter 15 on research ethics).

Clinical trials of HIV vaccines raise most of the same ethical concerns and challenges as trials of other new medicines, and they follow the established regulations. But there are also new issues that arise when dealing with a stigmatized disease like HIV/AIDS, and when products developed in wealthy countries are tested in poor ones. For large-scale (*Phase III*) studies, there are also concerns about what is sometimes called the “double vulnerability” of participants, who are usually drawn from populations at high risk for HIV infection—a vulnerability that most often arises

from being poorer, having less formal education and/or being exposed to some form of discrimination, e.g. racial or anti-gay discrimination. For these reasons, a set of special guidelines was developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to make sure that the specific needs of volunteers in HIV vaccine trials are met.^① While these guidelines are not legally binding, in practice they have been widely adopted.

what is informed consent?

One of the core principles of bioethics is the right to autonomy or self-determination, which in practice means that volunteers for clinical studies must explicitly consent to participate after being fully informed about the research. The decision to participate should be made without any form of coercion, including subtle pressure such as offering rewards for participation. Autonomy also assumes “first person consent”—each volunteer must consent her/himself, rather than someone else consenting on their behalf (except for studies involving minors, where parents must give consent).

Informed consent is a process (and not just a piece of paper) that has both legal and ethical aspects. Legally, it is a formal record of a person's willingness to participate in a clinical trial. Ethically, it is a decision-making process during which a person who is thinking about volunteering collects and then weighs the available information.

the elements of informed consent

Genuine informed consent involves five key components: information, understanding, voluntariness, capacity to decide and formal consent.

Information

Prospective volunteers must be fully informed about the purpose and procedures of the trial and about what participation entails. International guidelines specify the information that must be given to volunteers, which includes:

- › The aims of the trial, and its risks and benefits.
- › How many visits the trial involves for each volunteer and what procedures will be carried out (e.g., blood drawing, HIV testing, discussion of risk behaviours).
- › Policy regarding confidentiality of records and biological samples (such as blood).
- › What, if any, care and compensation will be given in the event of serious harm arising from trial participation.
- › Who to contact for more information about the study, or in the event of a research-related injury.

Understanding

It is not enough for trial staff to simply provide information to volunteers. This information must use language and terms that are meaningful to the participants, who should be encouraged to ask questions. While this probably seems obvious, the reality is that researchers may have trouble explaining the study in easy-to-understand terms, and volunteers may feel uncomfortable questioning doctors or researchers who they sometimes see as more powerful than themselves. The trial site's *Community Advisory Board (CAB)* and perhaps other community organizations can help bridge this gap (for example, by helping to develop appropriate informational materials and consent procedures, and being available to answer volunteers' questions). The various committees charged with approving and monitoring trials also pay close attention to this issue. But ultimately it is the responsibility of the trial researchers to ensure that participants fully understand the essential information.

It is the researchers' responsibility to ensure that participants fully understand the essential information about the trial.

Voluntariness

Potential participants must feel free to decide about volunteering without pressure from researchers, family or others. Volunteers also have the right to change their minds about participation and withdraw at any stage of the trial, without having to explain their decision or suffering any penalty.

Capacity

Each country stipulates the minimal age of consent. Volunteers must either be of legal age to consent or, for trials involving minors, have the consent of parents or legal guardians (except for specific circumstances, such as where married teenagers are considered legally emancipated). They must also have the mental capacity to understand the information about trial participation.

Formal consent

Once both volunteer and researchers are satisfied that the volunteer understands the implications of trial participation and expresses willingness to enroll, he or she is usually required to sign a formal document to this effect in the presence of a witness. Separate consent may also be required for certain procedures, such as HIV testing. Where participants are illiterate, alternate arrangements (such as a record of thumbprints) can be made.

culture and informed consent

Although these principles of informed consent are widely recognized and practiced in health research, HIV vaccine trials in developing countries have also raised questions and controversy about the impact of culture on how consent is understood and implemented—for example, in countries where participants' beliefs about health and illness differ from those of medical researchers.^{②③④}

This has led to calls for greater sensitivity to local beliefs, values and practices, which can involve approaches such as:

- › *Using language and concepts* appropriate to the local culture and social context. For example, trial staff are often asked why it is impossible to become HIV-infected from the vaccine. One site in South Africa answers as follows. “Maize seeds are planted in order to grow maize crops. But if a maize seed is taken and crushed, and a small portion of the powder planted in the ground, a maize plant would not grow. Something similar happens in making HIV vaccines.”⁵ There may also be ways of sharing information that work well in particular communities (for instance, at times and places where people are most comfortable), and local taboos about sharing certain types of information.
- › *Incorporating locally relevant practices or traditions* into the informed consent. For example, assessments of how well volunteers have understood information about the trial can be done in ways that are culturally familiar—such as by asking people to tell stories about what the trial will involve, rather than by the conventional practice of posing test questions in writing. Trial staff with values and world views similar to those of the volunteers are also helpful, because they are better placed to understand the cultural issues that affect participants. For the same reason, community advisory groups can play a key role.

Trial staff with values and world views similar to those of the volunteers are better placed to understand the cultural issues that affect participation.

But cultural sensitivity does *not* mean unquestioning acceptance of cultural norms, which may conflict with international standards for consent and raise the risk that important ethical protections may be ignored in the name of respect for local culture. An example of this would be cultures which require that men always make decisions on behalf of women.

This issue raises a deeper concern about applying informed consent in non-Western (or non-Westernised) settings. The emphasis on autonomy and self-determination is sometimes seen as a reflection of Western values, which focus strongly

on individual people and rights. But many other cultures, especially African and Eastern ones, emphasize communities, or the so-called “collective”—a perspective captured in the isiZulu saying in South Africa that “*Umuntu ngumuntu ngabantu*” (people are only people by reason of their relationship with other people). In these settings, requiring every trial participant to give consent can seem out of step with local norms, while getting consent from traditional leaders or other community representatives might seem more fitting. But this approach can lead to situations where individuals may not feel free to decide against participation if a decision to go forward has been made on their behalf by community leaders.

The debate over how to balance these sometimes-conflicting sets of values continues, but two guidelines are emerging. First, getting first person consent guarantees that the rights of individuals are always respected, and that there is no risk of enrolling people against their will. Second, as just mentioned, the consent process can incorporate practices that speak to the local culture and values. For example, trial staff in some regions routinely ask local leaders for permission before entering a community and beginning to discuss trials or seek volunteers. In preparation for community-based trials in South Africa it is a common custom for the local traditional leader (*Inkosi*) to call a public gathering (*imbiz*) that formally establishes a partnership of the local community, health care providers and researchers. Such solutions offer ways to combine respect for individual autonomy with respect for traditional community norms.^③

myths around cultural sensitivity and informed consent

It can be easy, especially for outsiders, to assume that everyone in a cultural group has the same beliefs and values. But there is often more variation *within* cultural groups than *between* them, which makes it important for trial staff to avoid generalizing about people from particular cultural groups. For example, trial staff working in rural South African communities with strong collective values have found that, contrary to these cultural

norms, many women express a strong desire for first-person consent rather than having this decision made for them by community leaders or representatives. There is also evidence from many countries that people in rural areas are likely to share traditional values, but that as they become urbanized there is more diversity of beliefs and practices within these same groups.

INFORMED CONSENT IS A CRUCIAL PROTECTION for study participants and researchers in HIV vaccine trials. But making it a truly ethical practice and not merely the fulfilment of a formal legal requirement is an ongoing effort, especially as trial sites are established in parts of the world that are new to clinical studies. Doing the right thing will continue to take research, creative thinking and comparing notes and experiences around the world.

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community advisory boards

STEVE WAKEFIELD

IF ASKED about their hopes for an HIV vaccine, an AIDS researcher and someone from a highly affected community (whether in New York City or an African village) would probably wish for the same thing: a vaccine that protects everyone against AIDS and ends the epidemic once and for all. But when it comes to testing experimental vaccines in *clinical trials*, researchers and community members come to the table with different knowledge, perspectives, dreams and needs.

So how can we help ensure that clinical trials achieve clear understanding between them, and fairness to individuals and communities? One way that's often effective is through *Community Advisory Boards (CABs)*—groups of volunteers and/or elected representatives from the community where a trial is taking place.

who and what are these CABs?

They are people who represent the interests of the community to the researchers, help them understand and respect local customs, work for volunteer rights, create ways to teach volunteers what it takes to be in a trial, and listen closely to concerns expressed by neighbors, co-workers and family members. They also learn enough about the research to suggest how it can be done “right” for the place where they live.

One of the first challenges is trying to make sure potential trial participants are really the “community” that is represented. Serving on an advisory board is something usually left to those seen as senior or important enough to give advice. In Uganda, women who want to volunteer for a trial often look to their husbands for a decision because men are considered head of the family. In some parts of KwaZulu-Natal, South Africa, traditional healers make health care decisions and tribal chiefs decide what is good for each person in the village. These communities struggle when a scientist comes along and says we really want advice from “ordinary” people who have been in a research study, or are now considering it.

CAB members learn enough about the research to suggest how it can be done “right” for the place where they live.

Another challenge is to ensure that CABs truly represent the diversity of people and interests in the community. This can be difficult, since people of all ages, shapes, sizes, and social status may participate in HIV vaccine trials. Most study sites try to include people who understand HIV, perhaps are living with HIV; are parents, teachers or students, or people

who know about science or health; and people who know about people, because they live with friends and neighbors who are concerned about making life better. But each of them can speak only for others like themselves, so CABs need a broad mixture of people.

what do CABs do?

In theory, and often in practice, CABs can play an essential role in the conduct of clinical research. Hundreds of times they have pointed out potential problems for investigators or helped make trials more ethical, feasible or attractive to communities and individuals. In addition to their advisory and watchdog functions, CABs have also helped their communities by disseminating information and advocating for trial participants, people living with HIV and the community-at-large. (For more information on what CABs do, see Table 3.1 “Common CAB activities” at the end of this article).

In the broader sense, CABs are the front line community members who work with scientists to build a genuine partnership based on mutual trust—crucial ingredients for successful clinical research.^① This engagement between researchers and communities requires understanding each other's interests and points of view, sharing information openly, and often negotiating solutions that work for both the scientific inquiry and individual rights and needs, which cannot be compromised if the research is to succeed. But these relationships take time to establish, and can challenge both researchers and community volunteers to move beyond their comfort zones.

In addition to good will, CABs—which are voluntary in nature—require organizational support. This may include staff to help with administrative needs, a budget to cover costs, and access to technical support appropriate for the information age, such as cell phones, computers, copiers and video conferencing. CABs also need to get regular updates from trial staff at times convenient for CAB members, and they need other opportunities for ongoing learning and participation. And they require time and assistance to establish their own procedures for functioning well, including orientation and training for new members.

Relationships between researchers and community volunteers take time to establish, and can challenge both to move beyond their comfort zones.

the global challenge

The CAB model has worked well in Western societies, which value individuality, autonomy, choice, volunteerism and community assent. However, most of the challenges to success are enlarged when this model is applied to other cultures, especially in communities ravaged by AIDS and poverty.

For example, in many communities, scientists, tribal leaders, elders and sometimes age or gender dictate that a seat of honor is reserved. These communities have depended on the wisdom of their leaders in making decisions about what is best for the collective good. Yet the CAB model may suggest that the power dynamic which has guided their daily lives should be abandoned for one where each person's voice has weight.

Acknowledging local beliefs and health practices while moving forward with HIV vaccine studies is another challenge that can be addressed through partnerships between CABs and researchers. For example, in one community preparing for vaccine trials, researchers recognized the importance of traditional healers and brought several onto the CAB. There, one of them suggested that trial staff should offer a gift of recognition to the local health providers. Acting on this suggestion, researchers presented a live goat during a tribal festival celebrating the community's participation in vaccine work, as a sign of respect for local traditions.

In another community there was great concern about "vampirism," with local people fearing that harm can come to them if anything from their body (in this case, the blood that's routinely collected during vaccine trials) falls into the hands of someone wishing them ill. Most people in this community even remove any hair left in their brush or comb and carry it in their pockets so it can't be found by someone who could then put evil on them. It was a new concept for them to hear about laboratories that do research to improve health. CAB members were able to visit research sites and see the science in action, and they returned home to assure their communities that lab technicians processing the blood do not intend to inflict harm and, since the blood samples are anonymous, cannot link the blood to the person they came from.

Many other new situations arise for CABs in dealing with Western countries, scientists and research centers—especially when it involves travel to the gatherings of trial staff and collaborators held periodically by most trial networks or sponsors. At these events CAB members and community volunteers are suddenly immersed in a world completely unlike the rest of their lives. For example, at a recent scientific meeting in the US, CAB members who had flown for many hours arrived at their hotel and quickly had to learn how to use an elevator, that there was a high cost for the foods in the drawer and refrigerator, and that the room they would sleep in for three days was larger than the home they shared with 5 family members. This caused one person to remark, “It is hard to focus on the science when I am overwhelmed by your excess.”

It's a comment that illuminates one of the most deep-seated challenges to conducting HIV vaccine trials in highly affected, often poor, communities: designing research participation that fits into lives of varying means and power, and working through the many issues this raises in a world of inequities.

Table 3.1 Common CAB activities

Voice community issues and concerns related to proposed trials.
Collect and distribute information addressing concerns likely to arise during trials.
Provide recommendations regarding planning and review of the study objectives and implementation.
Provide investigators with informed commentary regarding trial design issues such as <i>cohort</i> selection criteria, questionnaire design, and follow-up plans; <i>informed consent</i> procedures; risk-reduction interventions; community education and outreach; and recruitment and retention planning.
Support judicious recruitment efforts and promote health care arrangements for trial participants.
Help address issues of informed consent, such as the potential for discrimination related to HIV vaccine trials (e.g., being stigmatized as belonging to a high-risk group).
Address fears and avoidance of HIV testing.
Provide recommendations regarding planning and review of the study objectives and implementation.

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www.hvtn.org/community

This website, from the US HIV Vaccine Trials Network (HVTN), has a bimonthly newsletter about community involvement in HIV vaccine trials; material and links pertaining to ethics and community education; and links to sites around the world where trials are ongoing or planned.

www.iavireport.org/Vax/currentVAX.asp


VAX. A bimonthly newsletter of science and news about HIV vaccine trials around the world, published by the International AIDS Vaccine Initiative. Available in English, French, German, Spanish and Portuguese.

www.icaso.org/vaccines.html

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community education: working together

MÔNICA BARBOSA DE SOUZA / brazil



IN 1995 I started working as a counselor at the Rio de Janeiro HIV Vaccine Trials Unit (HVTU). My job was to explain the concept of a preventive HIV vaccine to potential volunteers for our study on HIV infection rates in gay men and to assess their willingness to participate in future vaccine trials. At that time there was little public awareness about HIV vaccines, it was unclear when any product would be ready for testing, and the stigma of AIDS was huge. But despite all this, hundreds of men declared their willingness to participate in a vaccine trial.

Almost ten years later there is still no effective HIV vaccine on the horizon, and only three HIV vaccine trials have been done in Brazil. But despite this frustratingly slow pace, we still ask people from all walks of life to support, believe and participate in vaccine trials.

During these years our HVTU research team has been working to build strong relationships with the community, establish dialog with different sectors of society and keep people interested in HIV vaccines, even though they have reason to be skeptical. We've also developed strategies to spur community leaders and policy makers to advocate for vaccines,

and to motivate people to participate in trials. In 1999, to give more focus to community affairs, we established the HVTU's Community Education Unit.

The Community Education team has grappled with finding the right communication channels and developing the right messages and tools to engage communities about HIV vaccine research. One of the first lessons we learned is that the key to effective communication is effective listening. Thus, our main daily activity is to listen and learn from our community members. We talk with members of non-governmental organizations (NGOs), government representatives, health professionals, users of HIV testing centers, parents, media professionals, taxi drivers, waiters, hairdressers and friends to hear about their perceptions of HIV vaccine research and about the barriers to their involvement. This knowledge is crucial so that trial units can design sensitive strategies for approaching the community.

what communities tell us about HIV vaccines

Slow progress and heavy bureaucracy de-motivate potential volunteers.

When people first visit our clinic for information about vaccines and trial participation, they often come with a list of concerns, and some misperceptions. The most common ones are:

- › *The slow progress so far.*
After nearly two decades of research we are still far from having an effective HIV vaccine. Besides the scientific difficulties, heavy bureaucracy is also a factor in many settings, where the process of reviewing a proposed trial can take two years or more from start to finish. This de-motivates potential volunteers and makes the community suspect a lack of real interest in developing a vaccine.
- › *Difficulty in understanding scientific language.*
The specialized language of science is a big obstacle to communication with non-scientists. People usually fear what they do not understand. Community members may feel

insecure about participating in an HIV vaccine trial when they cannot clearly understand its purposes, risks and benefits—for example, when confronted with an *informed consent* form of 20-plus pages. This makes some people mistrustful that researchers are not completely leveling with them.

- › *Misunderstanding over how (well) an HIV vaccine may work.*
Most people have high expectations for HIV vaccines. Many expect that it will cure the disease in infected people or prevent any new infections in the population. The public (particularly people who are already infected) usually feels dissatisfied when they hear that at least the first vaccines are likely to be only partially effective and may only be able to modulate the infection.
- › *Fear that vaccine research may jeopardize treatment development.*
There is a sense in the community that vaccine research takes away funds from treatment research, a misconception that falsely pits prevention and treatment against one another. Also, Brazil's policy of universal access to *antiretroviral* therapy has led many community-based NGOs to focus their full energies on sustaining treatment programs. While these groups show interest and support for HIV vaccine research (and for the efforts of NGOs that are highly engaged in vaccine issues), they haven't diverted scarce time and resources away from the immediate issues of providing treatment and services for infected people.
- › *Mistrust that wealthy countries have a hidden agenda when they test vaccines in developing countries.*
After a long history of abuses it's sometimes difficult for communities to believe that vaccines produced in developed countries need to be tested in developing countries for important ethical, scientific and humanitarian reasons. They fear being treated as guinea pigs. There is also a worry that, as with ARVs, the most affected countries won't be able to afford a successful vaccine—so poor populations would be used to test products, but will never benefit from them.

- › *Decreasing public sense of urgency about AIDS.*

In Brazil, widespread access to ARV treatment has dramatically reduced the numbers of deaths due to AIDS. So in the public's view, AIDS is less pressing than other emerging social problems, such as rising violence and poverty.

Our trial participants cite solidarity with HIV-infected people and HIV-affected communities as one of their most important reasons for volunteering.

ADDRESSING THESE PERCEPTIONS takes a combination of strategies—to accelerate the research, ensure volunteers safeguards, stimulate vaccine advocacy and target education to reducing these misunderstandings.

Fortunately, community members also report important reasons to believe and participate in HIV vaccine research.

- › *Brazil's long tradition of vaccination as an effective public health strategy.*

The Brazilian population usually understands and supports vaccination, and in general, community members recognize the merit of an HIV vaccine.

- › *A positive experience in building a national response to AIDS.*
Brazil's AIDS policies, which have been praised around the world, rest partly on strong community mobilization and self-determination (see chapter 40 on Brazilian community involvement in HIV vaccines). This experience increased the population's trust and positive attitudes around efforts to combat AIDS. HIV vaccine research initiatives can benefit from this good atmosphere.
- › *Solidarity.*
The Brazilian population has an incredible ability to mobilize in solving social problems, and an enormous sympathy for the human drama. Our trial volunteers in Rio de Janeiro cite solidarity with HIV-infected people and HIV-affected communities as one of their most important reasons for participating.

› *Hope in the future.*

The present times are very hard in developing countries. Brazil's population has developed a strong hope in the future, perhaps as a defense mechanism against today's problems—a hope that's part of the Brazilian identity. It is also an important motivation for most of our trial volunteers.

what can community education achieve?

GIVEN THIS SET OF BELIEFS, perceptions and concerns in the community where we work, what can (and should) we do as community educators?

Our main focus is on raising awareness about the need for a vaccine and the state of the research, and overcoming misperceptions and mistrust. At another level we also try to stimulate communities to dream of a better future—a future without AIDS—by raising communities' awareness of their own power to influence the decision-making process. A community that can sit down with scientists to voice its questions, concerns and doubts is more likely to engage in the research.

We try to stimulate communities to dream of a better future—a future without AIDS—by raising awareness of their power to influence decision-making.

From the scientists' perspective, such dialog clearly promotes their interests by helping the research to go forward. At the same time, it increases the capacity of communities to be pro-active players in designing the life they want.

Developing a productive relationship and a common agenda is not easy. Researchers and community members not only speak different languages but often have different communication styles, which can create resistance on each side. For example, some community members may adopt a suspicious attitude toward researchers without even listening what they have to say, while researchers may see community members as radicals who are responsible for the delays in getting their trials approved. Researchers may bristle at “obvious” questions from community members, while community people may get impatient when scientists do not explain their work clearly and understandably.

AS OUR TEAM TRIES TO BRIDGE THIS GAP and establish respectful dialog with the community, we have adopted some basic principles to guide us. They are:

- › *Accept criticism.*
Criticism from the community is very important input for researchers. If the criticism is just, steps can be taken to address it. If it isn't, then it demonstrates that communication is failing and leaving room for misunderstandings. Do not take criticism or disagreements as a call to war.
- › *Put yourselves in your communities' shoes.*
Try to understand your community, listen to their concerns and needs and try to create a trusting atmosphere.
- › *Do not be dismissive towards community views.*
Accept that lay people have a lot to say about your work. Don't think of questions from the community as foolish. Respect community members as individuals who may not know what you know, but surely know many things you have no idea about.

But there's no fixed formula for making these relationships work. In the end the most important factors may be a strong will to succeed and an intense exercise of humility on both sides in recognizing one other's importance in the battle against AIDS. Community education efforts help create the chance for researchers and community members to come together and see each other, listen to each other, understand each other, and ultimately work together.

ensuring community participation and readiness: a conversation with janet fröhlich

JANET FRÖHLICH with PATRICIA KAHN / south africa

Since the mid-1980's Janet Fröhlich has worked to empower South African communities in combating AIDS on many fronts—from prevention and care interventions to participation in clinical research. Since 1998 she has focused her energies on rural areas, starting in a village several hours north of Durban, where she directed the HIV Vaccine Preparedness Study for South Africa's Medical Research Council (MRC). Those years engendered deep ties to the village, where they made her an adopted member and gave her a local name (*Ntombende*, “the tall lady”) as a sign of affection and esteem. As of 2002 she works in the KwaZulu-Natal midlands west of Durban and now holds several positions: a lectureship at the University of KwaZulu-Natal, Community Programs Manager for the Centre for AIDS Programme of Research in South Africa (CAPRISA, a community-based research unit) and co-investigator of an AIDS vaccine preparedness study in the North West Province.

YOU'VE BEEN INVOLVED with preparing and engaging communities in AIDS clinical research since this work first began in South Africa. How did you start?

We started in 1995–96 through the first US network for HIV vaccine trials, which was called HIVNET. The idea was to begin figuring out how to prepare a rural community for vaccine and prevention trials. Our first site was an isolated rural village in Northern KwaZulu-Natal, a province where the epidemic was growing fast. We worked in an area with very little infrastructure and very little public education, awareness or knowledge about AIDS. The work got an important boost in 1998, when several international sponsors of AIDS vaccine studies—NIH, IAVI, WHO—came together and threw their support behind the South African effort. That's also when SAAVI, the South African AIDS Vaccine Initiative, was born. With SAAVI in place, the mandate became more defined: to help develop AIDS vaccines based on HIV *clade C* [which accounts for nearly all infections in South Africa], and to work out how to fit these activities into our South African context.

Another watershed event that year was a HIVNET workshop in Harare for international prevention trial sites. We sent two community liaison people from our village, and they brought back the notion of a *Community Advisory Board (CAB)*. That got us started on working to create community structures and mobilize the community to prepare for AIDS vaccine research.



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SOUTH AFRICA

Community member receives a gift for correctly answering an Africa Centre “Road Show” quiz question. The popular “Road Shows” are one of the means by which the Centre communicates critical research-related information through theatre, song and quiz questions.

Did the community accept and support this?

Yes, it was well accepted. But what we didn't anticipate was the amount of attention this work would bring to the community—from other scientists, and especially from the media. People in the village started to feel like their community was being stigmatized as the “ground zero” of AIDS. That's why we don't go around any more talking about the communities by name. This was an early warning that we needed to think more about how to protect not only the rights of individuals, but also the rights of the communities where the work is being done.

In first approaching this (or any other) community, where do you begin?

The critical thing for us to keep in mind is that we are working among people who have not had a voice, who were suppressed—or still are, especially many of the women. So you can't just go in and immediately start talking about AIDS.

AIDS is still locked in silence, and there is a lot of denial in many communities—not even stigma. First you have to do some groundwork. People need to recognize their rights: that they have a voice, and a right to question, and to challenge science—not to stop it, but to participate in it as partners.

First you have to do some groundwork. People need to recognize that they have a voice, and a right to question and challenge.

Who do you talk to first?

There's always some level of leadership in the village or community. So you start there. There are also lots of informal structures. These sometimes emerge more slowly as the dialog begins—people begin to see that they already have resources they can tap into. Women's groups, church groups, youth groups and so on.

How do you build up to the next levels?

The next step is to facilitate dialog that goes beyond general knowledge about AIDS and asks whether people know what's actually happening in their community, and what their basic

Table 3.2 Examples of community preparedness activities

Goal	Activities
1 Community awareness	Build community awareness about HIV vaccine research. Disseminate information via meetings, posters, brochures, media.
2 Willingness to engage	Build framework for community support and informed consent. Build advocacy for community participation in research. Survey willingness to participate.
3 Build knowledge and understanding	Build community willingness to listen, learn and ask questions. Establish knowledge of HIV, vaccines and the research process (see Table 3.3). Develop community-sensitive lexicon of appropriate terminology for use in informed consent process and information materials and activities. Hold skills-building workshops for CAB members, to include ethical, legal and human rights issues; informed consent; AIDS vaccine development and AIDS treatment.
4 Preparedness	Map community structures, social networks and resources. Hold group discussions with community representatives, and use established community structures. Conduct baseline survey on community expectations about research participation. Ensure that mechanisms to resolve differences are in place. Involve CAB members in developing protocols and assessing community and volunteer readiness for trials.

needs are. This has to be verbalized. Once people get to this point, then you can start discussing what to do about it as a community. But it's a slow process. It usually takes about 18 months just to reach the point where you can start discussing where the community is at.

Based on these experiences, we developed a model for approaching and engaging communities. It starts by fostering a willingness to engage, and by talking about human rights. Only then can you start building the knowledge level around HIV. Once people have this understanding, you can move into next phase, when you explore their expectations about research, and about their community's participation—what are the positive and negative impacts that an AIDS vaccine trial could have on their community? What are the individual and community concerns? And then you move into how you develop sets of best practices. (See Tables 3.2 and 3.3.)

What are these early discussions of research like, considering that many of the concepts are completely new to people?

We get there gradually. We've worked a lot with wellness models. Before ARVs [*antiretroviral drugs*], how can you keep yourself as healthy as possible? From there, we can discuss the body of knowledge of science and research. Vaccines are a much easier intervention to get across than *microbicides*, because people know what they are—South Africa has a good program to *immunize* children at birth.

One of the ways we talk about vaccine development is to compare it to baking something new. Your first recipe might come out fine, but it's more likely you'll have to go back and try over and over again.

As you go on, you can tackle the harder things. For example, how do you engage communities in developing protocols? In the US they use the CAB model, which got started through treatment studies. We came along almost 20 years later, wanting to take the CAB notion and import it to resource-poor settings in South Africa. For me it was a big learning experience to take a model and adapt it, with community input, into something more locally relevant. Communities know what works for them.

Table 3.3
Critical activities of a community mobilization and education strategy

Goal	Activities
1 Community acceptance and support	Meet with influential community leaders and groups.
	Jointly develop education plan.
	Maintain continuous information exchange.
2 Training community educators (CEs)	Key areas for training:
	General HIV/AIDS and STD education.
	Introduction to research and vaccine trials.
	Communication and interviewing skills.
	Pre- and post-test counseling skills.
	Informed consent.
3 Supervision and support of CEs	Ethical, legal and human rights issues.
	Regular meetings.
	Continued education and training.
	Continued development of program facilities and design.
4 Program planning, monitoring and evaluation	Annual strategic plan.
	Plan and implement program, including problem-solving mechanisms.
	Develop indicators to measure community participation
	Disseminate information and feedback.

So before building a CAB, we worked through small groups, community meetings. And we had a sort of pre-CAB, a community research support group. We talked about what kinds of questions people would ask before participating in an AIDS study. We discussed what your role would be if you were to be voice for the community, and how to keep researchers informed about community issues.

What are some of the most difficult issues you wrestle with?

One big hurdle in communities devastated by high rates of HIV is how you balance these acute, immediate problems with talking about windows of opportunity—hope, light in the epidemic. A vaccine is a long way off. We helped people understand that research can take many years.

But once you enable community voices, what you hear is that peoples' main concern isn't vaccines. It's how are we going to care for all these sick people? On the ground you can't separate research from everything else. So you take the opposite approach: You link them.

This can be a challenge when you work for an organization with a specific focus or mandate, yet every day you face problems that are much bigger. The focus may be prevention, but the community also needs wellness programs, orphan care. So you can help them get an NGO [non-governmental organization] in place, and do other things to develop a spectrum of different interventions. Research is one aspect of this, and you help prepare the community to take responsibility for others. One community formed its own NGO focused on nutrition and orphan care. We took them through proposal writing and linked them to a well-established NGO that could be their mentors. At the end of the day this will impact the outcome of research because there's more buy-in.

On the ground
you can't separate
research from
everything else.
So you take the
opposite approach:
You link them.

What does this require in terms of people and funds?

It's *very* intense in terms of human resources and time. It takes a dedicated person who is either from the community or immersed in it. They must be in touch at all times; have their ear to the ground and squash any rumor-mongering before it gets big.

In terms of who pays, it's basically the research sponsors. For example, any grant application with NIH [the US National Institutes of Health] requires a community preparedness program that includes studies on how to engage people in clinical research.

When the study you're working on comes to an end, what then?

It's a very important question. When a study is over and the researchers move on, what's been left behind? Part of the goal is to leave more infrastructure and more trained

health personnel. But it's also to leave a more informed community that feels empowered, and has the capacity to take responsibility for its own problems and to influence issues affecting them. (See also chapter 20 on leaving communities better off.)

How have things changed since you first began doing this work, and what are the main challenges at this point?

Nowadays there are quite a number of sites—some rural, some urban like Soweto. So there's much more activity overall. Another change is that the CABs or community structures from some of the different trial networks are working more closely with each other, by having cross-CAB calls. These structures are coming together to have a collective voice: prevention and treatment as one agenda.

In terms of challenges, I think the key is to live up to our talk about *clinical trials* requiring full collaboration, trust and mutual understanding between researchers and the various stakeholders. We need to guard against tokenism, to make sure we engage with communities in true partnerships. Community participation is ethics in action.

vaccine trials: leaving communities better off

adapted from the AVAC REPORT 2004¹

WHAT WILL POOR communities in developing countries get out of agreeing to take part in AIDS vaccine *clinical trials*? The question is difficult, since the road to an effective vaccine is looking longer than many had expected.

Given the long haul ahead, AIDS vaccine scientists, who are rushing to establish international vaccine trial sites in developing countries, need to focus on a key issue:

How can they leave poor communities better off for having taken part in a trial, even if the vaccine being tested turns out not to work?

“Communities participating in AIDS prevention and treatment trials, whatever the results, are contributing knowledge that is a global public good,” says Seth Berkley, president of the International AIDS Vaccine Initiative (IAVI). “They should benefit in return.”

¹ AVAC Report 2004. “AIDS Vaccine Trials—Getting the Global House in Order.” Published by the AIDS Vaccine Advocacy Coalition, May 2004. The AVAC Report is published annually, and highlights the key issues of the past year and the upcoming challenges in the search for an AIDS vaccine.

no more safari research

Fortunately, the world has moved away from the “safari research” that used to be conducted by Western scientists in poor countries. It’s no longer considered ethical for researchers to simply arrive in impoverished communities, collect data, and then leave without engaging local researchers and without the community reaping any tangible benefits. Such an approach would violate international ethics guidelines, and most communities in the developing world would no longer accept it anyway.

But how, exactly, can AIDS vaccine researchers contribute to the health and welfare of poor communities where trials will be conducted?

Much attention over the past two years has focused on the issue of providing *antiretroviral drugs (ARVs)* to volunteers who become infected during the course of a trial. This is a critical issue—and a difficult one, since these drugs dramatically reduce AIDS mortality rates but are not yet widely available in most of the developing countries where vaccine trials will be conducted. But the major trial networks have all committed to making ARVs available as needed to trial participants. And they have laid plans for funding mechanisms (typically, an insurance fund) to pay for the drugs, although the source of these funds is, for the most part, not yet nailed down.

Other important questions—such as how long the drugs will be provided, whether infected family members will qualify, and whether efforts will be made to provide ARVs to entire communities—also still need to be worked out. But there is consensus among trial sponsors that these life-extending medicines will at least be offered for free to trial participants who become infected. This is an important advance. Nor should it break the bank, since only a small percentage of volunteers become infected during a trial. And ARV therapy is started only when an infected person develops certain symptoms, which takes at least a few years—by which time the drugs should be much more widely available (and perhaps cheaper) in developing countries.

ARVs are just one benefit

Providing access to ARVs for trial participants is just one way that AIDS vaccine researchers can leave poor communities better off. But there are many other benefits that trials can bring to host countries and communities.

Ideally, specific benefits will be decided at the grassroots level as vaccine researchers engage with national and community leaders and with *Community Advisory Boards (CABs)* at local trial units. Each community may want and need something different.

To stimulate the dialog, AVAC offers this list of possibilities:

- › *Voluntary HIV counseling and testing.*
Since vaccine trials enroll HIV-negative volunteers, people must be tested before they can participate. The screening process should be (and already often is) used as an opportunity to introduce rapid HIV testing kits to the community, and to train local people in using them and counseling those who test positive.
- › *Support groups for those who are infected.*
In many developing countries, AIDS carries more social stigma than it does in the industrialized world. By helping to set up support groups for people who test positive in trial screenings or become infected during a trial, researchers can establish ways to support HIV-positive people and help to end the silence and prejudice surrounding AIDS.
- › *Prevention of mother-to-child transmission (MTCT).*
A short course of the ARV drug nevirapine reduces HIV transmission from infected mothers to their newborns during delivery. Vaccine researchers can partner with local health officials to provide this simple, inexpensive regimen and educate HIV-positive pregnant women about its life-saving potential. Health care should also include long-term provision of ARVs for these mothers, along with counseling about the risks and benefits of breastfeeding in their particular setting.

› *Antibiotics and medicines for malaria and TB.*

Many communities in the developing world have little access to standard antibiotics and medicines to fight these two leading killers. AIDS vaccine trial units in developing countries should provide these drugs to participants, as many already are. They should also provide medicines for other sexually transmitted diseases (STDs) which, if left untreated, can greatly increase the risk of HIV infection.



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TANZANIA

HIV-positive participants in a clinical study in Mbeya, Tanzania gather at the trial site for an information session on home-based care.

- › *HIV prevention programs.*
AIDS vaccine researchers are ethically required to educate trial volunteers about HIV and how to keep themselves from becoming infected. Vaccine trials offer the opportunity to expand prevention efforts into the larger community, in partnership with local CABs.
- › *Professional training.*
Vaccine trials provide opportunities to increase the number of medical professionals, who are in short supply in many developing countries. Trials cannot take place without trained doctors, nurses, technicians, counselors and others—and the people best able to understand the needs of a community will come from within. Trials can offer both on-the-job training and further training at other institutions in the host country or abroad.
- › *Shared laboratory facilities.*
Most trial teams will set up laboratories to test blood samples from volunteers. Depending on the studies to be done, these labs may use sophisticated equipment and carry out a wide range of tests. In poor communities without access to advanced testing facilities, these labs might also provide services such as HIV *antibody* tests, *T-cell* counts and *viral loads*, to help in diagnosing and treating HIV and in tracking the local epidemic.

RESEARCHERS CAN PROVIDE benefits directly, or they can link up with others who provide them. The key factor is to ensure that whatever is put in place can be sustained after trials end. A chilling example of what can happen without a commitment to sustainability comes from an AIDS prevention study in Zambia. A temporary halt in the program due to a funding glitch led to a doubling of mortality rates among trial participants, since they no longer had access to TB and malaria medicines.

kericho: a model program

While AIDS vaccine trial sponsors have worked to improve public health at many sites in the developing world, one outstanding effort is underway on the highlands of western Kenya. In the district of Kericho, the United States Army Medical Research Unit (USAMRU) is engaged in a comprehensive effort to prepare for a large-scale trial of a vaccine now in development.

The site is a tea plantation owned by the British-based James Finlay & Co Ltd., a global tea conglomerate that employs about 30,000 Kenyans as pickers or tea processors. The workers live in company housing and receive medical care at a company hospital. An estimated 15% of them are infected with HIV. USAMRU and Kenyan researchers are working with Finlay's senior management, employees and family members as well as the overall Kericho community and Kenyan Ministry of Health. A successful vaccine would reduce the number of workers who become infected and sick while boosting their productivity.

The site team views improvement in public health for the entire Kericho community as integral to the trial. "Our goal is to get a handle on AIDS—whether we do vaccine research, primary prevention, or treat disease," says Fredrick Sawe, a Kenyan doctor in the project. "The end is the same. We are trying to stop this disease in its tracks."

With that aim, the researchers have conducted a community-wide education program to teach people about behaviors that put them at risk of HIV infection. The message has gone out not only in conventional brochures, but also in rap performances and condom distributions at pre-game soccer shows and traditional community meetings, where research staff perform dramas about HIV prevention in both Kiswahili and English.

The team has also introduced ARV treatments to Kericho, starting with an MTCT program housed in Kericho's first antenatal clinic (built with funding from the Elizabeth Glaser Pediatric AIDS Foundation). In addition, short-course nevirapine is available at 22 other nearby centers upgraded

as part of the program, which so far has trained 56 nurses and counselors, and 36 people to do rapid HIV testing. And in April 2004, they reached another milestone when they began providing ARV treatment (in Kericho and one nearby district) to HIV-infected people meeting specific clinical criteria. So far, 600 people are on ARVs, and plans call for scaling up capacity to treat 30,000 people in the wider area by 2008.

The impact of introducing ARVs has been profound, according to the USAMRU's COL. Debbi Birx—not only for the sick people now regaining health, but on willingness of people in the community to be tested (see interview, chapter 32). “Suddenly men are coming in for VCT,” she says. “Up to now, all we’ve done is bring in pregnant women, who want to protect their babies. They’ve come in for testing and could get nevirapine single dose, but no long-term therapy. For this they had to identify themselves as positive, while very few men in the community were identified as positive. But the availability of ARVs is bringing men, and even whole families, to the table.”

The impact of introducing ARVs has been profound—not only on sick people but on willingness of others to be tested.

Who pays?

How ARV therapy for trial volunteers will be paid for hasn't yet been fully worked out. In the case of Kericho, the US President's Emergency Plan for AIDS Relief (PEPFAR)—which will pump \$9 billion of new funding into AIDS treatment and prevention in 14 countries over 5 years—has provided the funding, but more is needed if drugs are to reach the wider community. So far PEPFAR has not used cheaper generic drugs (which would allow it treat many more people), although this could change. Another potential source is the Global Fund to Fight AIDS, Malaria and Tuberculosis, but for now the Fund is struggling to finance even already-approved projects. Other stakeholders in particular sites (such as Finlay in Kericho), or multilateral agencies involved in AIDS vaccine development, are also possibilities.

BUT SUCCESS in using AIDS vaccine trials to leave poor communities better off is not just a matter of money. Fundamentally, it's attitude. Instead of doing research *on* communities, scientists need to do research *with* communities. Instead of focusing only on trial outcomes, sponsors need to invest in the overall health of individuals and their communities.

hiv vaccine trials in uganda: personal experience as an investigator

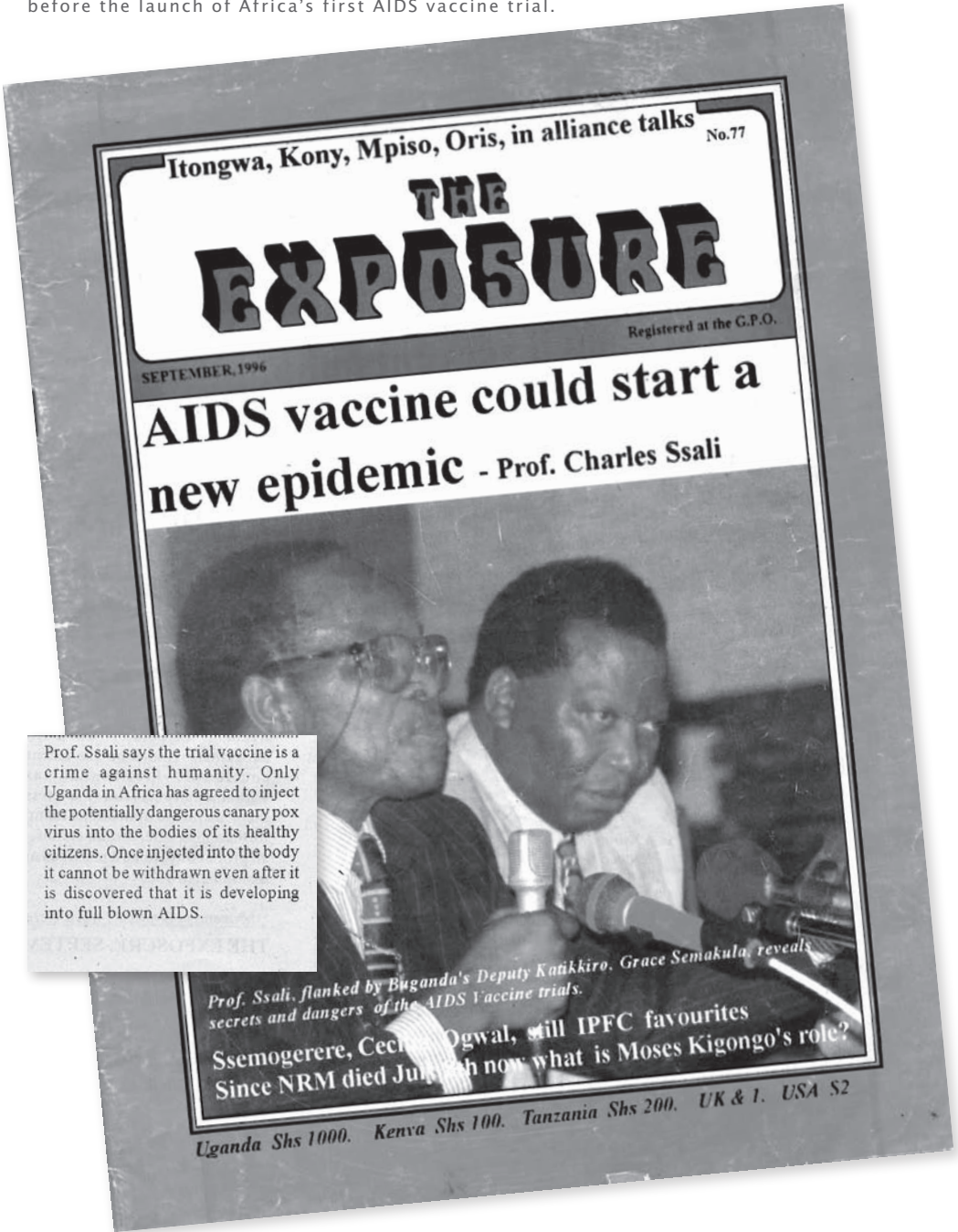
PONTIANO KALEEBU / uganda

IN 1999, UGANDA LAUNCHED Africa's first HIV vaccine trial, a small *Phase I* safety study involving 50 volunteers. No other research study in the country has ever generated so much public controversy, or gone through such a long process of gaining the approvals and support needed to move forward. Although some of the debate involved genuine scientific and ethical issues, which are important topics of discussion for a country new to this area of research, most of it was fueled by extreme misinformation and misconceptions that were widely reported in the press.

As I now write this article five years later, so much has changed. The “enabling environment” solidified over these years—based on staunch government support, a national AIDS plan that includes vaccines, established international partnerships and strong community engagement—has helped HIV vaccine research become firmly rooted in Uganda. We are now running our second trial, which has been well received by the public. And we’re no longer alone doing this work in Africa: HIV vaccine studies are going on in five other African countries, with several more doing “vaccine preparedness” studies that will help prepare the ground for future trials.

UGANDA

Cover from a Ugandan magazine (September 1996) three years before the launch of Africa's first AIDS vaccine trial.



As Uganda's experience shows, it can be difficult to introduce HIV vaccine research into developing countries (see chapter 40 for a discussion of how this went in Brazil). In this short article I look back over the journey that took us from the first trial to where we are today, and on the lessons we learned along the way. I write from the perspective of a scientist who was involved in this work from early on, and who believes strongly in its importance. I hope it also offers lessons for other countries embarking on this journey, since many of our experiences seem to be common to other settings.

trial 1: treading new ground, weathering the storm

Uganda's interest in conducting the 1999 HIV vaccine trial came from a desire to help control the epidemic, which has had such devastating effects on our population. The original discussions with the US National Institutes of Health, which sponsored the trial, began several years earlier. But there were many obstacles to overcome.

Genuine concerns from the public revolved around safety, compensation for volunteers in case of harm, and intellectual property issues. Another important issue was *clade*: The particular genetic *subtype* of HIV used to make the vaccine was common in North America, but not in Uganda—leading to fears that Ugandan volunteers were being exploited as “guinea pigs.” Although a vaccine based on a common East African subtype was in the works, it would be another year or two until it was ready—leading scientists to favor going forward with the clade B version, since the study was simply meant to test safety, not whether the vaccine worked. And ironically, in the end this trial yielded some of the first evidence that HIV vaccines can induce *immune responses* that work across clades. (See chapter 10 for a discussion of clades and vaccines.)

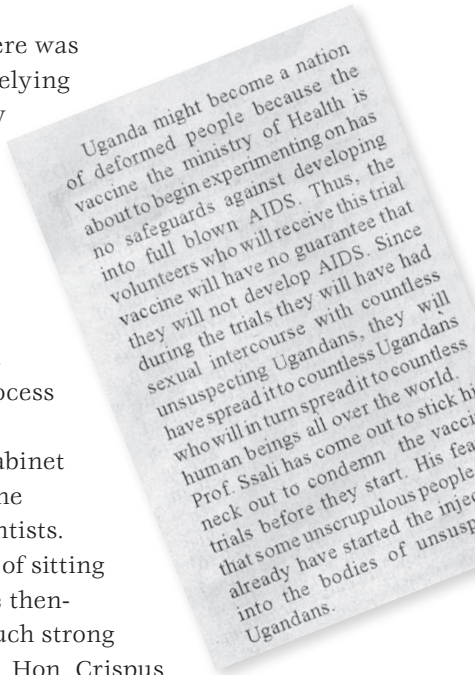
But the substantive issues were largely overshadowed by negative, misleading media reports. One leading news magazine ran a major article with a headline quoting well-known scientists saying that “an AIDS vaccine could start a new epidemic and should be condemned.” On the very day of the

first vaccination, one member of the Ugandan Parliament said on a live radio program that “this vaccine should be tried on animals in the national parks.”

Amid this heated atmosphere, there was nervousness in some quarters about relying solely on Uganda’s standard review by its existing scientific and ethical committees, which meant that there was no clear pathway for seeking regulatory approval for the study. The solution was to involve a much broader set of stakeholders, including seven local committees and additional international groups—a process that took over two years.

It even involved meetings with Cabinet and Parliament members to explain the research—an unheard-of step for scientists. But I will never forget the experience of sitting in the Cabinet meeting chaired by the then-Ugandan Vice President. There was such strong support from then-Minister of Health, Hon. Crispus Kiyonga, who set up regular meetings with us researchers to stay up-to-date on the preparations. He wisely advised us that we would be protected from criticism if we had broad public support and endorsement from high political leadership. During this time, as we attempted to work through the approvals process while preparing clinics, laboratories and communities for the trial, we sometimes had the surreal sense of building a ship and trying to sail it at the same time.

However, in the end, there was no doubt that the trial was successfully conducted in terms of scientific knowledge gained, capacity built, sensitization of the communities and compliance with the highest international ethical guidelines. Passing these first hurdles therefore paved the way to move ahead with other vaccine trials.



the second trial: calmer waters

IN 2003, UGANDA LAUNCHED its second vaccine trial, this time with the International AIDS Vaccine Initiative (IAVI). This Phase I safety study is testing a combination of two vaccines based on HIV subtype A, which is common in East Africa. The trial enrolled 50 volunteers and ran until February 2005.

This time around we faced a more streamlined approvals process, boosted by much-strengthened in-country capacity for review. As a result, the study *protocol* took less than half as long to discuss with stakeholders, and the review involved only two major local committees plus an expert committee from the World Health Organization/UNAIDS.

We also took a different approach to the media, engaging them pro-actively from the start in an ongoing dialogue aimed at de-mystifying the trial process. As researchers we have also tried much harder to learn how to speak more understandably with the media. And our public support has been greatly bolstered by the smooth conduct of the first trial, the fact that no monsters emerged, and the strong engagement of several of these early volunteers, who have since gone public with their experiences.

Another crucial difference is a much greater community involvement in our activities, which has crystallized through a very active *Community Advisory Board (CAB)*. The CAB members include former trial participants and civil and church leaders. Recruitment strategies for study volunteers were worked out collaboratively by the study team and the CAB, creating some community ownership. Recruitment of volunteers from the surrounding communities began with public announcements on radio, posters, and public gatherings, followed by general information seminars for interested people, and then by more detailed seminars before screening. We have also set up a vaccine newsletter where CAB members and the study team jointly participate in its editing.

We also took a different approach to the media, engaging them pro-actively from the start in an ongoing dialogue aimed at de-mystifying the trial process.

Our participants are ordinary men and women whose motivation is a desire to contribute to fighting AIDS, and we use our information seminars and screening process to weed out those whose motivation is other than altruism (for example, the belief that they will be protected from HIV). Some volunteers have lost friends and close relatives to AIDS. Others work in AIDS prevention or care and are proud to make their participation known to others, as a way of raising awareness about the communal responsibility to help control the epidemic.

challenges amid success

ALTHOUGH THINGS ARE GOING WELL, this doesn't mean there are no challenges in conducting these studies. Trial procedures must conform to strict international ethical guidelines and study teams must fully understand and implement the *Good Clinical Practices* governed by international ethical requirements, all of which demands constant vigilance and quality control. Trials of this nature also require very dedicated staff who can help keep the volunteers motivated and sticking to their regular appointments.

Participants' frequent visits to the trial center create a strong relationship between them and the researchers. When trials end, volunteers may wish to maintain this bond, as we found with our first study. Channelling this energy can help build advocacy and support for the broader vaccine effort. (For one example, see chapter 34.)

Another challenge is to encourage more women to volunteer for trials (see chapters 24 and 25). Cultural barriers sometimes hinder their participation, since many women make their decisions only after consulting their husbands. The requirement to use reliable contraception and avoid pregnancy during trials is another disincentive for many women.

Vaccine research is also filled with disappointment. I once gave a talk that covered the two *Phase III* trials in the USA and Thailand, which showed no *efficacy*. One participant asked, "How often shall we come here and you tell us about failed vaccines? Why don't you try more vaccines at the same

time rather than one at a time?” We researchers are therefore challenged to explain ourselves, and the vaccine development process, more fully so we can keep communities motivated even after vaccine trials fail to show efficacy—while at the same time not raising unrealistic expectations.

facing the future

Having participated in preparing and implementing two trials in a country completely new to such research, there is no doubt that this is a challenging but not impossible exercise. Many researchers in developing countries will find that the first trials are difficult. But each one is a learning experience that makes the next ones easier. We should learn from our mistakes and also share experiences within and across countries. A poorly conducted trial anywhere can take the whole field many years backwards.

resources

www.aidsuganda.org

Website of the National AIDS Commission of Uganda, with extensive information on the country's programs, its National AIDS Plan and links to important Ugandan agencies and non-governmental organizations (NGOs).

www.iavi.org/uganda

Website of the Uganda Virus Research Institute in Entebbe, where the second trial took place. Current and past issues of the CAB newsletter.

AIDS Vaccine Fails in Studies

The New York Times
February 25, 2003

Vaccine for AIDS appears to work

USA Today
February 25, 2003

USA

Initial confusion over the meaning of the trial's results led to contradictory newspaper headlines like these.

facing failure on the way towards success: lessons learned from the VaxGen trial

RICHARD JEFFERYS

IN FEBRUARY 2003, the long-awaited results from the world's first AIDS vaccine *efficacy* trial were announced. The trial (dubbed VAX004) tested whether a vaccine called *AIDSVAX* could prevent HIV infection in people with a high risk of sexual exposure—most of them gay men, plus a small number of women. The results were disappointing: there was no protection in the overall study group (*cohort*).

But the announcement also included a confusing and controversial claim by the vaccine's manufacturer, a California-based company called VaxGen, Inc. According to VaxGen, *AIDSVAX* *did* show protection of participants from certain racial minorities—namely those categorized as Black, Asian or Other—even though it failed to protect White or Hispanic participants.

More thorough review of the data in the following weeks and months found the claim to be wrong, the result of a statistical error related to the very small number of non-White participants.

But despite its disappointing outcome and controversial ending, the trial nevertheless offered some valuable insights into conducting vaccine efficacy trials among high-risk populations—an undertaking that some scientists had worried would be very hard to pull off. What follows is a discussions of the main lessons learned, in particular:

Although the vaccine showed no efficacy, the trial nevertheless offered valuable insights into conducting efficacy trials among high-risk populations.

- › The trial was able to enroll roughly 5,400 high-risk volunteers, and over 85% of them stayed with it for the full three years.
 - › The infection rate during the trial (2.8% per year for the men; 1.5% for the women) shows that HIV *incidence* is significant in these high-risk groups, and that efficacy trials can be done in certain populations in the US.
- › The trial gave clear answers to the questions of whether the vaccine could protect against HIV infection or slow progression of infections that occurred after vaccination. (Progression was measured by following changes in *CD4+* *T-cell* count and *viral load* over time.) This may not sound like a major accomplishment, since the vaccine didn't work, but it is; a variety of scenarios could have led to an ambiguous outcome about the vaccine's efficacy.
 - › Risk behavior among participants didn't appear to increase as a result of being in the trial—another early fear that proved to be unfounded.
 - › Confusion over the results in racial subgroups drove home the importance of doing efficacy trials in diverse study populations of both men and women. It also emphasized the dangers of publicly releasing results from the trial without careful review to ensure absolute accuracy.

a brief history of the trial

The AIDSVAX vaccine was originally designed well over a decade ago. The formulation tested in VAX004 contains two versions (*genetic variants*) of the HIV outer *envelope protein*, called *gp120*. The hope was that the vaccine would trigger production of *antibodies* which would bind to the *virus* if a vaccinated person was exposed to HIV and prevent it from infecting cells in the body. (This is called *neutralizing* an infection.) Many scientists were skeptical about the potential of AIDSVAX because the antibodies it induces neutralize gp120 only from HIV *strains* grown in the lab, not from HIV *isolated* directly from infected people. What's more, gp120 *proteins* are notorious for constantly *mutating* and changing shape, making them a difficult (and moving) target for antibodies.

Altogether the VAX004 trial enrolled 5,417 HIV-negative volunteers at 61 sites in the US, Puerto Rico, Canada and the Netherlands, beginning in 1998 (see Table 3.4 for a breakdown by gender and demographics). Each volunteer received seven vaccinations over a 30-month period. At each study visit, they also received HIV pre-test counseling and then had blood drawn to test whether they'd remained HIV-negative and to measure their *immune responses* (i.e., level of antibodies) to the vaccine.

Table 3.4 Race, gender and the VAX004 trial volunteers

Group (average age 36)	Number of volunteers	Percent of volunteers
Male	5,095	94%
Female	308	6%
White	4,489	83%
Hispanic	367	7%
Black	349	7%
Asian	77	2%
Other	121	2%

the results

The trial data clearly showed that AIDSVAX failed to prevent HIV infection in the study cohort as a whole (see Table 3.5, below), since there was roughly the same rate of infection among study participants who received the vaccine and those who got a *placebo*. Nor did the vaccine show any effect on CD4+ T-cell counts or viral load levels in vaccinated volunteers who later became infected.

But VaxGen initially claimed that the vaccine *did* reduce infection rates by about two-thirds (66–67%) in participants whose race was categorized (by the participants themselves) as Black, Asian or Other.

Even major newspapers were uncertain how to report VaxGen's claims. Some focused on the overall results and wrote that AIDSVAX had failed. At least one paper wrote that the vaccine “appears to work.” Understandably, many groups representing Black and Asian communities were concerned that the apparent success of the vaccine in these subgroups was being ignored or downplayed because it hadn't worked among whites.

Table 3.5 VAX004 trial results: infection rates in vaccine and placebo groups

Group	Number infected	Percent infected, vaccinees	Percent infected, placebo	Percent vaccine efficacy*
Overall	368	6.7%	7.0%	6%
White/Non-Hispanic	309	7.1%	6.6%	-7%
All non-white	59	5.0%	9.4%	47%
Hispanic	23	5.9%	7.0%	15%
Black/Hispanic	15	2.6%	7.8%	67%
Asian/Pacific Islander	6	5.4%	14.3%	66%
Other	15	9.2%	17.8%	50%

*Vaccine efficacy is the percent reduction in infection rate due to the vaccine (compared with the rate in the placebo group).

At first glance, the results in the table *do* seem to suggest some protection in these two subgroups. But the suggestion rests on a very small number of infections (15 and 6, respectively)—which is where the complicated science of statistics comes into play.

One of the most important things to remember when looking at results from any *clinical trial* is that small numbers of events (in this case, HIV infections) increase the possibility that apparently positive results will occur purely by chance. Think of flipping a coin five times. It is quite possible—although unlikely—that the coin could come up heads five times in a row. If you flip a coin 100 times, it's much more likely that heads and tails will come up roughly equal numbers of times. If the coin came up heads 100 times in a row you would think that there must be a cause (like the coin having more weight on one side).

When it comes to clinical trial results, the purpose of statistics is to decide whether a result happened by chance, or if it was caused by the medicine or vaccine being tested. After VaxGen's announcement, an in-depth statistical analysis of the data (done by experts from the US Centers for Disease Control, the National Institutes of Health, the HIV Vaccine Trials Network and VaxGen) found that the subgroup results were almost certainly a result of chance due to the small numbers involved, like a coin randomly coming up heads several times in a row. It turned out that VaxGen had not used the proper statistical tools to correct for the small numbers of minority volunteers, or for the total number of subgroups analyzed.

risk behavior among trial participants

ONE OF THE MOST IMPORTANT questions surrounding this (and future) efficacy trials is whether high-risk participants may increase their risk behavior based on a false sense of being protected. Behavior was therefore closely monitored throughout the trial, and at each study visit participants were counseled on how to reduce their risk of infection and reminded not to assume they're protected. They were also asked about any instances of unprotected sex with any partner, or with a partner

known to be HIV-positive (for gay men, specifically about unprotected anal sex; for women, vaginal sex).

The results showed a significant drop in the number of gay male participants reporting unprotected anal sex with any partner during the first six months of the study (from just under 60% of the men to around 50%). From then on, the reported frequency stayed low, despite a small increase over time. The incidence of unprotected anal sex with a known HIV-positive partner also declined initially (from roughly 20% of participants to about 10%), and this decline was maintained. The rate of new infections among the men stayed at around 3% per year throughout the trial.

Results for women were not as statistically robust since there were so few female participants. But the overall pattern was similar: Unprotected vaginal sex declined somewhat at the beginning, and then remained near the baseline level for most of the study (with about 50% of women reporting this risk behavior). Unprotected vaginal sex with a known HIV-positive partner declined from just over 10% at baseline to around 5% at month 36.

Overall, these results are encouraging. But the researchers involved have pointed out several limitations. First, the trial population was primarily gay white men, so it's not clear whether these findings would apply to a broader cross-section of high-risk populations. Second, these studies didn't prove beyond any doubt that there was no "vaccine optimism" (false sense of security) affecting the volunteers' risk behavior. Rigorous proof would require comparing VAX004 volunteers to a similar high-risk population that got the same regular risk-reduction counseling and medical care. And when researcher Susan Buchbinder from the University of California at San Francisco did this type of comparison (using a non-vaccine cohort recruited two years after VAX004 began) she found that risk behavior did decline more in the non-vaccine group than in the VAX004 volunteers—and so did HIV infection rates (slightly). So, while once again the results don't give 100% proof (since these two groups were not studied in parallel), they may hint at a small effect of "vaccine optimism."

One of the most important lessons to take away from VAX004 is that future trials must assemble racially diverse study cohorts of both women and men so that possible differences in vaccine effects can be detected. To put the issue in perspective, so far there are no examples of licensed vaccines known to work better or worse among different racial groups. But there is a fascinating (and surprising) example based on gender: the still-experimental vaccine against genital *herpes* (see chapter 30) seems to work only in women—a finding that researchers are now attempting to confirm in a new study. So, while it will usually not be feasible for a single efficacy trial to give *statistically significant* results on every subgroup of participants (since this would require huge numbers of volunteers), it's essential that trials are designed to detect hints of any differences, which could then be tested through follow-up studies.

The controversy surrounding VaxGen's initial claims of efficacy among racial subgroups also shows how important it is for trial results to be rigorously evaluated before they are made public. It can be tempting for commercial companies to give a positive spin to their products, as a way to help ensure corporate survival. But plain errors, spin or anything else that oversells the promise of an AIDS vaccine will undermine public confidence. It would also be helpful for community activists to work together in the future to quickly sort through the meaning of uncertain results if such a confusing situation ever arises again.

Future efficacy trials will also need to remain vigilant about monitoring risk behavior, since each trial will involve a different study population. It will also be important to compare risk behavior among trial participants to risk a similar cohort that isn't taking part in the trial but gets the same level of counseling, to fully assess the possible effect of "vaccine optimism."

The controversy shows how important it is for trial results to be rigorously evaluated before they are made public. Plain errors, spin or anything else that oversells the promise of an AIDS vaccine will undermine public confidence.

resources

<http://avac.org.ph/temp.com/pdf/UnderstandingAIDSVAX.pdf>
Understanding the Results of the AIDSVAX trial. AVAC website. This document discusses the confusing findings, and the follow-up work done to clarify the confusion, in simple language. Available in English, French and Spanish.

testing vaccines in injecting drug users: VaxGen's efficacy trial in thailand

introduction by PATRICIA KAHN

Injecting drug use is an important component of the global AIDS epidemic. In Eastern Europe and the former Soviet Union, regions with two of the world's fastest-growing epidemics, injecting drug users (IDUs) account for the majority of people newly infected with HIV, and they are a big part of the fast-evolving epidemics in China, India and other Southeast Asian countries. Within these regions, it's common to find that 20–60% of IDUs are infected, according to UNAIDS (2004). Altogether, 136 countries reported injecting drug use within their borders in 2003, and estimates say that about 15 million people worldwide inject drugs—the majority of them living in developing countries.¹

From a scientific perspective, it's not at all clear whether vaccines that work against sexual transmission will be equally effective—or will work at all—against intravenous infection (see chapter 11). And there's only one way to find out: by testing vaccines for *efficacy* in populations where one or the other risk factor predominates.

But the barriers to carrying out clinical research among IDUs are formidable. Injecting drugs is illegal everywhere in the world, and is severely punished in most countries. The result is that IDUs usually live as marginalized populations, vulnerable to human rights abuse and chronically underserved by health and social systems (see chapter 27). And few governments have taken the steps needed to reduce HIV infection risk in drug users. On the contrary, harsh criminal penalties, combined with the scarcity (and often illegality) of harm-reduction services such as syringe exchanges and long-term methadone maintenance, only fuel the fire. Yet without efficacy trials in IDUs, prospects for a vaccine that works for them could be much dimmer.

The year after VaxGen began testing its vaccine for effectiveness in a North American/European *Phase III* study (see chapter 22), a second trial was launched in an IDU population in Thailand. Under the prevailing laws, the study's prevention services could not provide clean needles. [Counseling did include information on reducing risk by injecting safely and not sharing needles or, failing this, on how to sterilize them. Safe sex information and condoms were also provided.] Another key issue was the high rate of arrest and incarceration of IDUs: Nearly 20% of the volunteers reported at the start of the trial that they had been imprisoned within the past six months. Without the ability to conduct trial visits within jails, the study would have collapsed due to loss of volunteers to follow-up.

¹ "Regime Change? Drug Control, Users' Human Rights and Harm Reduction in the Age of AIDS." Background paper for "Human Rights at the Margins: HIV/AIDS, Prisoners, Drug Users and the Law," a satellite meeting at the 2004 International AIDS Conference in Bangkok. www.aidslaw.ca/bangkok2004/e-bangkok2004.htm

For this reason, long discussion and negotiation took place between trial staff and the Department of Corrections, leading to an agreement that study visits could take place in prison for volunteers who were incarcerated during the course of the trial. Counseling remained a standard part of these visits, but the clandestine availability of drugs in prison—but not clean needles or condoms—meant an increase in the rate of infection among imprisoned volunteers, as documented earlier.²

The article which follows, by several of the trial's US and Thai researchers, describes the protocol of these prison visits and the process that led to it.

² Choopanya, K. et al., *J. Acquir Immune Defic. Syndr.* 29: 86–94 (2002).

providing care and maintaining followup of incarcerated participants in asia's first phase III hiv vaccine trial

MICHAEL MARTIN, SUPHAK VANICHSENI, PRAVAN SUNTHARASAMAI,
FRITS VAN GRIENSVEN, JORDAN TAPPERO and KACHIT CHOOPANYA / thailand

THE FIRST PHASE III HIV vaccine trial in Asia was completed in Bangkok in June 2003, in a population of 2,546 intravenous drug users (IDU).^① Years of work by vaccine trial staff, local government officials, community volunteers, and many others set the stage for the this trial, and although in the end the vaccine did not work, the trial succeeded in giving a definitive result.

One of the biggest potential obstacles in getting this clear answer, however, emerged from a three-year vaccine preparedness study that preceded the trial. This study showed that IDU volunteers in the *cohort* were frequently arrested and incarcerated, and that incarceration was associated with an increased risk for HIV infection.^② For these reasons, if the trial was to retain its participants over the full three years, vaccine trial staff would need to work with justice and prison officials in seeking permission and developing procedures for follow-up of incarcerated volunteers. In this article, we explain how these arrangements were established and how visits were conducted.

In developing a Standard Operating Guideline for working with incarcerated participants, we started from established international codes for the ethical conduct of clinical research, in particular the *Nuremberg Code* of 1947, the *Declaration of Helsinki* and *The Belmont Report*. (These documents are described in chapter 15 on ethics, and online citations listed.) We also followed the recommendations in the US Code of Federal Regulations for additional safeguards for the protection of prisoners involved in research.^③ Our guideline, along with the entire trial *protocol*, was reviewed by the ethical review committees of Mahidol University, the Bangkok Metropolitan Administration (BMA, which runs the city's methadone treatment programs where the volunteers were recruited, and was a partner in the trial), and the Thailand Ministry of Public Health, and by the institutional review board of the US Centers for Disease Control and Prevention (CDC). Once the trial was underway, its Principal Investigator (PI; author Kachit Choopanya) invited the Joint United Nations Programme on HIV/AIDS (UNAIDS) to carry out an ethics review, as described more fully below.

The vaccine trial preparatory study was launched in 1995. We enrolled 1,209 IDU volunteers from the BMA's methadone treatment clinics.^② Participants visited the clinic every four months for three years. Since we had anticipated that a high percentage of volunteers would be incarcerated at some point during the trial, the trial PI sought the cooperation of the Department of Corrections in the study. He discussed the purpose of the preparatory study and the importance of maintaining follow-up of incarcerated participants with the Director General of the Department of Corrections. After several meetings between trial staff and Department of Correction's staff, permission for these visits was granted, procedures were established and the preparatory study was carried out as planned, including prison visits where necessary.

In preparing for the vaccine trial, the PI met again with the Director General in 1999 to review the preparatory cohort's procedures and results, and to plan for prison visits during the upcoming vaccine trial. This led to a new round of meetings between trial staff and Department of Corrections, which


involved presentations about the trial and reemphasized the importance of follow-up. Once again, the visit procedures were reviewed and revised where necessary.

From March 1999 through August 2000, we screened 4,943 potentially interested IDU volunteers from the BMA's 17 methadone treatment centers in Bangkok, and 2,546 enrolled in the vaccine trial. The median age of the enrolled volunteers was 26 years old, 93% were male, and 95% had completed primary education. A history of incarceration was reported by 78%, and 17% had been incarcerated at least once in the previous six months.⁴

The importance of follow-up visits during the vaccine trial was explained to potential participants as part of the *informed consent* process. Participants were asked to provide contact information, including a personal address and phone number, and to identify family and friends that trial staff could contact if the volunteer missed a visit.

When clinic staff learned through these channels that a participant was incarcerated, a study visit was scheduled and a letter requesting permission to carry out the visit was sent to the prison director. A typical visit began when the clinic team—consisting of a doctor, nurse, clinical research assistant, and counselor—arrived at the prison. The team reported to a reception area and waited for prison officials to verify their identities and escort them to the meeting point. Study visits took place in private settings, usually the infirmary. At each visit, the volunteer was reminded that he/she had the right to refuse or withdraw from the study at any time. If the volunteer agreed to continue trial participation, the standard behavioral data and blood and urine specimens were collected just as in the trial clinics, and risk-reduction counseling was carried out.

In order to maintain participant privacy regarding HIV status, all study participants received daily pills at the infirmary, HIV-negative subjects received multivitamins and HIV-positive subjects received multivitamins plus antimicrobial prophylaxis, *antiretroviral drug* treatment, or both as needed.



78% of the trial participants had been incarcerated before—17% in the last 6 months.

Research data were treated confidentially and were not shared with the prison staff. Pre-test and post-test counseling was conducted in a private setting with no correctional personnel in attendance. No study documents, complete or incomplete, or medical equipment were left behind or stored at the prison.

Trial participants all received financial reimbursement for each study visit, and this continued if and when they were in prison. During this time, the reimbursement was given to staff of the correctional facility who stored the money for the participant. The participant was able to access this money upon request and upon release from prison.

Once the trial was underway, the PI invited UNAIDS to provide an on-site, independent assessment of the ethical aspects of trial conduct. In June 2001, a UNAIDS team visited several trial sites, reviewed trial materials, interviewed staff and trial participants, and accompanied trial staff to a prison to visit an incarcerated participant. The overall conclusion of the assessment team was that the trial "...is being carried out in an ethically responsible manner."

However, the team made several recommendations regarding follow-up of incarcerated volunteers. These including that letters sent to prisons should not identify volunteers as participants in an HIV vaccine trial, IDUs or attendees of methadone clinics and that a prisoner representative (prisoner advocate with knowledge of circumstances in Bangkok prisons) should be appointed to one of the Thai Ethics Review Committees. In response to these recommendations, letters to the prison were subsequently written on health clinic letterhead (not drug treatment clinic), the letter stated the participant was in a "research study" (not HIV preventive vaccine trial), and a prisoner advocate was appointed to the Ethics Review Committee of Thailand's health ministry.

From that point on, we followed these same procedures until the trial was completed in June 2003. Overall, we conducted 3,450 visits in prison. Participant follow-up during the trial was over 90% and risk behavior monitoring during the trial showed overall reductions in reports of injection drug use and sharing of injection equipment.^⑤

The first phase III HIV vaccine trial in Asia was made possible by the effort of many, many people. We would like to recognize the Department of Corrections in facilitating our visits and assisting our teams. In addition, we are extremely grateful to the participants in this vaccine trial for their patience, understanding, and selfless contributions in the search for an effective HIV vaccine.

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communities and cohorts

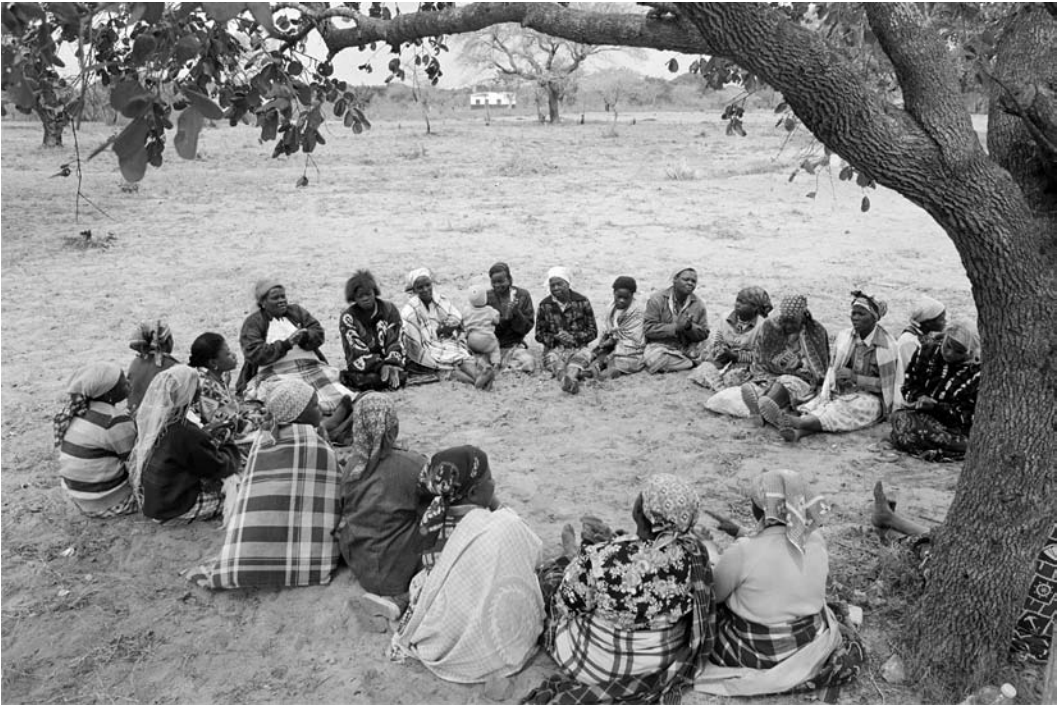
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TANZANIA / previous page

Volunteers in a clinical study on HIV in the Mbeya region of southwest Tanzania, a high transmission area along the Trans-African highway.



©Gideon Mendel/Corbis

MOZAMBIQUE

Rural women discuss sexual relations and AIDS transmission in their community as part of Action AIDS "Stepping Stones" program in Maputo, Mozambique.

women, aids and the search for a vaccine

SUSHMA KAPOOR / india



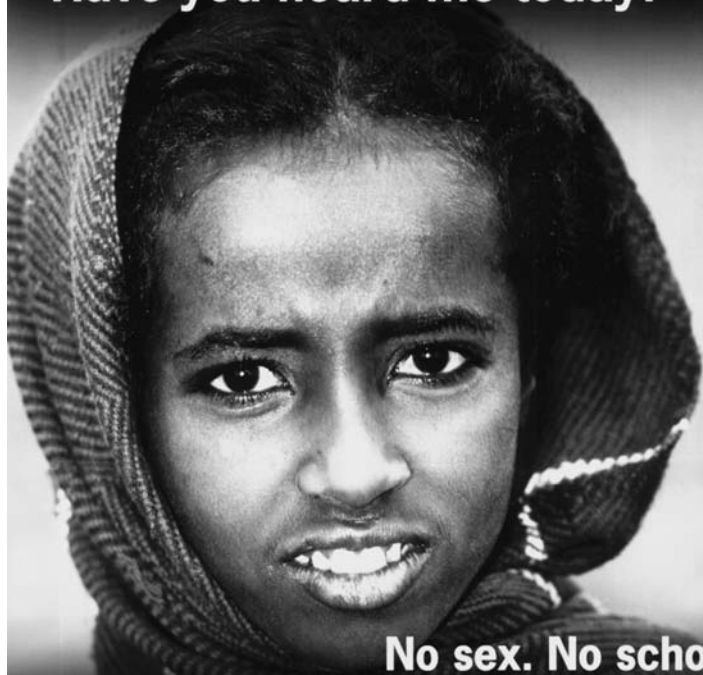
“THE FEMININIZATION OF AIDS”

“WOMEN AND HIV: CAN WE AVERT CATASTROPHE?”

Headlines like these have become all too familiar, with young women—even married, monogamous women—now one of the fastest-growing risk groups for HIV infection in many parts of the world. The numbers describe a growing disaster. Nearly two-thirds of all infected 15–24-year olds worldwide are female, and women account for 57% of all sub-Saharan Africans living with HIV.^① In Russia, the proportion of women among those living with HIV/AIDS climbed by 50% from 2001 to 2003,^② while in the US, it's nearly quadrupled in the past two decades.^③

The numbers also show that it's often not women's own behavior that puts them at risk, but that of their husbands or steady partners. For example, 90% of Indian women who test positive in antenatal clinics report being in monogamous, long-term relationships.^④

Have you heard me today?



No sex. No school.

That's the choice I face. I know this makes me vulnerable to HIV but many of us can only afford to go to school by allowing our bodies to be used. This has to change.

Equality for women helps fight AIDS.



www.worldaidscampaign.org



The Global Coalition
on Women and AIDS

womenandaids.unaids.org



UNAIDS
United Nations Programme on
HIV/AIDS

www.unaids.org

©United Nations Joint Programme on HIV/AIDS (UNAIDS)

Poster from the UNAIDS World AIDS Campaign, 2004. The campaign focused on how gender inequality fuels the AIDS epidemic, and how to address the many issues around HIV/AIDS that affect women and girls.

Many of the reasons for the growing HIV burden on women are rooted in cultures that limit women's control over their own lives—by restricting their access to money, property, jobs, education and healthcare, and to knowledge about their bodies and how to avoid infection. Sex between older men and adolescent girls, sex for food, shelter, or money, sexual coercion and violence are also part of the mix. Some studies also suggest a biological factor, in that women, particularly young women, may be more easily infected than men.

But the most immediate cause of women's vulnerability in most settings is their limited power to negotiate safe sex, combined with the lack of female-controlled HIV prevention methods other than the female condom, which is costly for many women, not widely enough available and can't always be used without the partner's knowledge. That, in turn, makes the development of effective *microbicides* and vaccines—completely female-controlled interventions—crucial to curbing the epidemic.

At the same time, it's important to recognize that gender stereotypes also raise men's HIV risk. Cultural concepts of masculinity often encourage them to engage in high-risk behavior (for example, having multiple sex partners) and/or to avoid seeking information on sexual health and protection from HIV, since “real men” are supposed to already know all about sex.

Many of the reasons for the growing HIV burden on women are rooted in cultures that limit women's control over their own lives.

vaccine efficacy—a gender issue?

But while having an effective vaccine could dramatically increase women's power to protect themselves, what does gender have to do with *developing* one?

More than you might think. First of all, scientists can't assume that an AIDS vaccine will work equally well in men and women. That may seem surprising, since the many different vaccines in routine use—against diseases like polio, measles, hepatitis B—seem to protect both sexes just fine. But the first

exception may be around the corner: an experimental vaccine against genital *herpes*, a sexually transmitted *virus* that causes painful sores, appears to work only in women (see chapter 30 on vaccine trials in adolescents). Further trials are now underway to confirm this finding, and to try to explain it—with most theories centering on differences in *immunity* within the linings of the male and female genital tracts, in the *mucosal tissue*. But whatever the reason, this startling result (assuming it holds up) has alerted vaccine developers to the possibility that the same thing could hold true for vaccines against other sexually transmitted diseases, including AIDS.

And the only way to find out is to test vaccines carefully for effectiveness in both men and women.

But many of the factors that make women vulnerable to HIV infection also come up in the context of AIDS vaccine trials. So if the field is to successfully test vaccines for *efficacy* in women, it's important to identify the potential social barriers in advance, and to take steps to overcome or minimize them.

getting started in india: the consultative process

In early 2002, when the International AIDS Vaccine Initiative (IAVI) began working in India to prepare for vaccine trials, it was clear that gender concerns would loom large. The country has a sad history, going back several decades, of women being enrolled in contraceptive trials without full understanding of the products being tested, the risks involved and in some cases without even their knowledge that they were part of a study. This history left a legacy of deep mistrust towards clinical research, especially amongst women's health and advocacy groups.

So we began by meeting with a broad range of people, including women's and reproductive rights advocates, women's health activists, people infected and affected by HIV, non-governmental organizations and scientists, asking for their advice on how to move forward with AIDS vaccine trials in ways that were sensitive to women's needs.

In the beginning, we encountered a fair amount of skepticism. But dialog led people to recognize the potency of an AIDS prevention tool that can be used without a partner's knowledge—much as their experience in family planning had taught them that Indian women often prefer contraceptive methods they can use in this way. For many, this sealed the argument that women should take part in these trials. Many participants in these early discussions also realized that vaccine trials presented an opportunity to advance the agenda of HIV education, counseling and care geared to women.

From there, we expanded to a more formal consultative process, bringing together a group of experts and stakeholders to map out the key issues. They raised many important questions—about stigma, women's lack of autonomy, counseling and confidentiality, and making trial sites woman-friendly. On their recommendation, we established a standing Gender Advisory Board of independent experts, with the mandate of helping IAVI follow through on making its trials sensitive to women's needs, from start to finish.

Working with the trial team, this group became active on many fronts. They've been spokespeople at ethics review committees, helping to ensure that gender-sensitive procedures are integrated into *protocol* development and program design. And they've helped crystallize the many issues and strategies outlined below.

issues and recommendations for gender-sensitive trials

It's too early to know what sorts of barriers will arise in recruiting women into vaccine trials in India, since the first trials will only begin in 2005. [For a perspective from the Kenyan AIDS Vaccine Initiative, which has been running *Phase I* and *I/II* trials since 2000, see chapter 25]. But we've identified a series of gender-related issues to address in trial planning, as summarized briefly below (and discussed more completely in references).^⑤

- › Many women lack autonomy in making decisions, and are used to relying on husbands or partners. This is important to consider as we develop educational materials, recruitment strategies and procedures for *informed consent*. For instance, it's crucial to clearly (and often) reinforce that each volunteer has the right to make her own decision about participation, and we must scrupulously avoid even a hint of pressure or coercion.

Maintaining strict confidentiality will be critical, since any breach could lead to severe consequences for women volunteers.

- › Maintaining strict confidentiality will be critical, since any breach (related to either trial participation or HIV status), could lead to severe consequences for women in terms of stigma, blame, loss of economic support or even violence. Establishing the study site in a neutral location and under a neutral name also helps in this regard, since visits to an HIV/AIDS or STD clinic can themselves be stigmatizing.
- › Voluntary counseling and testing can be quite scary for both men and women; women's added vulnerability, especially if they turn out to be infected, requires extra care. While HIV test results should be shared only with the woman herself, there should also be support for sharing results with a partner, plus a strong effort to involve couples in VCT—which can facilitate couple communication and mutual support. If one of the two tests positive and the other negative, it can help the couple protect the negative person from infection and obtain care for the positive one. But since women are so often at risk from their partner's behavior, counseling must help them recognize this risk and empower them to protect themselves.
- › The benefits of participation must also be well-planned and well-delivered. These usually center on education and counseling to reduce infection risk, and health care for common illnesses. (For a discussion of benefits at the community level, see chapter 20).

- › The trial site should be set up in a woman-friendly way—including a convenient location and opening times, availability of childcare, and privacy for all trial-related procedures. It should also have female staff for procedures involving contact with volunteers (counseling, medical exams, etc.).
- › Ongoing training of the trial team is important for recognizing and meeting women's needs. In our case, the first training was a 3-day session held in August 2003 for the full 18-person trial staff, covering the range of issues described above. This will be followed by training in specific areas targeted to different groups—for example, counselors, ethics review committee members, protocol managers and *Community Advisory Board (CAB)* members.
- › Clear mechanisms are needed to ensure accountability. These should be based on specific indicators of gender sensitivity across all aspects of the trial. Monitoring can be incorporated into the work of the Ethics Committee.

beyond trials

JUST AS traditional gender norms affect women's participation in vaccine trials, they're also likely to affect acceptability of a successful AIDS vaccine for women, or limit their access to it—ensuring that their influence on women's risk will continue even when an effective product is found.

Technologies alone will not solve these problems, or replace the need for behavioral change. So when we advocate for vaccines, we need to focus on empowering women, on increasing their access to health care and combating the social dynamics that make them so vulnerable to HIV—and on how gender stereotypes fuel the overall epidemic.

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challenges recruiting women into trials

SABINA WAKASIAKA / kenya

IN KENYA, developing an effective AIDS vaccine is a high priority for women, because they bear the greatest burden of the disease. Yet our site at the University of Nairobi, which has been involved in four *Phase I* and *I/II* trials since 2000, is finding it difficult to recruit women: Of 106 volunteers so far, about 15% are female. Our experience with these (and other potential) volunteers, plus consultations with women's health and community groups and outside experts, have given us first-hand information on the barriers to women's participation.

Many of the obstacles are deeply rooted in the lower status of women and their lack of economic power. Traditionally, a man is the wage earner, household head and decision-maker. Since he is her sole provider, a woman may knowingly continue living with a man whose behavior puts her at increased risk of infection, for the sake of her children and for the bread he puts on the table. Yet it is often the woman who is blamed for bringing HIV into the family.

These dynamics also mean that women will usually not participate in a vaccine trial if her spouse or boyfriend is opposed. Our society is strict in expecting a woman to be “loyal” to her husband, boyfriend, brothers and parents, even when these men contribute little to her well-being.

At the Kenyan AIDS Vaccine Initiative (KAVI), we continue to work towards including women in trials for several reasons. We recognize the importance of ensuring that vaccines will be effective in women, and of understanding factors that could affect how well they work (e.g., contraceptive use; presence of other sexually transmitted diseases). Women are also important allies in helping their communities prepare for the day when an effective AIDS vaccine is available, since they almost always bear sole responsibility for getting their babies *immunized* against common childhood diseases. And their perspectives are sorely needed—on *Community Advisory Boards (CABs)* and *protocol* teams—to increase the involvement of other women.

In talking with potential volunteers, we hear several worries. The enormous stigma attached to AIDS makes women afraid to get tested. If a woman tests positive at screening or during the trial, her husband or boyfriend may accuse her of promiscuity, which can lead to extreme consequences: Her

husband may divorce her, which would mean losing her children and her property rights. She could become homeless, and face even worse mistreatment, violence or rejection by her family and community. Even if she is allowed to leave with her children, their future is likely to be dim, since they would be left to languish in poverty and misery. It's no wonder that many women prefer the status quo, bad as it may be.

The enormous stigma attached to AIDS makes women afraid to get tested...It's no wonder that many women prefer the status quo, bad as it may be.

We also find that women tend to be cautious, since the traditional expectation is that men should be at the forefront in taking risks. Another disincentive for some women is the requirement to use contraception during the trial, and avoid pregnancy. Our Phase I studies have sought recruits among college students, and this issue arises with women who often expect to marry upon graduation and have children as soon as possible.

Among women who do enroll (or who enroll without their partner's initial knowledge and then reveal their participation later), a few find—often to their surprise—that their partners are supportive. But more often the man refuses to agree to her participation. Occasionally he agrees initially, and then withdraws support later on. Sometimes women say that this negative reaction is based on fear that participation will confer protection against HIV, freeing the woman to have sex with other men.

Over time we're learning to deal with some of these issues, and are slowly increasing the pool of willing female volunteers for future trials. Our strategies include seeking out couples in our community outreach work, reinforcing to women that their participation will be completely confidential, and other measures described in the article on women, AIDS and vaccines (see chapter 24).

aids research with sex workers: lessons learned

EMILY BASS

Millions of women around the world exchange sex for money or food, often as their sole way of earning a living. It's an exchange that brings meager benefits and comes with staggering health risks.

IN DURBAN, South Africa, a woman sends her children to school and makes her way to a dusty roadside truck stop that smells of diesel fuel. In Pune, India, a teenage girl wakes up in a cubicle she does not have the freedom to leave. In Chicago, USA, a woman in a dilapidated building wonders how she'll pay the rent for an apartment with a leaking roof over her head.

At some point in the day, each of these women will exchange sex for shelter, food, money. Although good estimates are hard to come by, many millions of women around the world exchange sex for money or food, often as their sole way of earning a living.

It's an exchange that brings meager benefits for most of them, and comes with staggering health risks. Many are not able to insist on condom use, or they get paid more for not using a condom—making them vulnerable to infection with HIV and other sexually transmitted diseases. This is borne out in sobering statistics: For example, 50% of Bombay's roughly 100,000 female sex workers (SWs) are HIV-positive, as are 15% of those in Hanoi and 50% of SWs on the truck routes around Durban.

Sex workers in these three cities have something else in common: Some of them have participated as study volunteers in clinical research on AIDS—for example, to test *microbicides* (topical creams or gels designed to prevent sexual transmission of HIV), prepare for HIV vaccine trials, or learn more about the link between sexually transmitted infections and the risk of HIV infection. The best of these trials are models for research that helps build community. Many of them have crossed tangible and intangible barriers—brothel doors, criminal penalties, stigma and social judgment—that can isolate SWs from medical services and information. Their efforts hold important lessons for the AIDS vaccine field, since SWs will be an important group to enroll in vaccine trials and to reach with an eventual licensed vaccine. (Sex workers are, of course, not always female—for example, sex tourism in some parts of the world involves male SWs as well. But, with a few exceptions, this group has not been the focus of AIDS-related studies.)

involving SWs in prevention research: experience to date

Female SWs have been involved in AIDS clinical research for more than two decades. Some of the earliest studies found that, in countries with new or emerging AIDS epidemics, rates of HIV infection climb in this group before the *virus* spreads widely in the general population. Many factors contribute to this, including the fact that SWs have many partners, and may be exposed to tourists or migrant workers from regions with high rates of infection. Another is that they usually have higher rates of other sexually transmitted diseases (STDs), such as *herpes*, which increases the risk of acquiring HIV.

Unfortunately, these data are sometimes used to blame SWs for the spread of HIV; at the 13th International AIDS Conference in Durban, South Africa, a World Bank official memorably referred to SWs as “epidemiological pumps” for HIV. They have also been used to justify harsh sanctions against SWs, although such sanctions are rarely applied to their male clientele.

But these statistics also underscore the need for AIDS interventions that reach SWs and their clients, and have fueled a variety of research projects focused on these two groups. These studies have yielded important insights into how to best reach, serve and partner with women (and men) engaged in sex work. Some of the key lessons so far:

Come out of the clinic.

When asked how their projects with SWs started, researchers almost always say that the first step was to meet with the women in the streets, slums and brothels where they live and work. Meeting women in their work environments, rather than asking them to come into the clinic straight away, is an important step in building trust. “Sometimes you have to go to a bar at night to do interviews,” says Elizabeth Ngugi, the leader of a team conducting a vaccine preparedness study in the sprawling Nairobi slum of Kangemi. “There can be so much noise [in the bar] that it’s deafening, but you have created a relationship so that they are only looking at you.”

As simple as it sounds, this step usually involves lots of legwork, since SWs often work in the poorly mapped margins of cities and roadsides. The Kangemi team mapped the streets, down to the last food stall, corrugated metal hut and bar. The result—an intricately coded map—hangs on the wall of the project’s small clinic space, divided into “zones” which a team of outreach workers visits on a rotating basis.

Engage women as active partners in research.

Successful research projects have involved individual SWs and SW-led organizations in developing outreach and education projects. Some have also trained SWs as research assistants, since they can often reach other SWs and clients who would be reluctant to talk with the trial staff. For example, at the AIDSInfoShare project in Moscow, SWs are helping to collect data from other sex workers. And in South Africa, truck stop SWs who participated in a microbicide trial helped conduct a

Researchers almost always say that the first step was to meet with the women in the streets, slums and brothels where they live and work.

study of HIV *prevalence* among their truck driver clients. “I had male nurses who tried to talk to the truck drivers, and it didn’t work,” says Gita Ramjee of the Medical Research Council in South Africa. “So I spoke to the [SW] community liaison officers and asked them, ‘Is it possible to collect blood samples [from a needle prick to the finger] from the men you have sex with?’ and they said yes. They all knew what *informed consent* was—because they had gone through it themselves.”

Understand and address concerns about confidentiality.

Like injection drug users, SWs may risk police harassment or imprisonment simply for admitting that they practice a criminalized behavior. Some women may have husbands and families who don’t know that they exchange sex for money; others may have a pimp or madam who tries to control their activities. These are just some of the scenarios that can pose challenges around confidentiality for SW study participants. In each case, the trial staff must work closely with local and national authorities, and with the women, to minimize the risks of disclosure through their trial participation.

Sometimes, this means engaging the “gatekeepers” to the SWs. “The brothel keepers should be involved and taken into confidence,” says Smita Joshi, who helped establish a research project and clinic for SWs in Pune, India in 1996. Joshi and her colleagues had meetings with brothel owners, local AIDS NGOs and clinicians working in the area both before launching a microbicides trial and while it was going on.

When Gita Ramjee and her team conducted a trial of the spermicide N-9 as a potential microbicide in HIV-negative women, they found that “confidentiality with HIV test results [during the process of screening volunteers for the trial] was a major issue,” recalls Ramjee. “Sex is their trade, and there may be issues with competition to get clients. So we needed to be very careful about preserving confidentiality of serostatus.” One strategy Ramjee and her staff used was to work with potential volunteers found during screening to be HIV-positive, helping them practice explaining why they were not participating in the trial without disclosing their HIV status.

Offer non-judgmental treatment and care.

Perhaps the most important lesson from SW projects, according to several research staff, is the need to provide care and counseling in an environment free from stigma or stereotypes about SWs. “These women have values and vision. If you want to work with them, you need to keep building that trust and coming back to their values and vision,” says Elizabeth Ngugi. “Just listen to them.”

 scientific issues

In addition to the social and behavioral lessons learned, there are also scientific findings—and open questions—raised by studies in SWs.

Immune protection.

Scientific research on large groups of SWs followed over time has found that a small percentage of the women remain uninfected with HIV for many years, despite repeated acts of unprotected sex. These “highly exposed, persistently seronegative” (HEPS) or *exposed seronegative (ESN)* women appear to have immune defenses that help them resist HIV infection (although they are not 100% resistant, and some eventually do become infected). The nature of this protection remains a mystery, but several studies are trying to find an explanation. If researchers can identify the *immune responses* which give this protection, they can then try to make vaccines that stimulate these same responses.

HIV exposure, STD infection and vaccine effectiveness.

SWs often have higher rates of untreated STDs and of exposure to HIV than other women; these factors, in turn, may affect how well vaccines and microbicides work. The only way to answer these questions is to involve SWs and non-SWs in trials of these products, and to carefully gather information about types and frequency of sexual contact in both groups.

advocacy challenges

Today it is as difficult—and important—as ever to involve SWs in AIDS research, treatment and prevention activities. There are several enduring challenges:

Funding

In 2002 the US government decided to prohibit the use of federal dollars on overseas programs that work with SWs. AIDS advocates and women's groups have protested these restrictions, which have jeopardized some projects and forced others to take extreme caution in describing their work. Preserving funding for research and services that engage SWs is crucial for a truly comprehensive response to the epidemic.



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Human Rights

Sex work remains criminalized in many countries, and SWs are subject to human rights violations in many more. Researchers need to be cognizant of these circumstances, and at the very least ensure that enrollment in a sex worker *cohort* doesn't put the women in jeopardy. And where possible, they can act as allies in the realms of human rights and access to health care.

Representation

Stigma surrounding commercial sex work means that the world public rarely hears SWs describe their experiences in their own words. Giving SWs seats at the table at *Community Advisory Boards (CABs)*, conferences and policy-making forums helps break silence and stereotypes.

THE MOST EFFECTIVE WAY to address these challenges is for SWs, researchers and AIDS advocates to work together. This takes time, trust and careful thought about how to forge relationships that are beneficial and not exploitive. Many countries in Asia and the Pacific region are facing explosive epidemics, with SWs among the hardest hit populations. In these settings and around the world, reaching SWs is not only the right thing to do—it may well be essential to an effective response to the epidemic.

TANZANIA / facing page

Women in a clinical study of HIV among bar workers in the Mbeya region of Tanzania.



PAISAN SUWANNAWONG

©Karyn Kaplan

THAILAND

Paisan Suwannawong is a co-founder of the Thai Drug Users Network and, as a former injecting drug user who has been living with HIV for over a decade, an outspoken advocate on behalf of this extremely marginalized community. He also helped found several other HIV/AIDS advocacy organizations in Thailand and is active in many national and international policy arenas dealing with injecting drug use and HIV.

thai drug users network, aids and human rights: a conversation with karyn kaplan

KARYN KAPLAN with PATRICIA KAHN / thailand

Thailand is one of the few developing countries that has successfully curbed a runaway epidemic, cutting the number of new infections by almost 80% since 1991. But among injecting drug users (IDUs), who now account for about one-third of newly-infected people, the 40% *prevalence* rate hasn't budged over this time—reflecting a severe neglect of harm-reduction and HIV-prevention measures targeted to their needs. At the same time, IDUs have been not only criminalized, but more recently, subject to the government's violent "War on Drugs" that led to the killing of some 2,500 suspected drug offenders in extra-judicial killings, and to beatings, arrests and forced confessions among many thousands more.^①

Against this background, the Thai Drug Users Network (TDN) was formed in 2002 to advocate for basic human rights and health care for Thailand's estimated 100,000–250,000 IDUs and to provide peer-driven HIV prevention information. The next year they were awarded \$1.3 million from the Global Fund (GF), one of only two non-governmental organizations (NGOs) to receive funding so far outside the standard country coordinating mechanism. Here, Karyn Kaplan, International Advocacy Coordinator for the Thai AIDS Treatment Action Group (TTAG), who works closely with TDN, talks with Patricia Kahn about their work, the dire situation faced by Thailand's IDUs, and *clinical trial* participation by this highly vulnerable group.

AT THE 2004 AIDS CONFERENCE in Bangkok, Thailand's Prime Minister Thaksin announced a shift in government policy, towards more engagement in HIV prevention and care among IDUs. What's happened since then?

Thaksin said he's committed to promoting harm reduction in Thailand, and to working with the Thai Drug Users Network to make that a reality. He also said he's committed to equal access to ARVs [*antiretrovirals*] for all, including drug users. But nothing has happened yet.

Instead, three months after the conference he announced another repressive war on drugs that would employ brutal measures to crack down on people. Based on what happened last time, this only drives people underground and raises their risk for HIV.

Why the higher risk?

It's dangerous to be identified as a drug user, so people tend to go underground. There's more sharing needles, because people are afraid of being caught carrying them—police can charge you for paraphernalia possession.¹ They often use needles as evidence of drug use, or even as an excuse to plant drugs on people. A drug possession charge is much more serious.

Thaksin also spoke about introducing more harm reduction approaches. Can you describe what's offered, and whether it's changed?

Drug use is seen entirely as a moralistic, character flaw issue... There's no sense that drug use is a health issue, or that addiction is physiological.

There are tons of detoxification programs, methadone programs, therapeutic communities. But drug use is seen entirely as a moralistic, character flaw issue—if you just say no, then you can get off drugs. There's no sense that drug use is a health issue, or that addiction is physiological. There's still a lot of ignorance and resistance to harm reduction approaches, not to mention fear and misunderstanding of drug users. And stigma.

In Bangkok, 90-day methadone programs are available for free. But there's never been a successful outcome documented from giving methadone for less than two to three years. Then there are 45-day “taper” programs, which reduce methadone over 20 days, then cut it off and substitute sleeping pills or other drugs. The dramatic reduction in methadone feels terrible to drug users. And it puts them at a higher risk of overdose when they start using again.

But just last week [late November 2004], it was announced that free, long-term methadone maintenance will become available all over Thailand. The program isn't up to international standards—for example, the client has to “fail” 45-day methadone detox three times before being eligible, although there may be ways around this. And until staff are

¹Needles can be purchased in pharmacies and are legal for use in animals (for example, to vaccinate chickens), but not for injecting illicit drugs.

properly trained, my bet is that users will be pressured to *stop* methadone, which undermines the whole idea. But it's a step forward.

Have IDUs started to access ARV treatment programs, now that the rule excluding them has been dropped?²

The national guidelines no longer exclude high-risk behavior groups. But nothing has been done to promote equitable access, to pro-actively build capacity of the system to work with IDUs. For example, you can't give ARVs to IDUs without a strong methadone maintenance program—the World Health Organization (WHO) and other international experience has documented this again and again.

The government says that about 53,000 people are on ARVs through its program. Very few are drug users.

Tell us about the TDN. As a new organization tackling such enormous problems, where do you start?

One way is direct actions—appealing to the King, the Prime Minister, to stop the killing in the war on drugs. We also try to partner with government on policy issues, and push them to recognize the need for involving drug users in developing policies and making them work better.

Another approach is to work with the health care system to build awareness around drug users and harm reduction, and to build links to health services for IDUs. It's a huge challenge for the health system—they can't keep up. So we're pushing the UN and the government to allocate extra resources for training on harm reduction and capacity building, and to integrate harm reduction into AIDS care for drug users.

We also look for ways to do needle exchange without putting the workers at risk. For example, one methadone clinic where TDN members work provides needles bought with private funding to an NGO that offers peer services through the clinic. So the money never flows through government hands.

²Until April 2004, the country's guidelines for the use of ARVs specifically excluded members of particular high-risk groups, including IDUs.

What will the Global Fund money allow you to do?

The Global Fund project is mainly a peer- intervention to reach out to IDUs with information on HIV and harm reduction information, such as referrals to health care and HIV testing. Most of the money will go directly to train hundreds of peer outreach workers, educators and researchers, and to train trainers in harm reduction. We'll establish four fixed sites for harm reduction, one in each region of Thailand.

We'll also train people in collecting data. The idea is to develop a whole research network to collect data by and for drug users, from their communities—the most hard-core drug users who are never reached in current research. We're working with Thai researchers and scientists from the British Columbia Center on HIV/AIDS Excellence, which is a model of peer research. Using these data, we'll make policy recommendations based on the drug user's perspective of what they need.

How broad a net will you be able to cast?

The war on drugs throws up enormous barriers to reaching the highest-risk drug users. As things stand it's very dangerous for us.

Initially we'd hoped to reach at least 20,000 people in terms of peer support, education, linkages and so on over three years. But we've had to adjust downward because the war on drugs throws up enormous barriers to reaching the highest-risk drug users. As things stand it's very dangerous for us to go out in the field and do HIV prevention work. We've gotten no signal from the government that they will help ensure the safety of our workers.

We're trying to negotiate and navigate in the government. There needs to be some genuine support, even if it's behind the scenes. Other parts of the government, like the Bangkok Metropolitan Authority and sections of the Ministry of Health, are also initiating peer outreach interventions among drug users. We don't know how the government thinks it will protect even its own workers in this climate.

Let's turn to vaccines and clinical trials. Did the VaxGen trial leave an impact on the IDU community?

I'm not sure people would claim that anything is better for drug users because of the VaxGen trial. Obviously the point of the trial wasn't to improve the situation of drug users. But that's *our* agenda as a drug user advocacy and human rights group.

That's really hard, I understand. Until TDN there *was* no community—because of their illegal status, IDUs can't form an NGO. [The TDN is an informal network rather than an official organization.] So there were no drug users who could say they represent other drug users, and no NGOs working on drug user issues. But without this, who's protecting the interests of the drug users in the context of a trial?

Looking ahead, we're wholly supportive of any intervention that can benefit the global AIDS situation. But we're going to have a hard time supporting trials that don't give due consideration to the human rights situation of drug users here. It's not risk-free to be involved in a clinical trial as an IDU in Thailand, given the current climate.

Is TDN involved in discussions about any upcoming clinical trials?

We were approached by Thai/US CDC³ staff. They're planning a tenofovir prevention trial⁴ among high-risk groups in Thailand, including IDUs, and they want us to be involved. We were very glad for the opportunity to sit down with them and raise some initial questions. We're trying to bring in the broader Thai NGO and PWA and drug treatment communities, learn more about the trial plans and see where we can have influence in making it better in terms of what the participants will be offered. We don't know how much we'll be able to influence the *protocol*, but we're talking with the researchers.

³A long-standing collaboration between researchers of the Thai Ministry of Public Health and the US Centers for Disease Control, which also carried out the VaxGen trial.

⁴This international study will test whether a once-daily dose of tenofovir, an ARV drug, can prevent HIV infection in people at very high risk.

As it now stands, the other groups being enrolled in the trial are at risk for sexual transmission, and they'll all be given condoms. But IDUs still don't get clean needles. It's a taboo that just won't break.

Have other community advocates taken up issues around clinical trials?

Although Thailand has PWA groups, and tens of thousands of IDUs living with HIV, very few are involved in advocacy. Even in other [treatment] trials, the PWA groups are often hospital-based, and they're more about medical information.

But almost no one living with HIV/AIDS in Thailand knows about how clinical trials work, what are my rights, what do I need to ask. So people often look at trials as something they need to do because they've got AIDS, they're made to feel that their lives are a mess, and this is an opportunity to do something good. And they receive services through the trial, so they won't say no. It's a very un-level playing field.

There are a few people out there trying to focus on community involvement in clinical trials, in vaccine trials. But there's too much going on right now with ARV scale-up, where PWA organizations are doing a huge amount of work providing services. There's nobody left to do anything else, like advocacy.

Part of the problem is also that people focus on their own agendas. We have our advocacy priorities, and the researchers are focused on getting their trials off the ground. There are very few people in the IDU community with the capacity to serve on a *Community Advisory Board (CAB)*, and it's not their priority.

Can trials somehow be part of the solution?

So far the trials haven't spent enough time or money on community preparedness, education, literacy. They need people whose job it is to do this work, not just depend on overburdened, unpaid PWAs.

When it comes to IDUs, trial infrastructure rarely includes anything for participants that's sustained beyond the trial.

There needs to be much more investment in the services they offer—for example, for people who turn out at screening to be HIV-positive. Trials need to provide strong linkages and referrals to ARV programs, and to invest in strengthening IDU services at ARV treatment sites.

There also needs to be more investment in the community. Do a better trial that has a longer-term impact, both for the participants and the broader community. Create real opportunities for community discussion. Have community liaisons with real input. Ask the community what we can set up that might build capacity in terms of trials. Work to make trials healthy for the community.

These issues are new here, since real community involvement is new. There haven't been people at the table before talking about what we're getting after the trial is over. Most people see trials as access to health care, or things they'd never get otherwise. But IDUs are going to fight for access to treatment *without* having to join a trial.

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resource

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ADOLESCENTS

People between the ages of 13 and 25 account for about half of all new HIV infections worldwide, and 40% in the US. Unless adolescents are included in HIV vaccine trials that could lead to licensure, they may not have access to an effective vaccine as soon as one becomes available—preventing them from sharing in the benefits of vaccination right away and hindering efforts to curb the epidemic. But including young participants will mean working through the extra challenges and planning trials in ways that meet their needs.

adolescents and aids vaccine research in the united states

AUDREY SMITH ROGERS / usa

HIV THREATENS young people as never before. Worldwide, about half of all new infections among adults are in people under age 25, and the numbers keep getting worse. In the US, this age group accounts for roughly 40% of newly infected people.

This makes adolescents one of the most important groups to reach with effective prevention steps. It also means that an HIV vaccine, or any other new prevention tool researchers are trying to develop, *must* work for adolescents if it's going to have the most impact on the epidemic. For these reasons, launching an HIV vaccine trial that could lead to licensure, but not including adolescent participants in the trial, is simply not an option that makes public health sense.

But involving adolescents in vaccine trials raises some issues that don't come up, or are easier to resolve, with adult volunteers. So it won't be enough to simply mandate the inclusion of youth—it will take attention to working through these extra challenges and developing trial procedures and practices that meet the needs of young participants.

some key challenges and what we can do about them

Permission from parents

People below the legal age of consent (18 in the US) can participate in a *clinical study* only if a parent or legal guardian gives permission. In the US (and most countries) this is a federal regulation and is meant as a protection for teens—who are able to understand information as well as adults but usually don't have the judgment born of experience.

Parental permission brings in some complicated issues. Trial staff must include a parent or legal guardian in the *informed consent* process. Staff must also make sure that both parent/guardian and adolescent fully understand the information they've been given and get answers to all their questions. At the same time, staff need to honor and protect the adolescent's privacy, since his/her personal behaviors when it comes to drugs and unsafe sex will be discussed with the trial's HIV counselors.

Engaging communities

Faced with a decision about their son or daughter's participation, parents may look for guidance from people they trust and respect in the community. This means that the vaccine education process shouldn't stay within the clinic walls or involve only prospective participants. Nor can it be a passive exercise of simply providing information. What's needed instead is active engagement with influential people and representatives from "anchor" institutions in the community, such as churches, youth-serving organizations, and local professionals, where parents will turn for advice. But more importantly, an invitation to the community's key social structures to "co-own" the vaccine effort establishes an extra layer of protection for teen participants.

Countering "vaccine optimism" and adjusting to teen behavior

One big worry among community members is that the idea of receiving a preventive vaccine might influence young people

to behave in riskier ways, because they think they're protected from HIV. Therefore, young participants will need risk reduction counseling tailored to their needs and subculture. They will also need other types of customized care, since the rigor needed for research trials (for example, in keeping regular clinic appointments) is not a natural fit with the unstructured lives of many teens. Extra support from trial staff can help young volunteers adapt to the responsibilities of participation.

Explaining vaccine seropositivity

Another issue needing special attention is the possibility that a vaccine may induce *immune responses* that give a positive result on an HIV test even in an uninfected person. Parents in communities hard-hit by AIDS have seen HIV-infected family members or neighbors shunned, and are deeply fearful of their own teens getting infected and falling to the same fate. So the prospect of a test result that unfairly stigmatizes their children would be very difficult to accept. This makes it especially important for trial staff to explain clearly that this potential problem can be avoided, and to make sure that parents and participants know what to do if the issue arises.

community acceptance of youth in vaccine trials

IT'S WELL DOCUMENTED that many ethnic and racial minority communities in the US (especially among African Americans) are resistant to participation in clinical research. Their reluctance is easy to understand, based on history: The legacy of mistrust left by past instances of highly unethical *clinical trials* doesn't vanish quickly. When the stigma associated with HIV is added, it should come as no surprise that the number of minority volunteers in HIV vaccine trials in the US is much less than what might be expected, considering the impact of AIDS in their neighborhoods.

This issue made headlines around the world in February, 2003, when the biotech company VaxGen claimed from its just-completed *efficacy* trial that the company's HIV vaccine

candidate seemed to work in African-Americans, Asians and mixed-race people, but not in Caucasians. But outside scientists quickly spotted an error in VaxGen's statistical analysis, based on the fact that there were too few African Americans in the trial to draw any firm conclusions about them as a distinct "sub-group"^① (also see chapter 22 for a discussion of this trial). In the months that followed, more in-depth analysis confirmed that the vaccine was ineffective.

But the episode stunned the African-American community by sowing confusion and laying bare what's at stake in clinical studies of vitally important vaccines and drugs. Time will tell if it also changed peoples' attitudes about getting personally involved. But even (or especially) if it did, this won't change

what it will take to win the trust of minority communities if their healthy young people are asked to take part in HIV vaccine studies.

It gets more difficult every day for parents in hard-hit areas to deny the impact of HIV in their midst. The big unknown is how they balance the perception of this new and

devastating risk to their children with the perception of risk from exploitation at the hands of a clinical research system that historically broke trust with them. Helping to sort out the different, sometimes conflicting attitudes of family members about allowing their teens to participate in vaccine research is difficult, but it needs to be done.

In 2001, the US National Institutes of Health (NIH) held a consultation with representatives from ethnic and racial minority communities on adolescent participation in HIV vaccine research. These representatives voiced very clear positions. First, they emphasized that communities have the right to decide for themselves about participation, and the government has the responsibility to give them all the information they need to make informed decisions. Second, no one should expect that communities will accept a vaccine trial as the only HIV prevention intervention for their youth. In other words, these communities will consider vaccine trial participation only if it is offered as part of a spectrum of prevention activities that provide a safety net for their young people.

It gets more difficult every day for parents in hard-hit areas to deny the impact of HIV in their midst.

preparing the ground: prevention infrastructure

Within the US, responsibility for establishing this infrastructure belongs to the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). The ATN is a network of 15 research centers with a broad, adolescent-focused HIV research agenda that includes both prevention and treatment studies. In building prevention infrastructure, ATN works with the HIV Vaccine Trials Network, both of which are funded by the NIH.

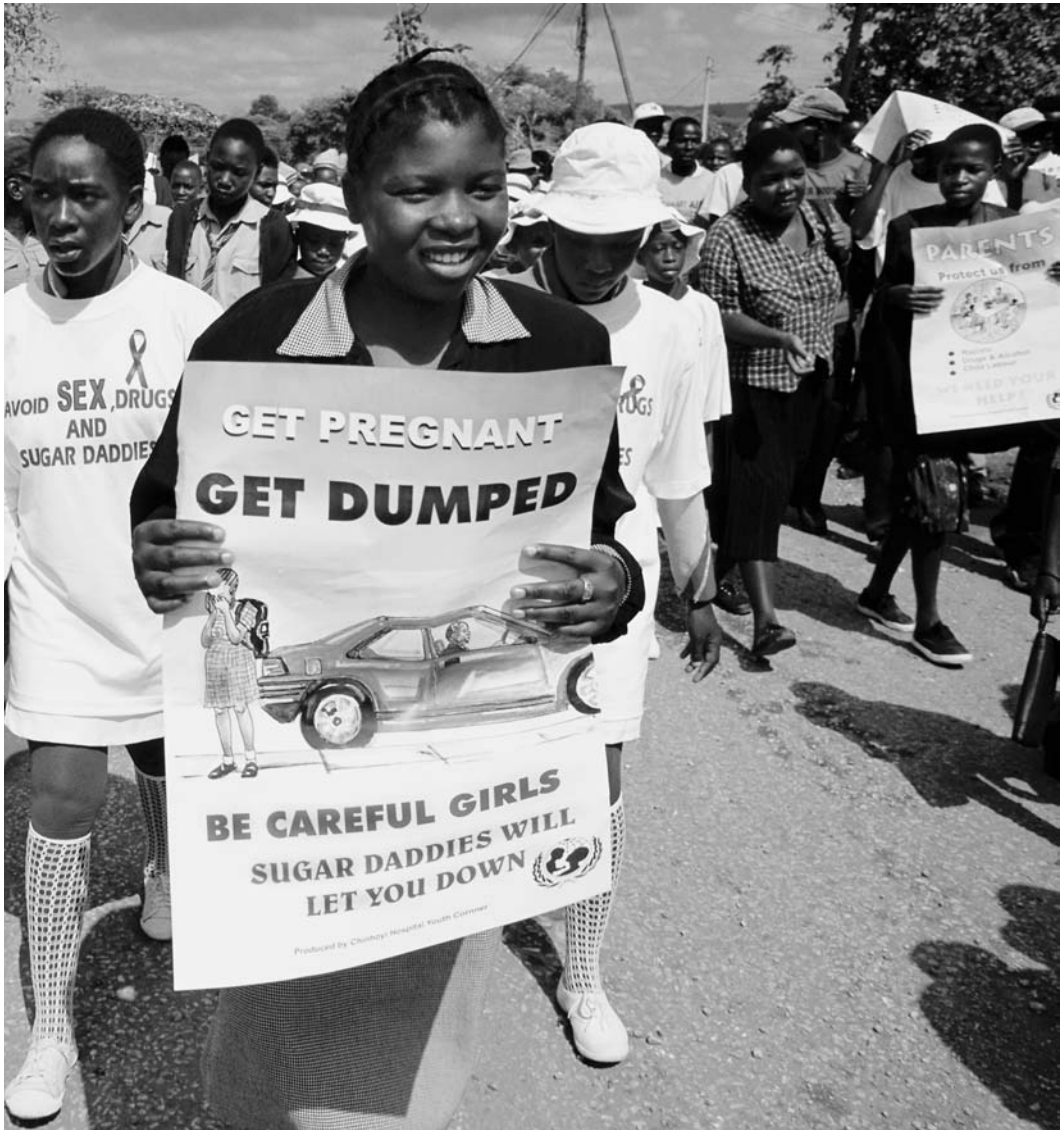
The centerpiece of these efforts is an ambitious community mobilization project called Connect To Protect® (C2P), which involves three phases. The first one identifies areas with clusters of high-risk behaviors (which mean higher risk of HIV infection) and then looks more closely among youth at what drives these high rates. The second phase seeks out potential community partners and invites them to the table to collaborate in deciding on the prevention strategies likely to do the most good. The last phase, the actual community mobilization, works on making sustainable changes in the community to improve the health of its youth. It is in this last phase that communities should be able to consider HIV vaccine research as an addition to their prevention efforts.

Planning vaccine studies that can incorporate teens and meet their needs will be labor- and resource-intensive; it will be frustrating and costly. It will require clinical researchers to break out of their traditional, comfortable approaches to recruiting volunteers and enter into a genuine partnership with the communities that ultimately have so much to gain if researchers succeed in developing an effective vaccine.

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For resources on Adolescents and AIDS vaccine trials, see chapter 29.



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ZIMBABWE

Zimbabweans holding signs and marching in a youth AIDS rally in Chinhoyi in Zimbabwe organized by the community group Batsarai (from the Shona word for help).

adolescents in hiv vaccine trials: perspective from botswana

TONYA L. VILLAFANA, NTHABISENG PHALADZE, CHRISTINE STEGLING,
RUPERT HAMBIRA, PENINAH THUMBI, JOSEPH MAKHEMA / botswana

HIV/AIDS IMPOSES a staggering burden on the young people of Botswana, a country that sits at the epicenter of the AIDS epidemic in sub-Saharan Africa. Infection rates begin rising sharply in the teen years, especially for females: Nearly 1 in 4 girls between 15 and 19 years old are already HIV-positive (23% compared with 2% for boys). By the time they reach the age of 25–29 nearly half of the women are infected—three times the rate in males.^① (The numbers become about the same for men and women only in older age groups.) Many of Botswana's neighbors show a similar pattern of very high *prevalence* rates in young women.

Prevention methods appropriate for youth are therefore desperately needed in this region. Yet the inclusion of adolescents in future trials of HIV vaccine candidates is a challenging and controversial issue.

The government of Botswana has been a regional leader in the area of HIV/AIDS awareness, prevention and treatment, and was the first to implement several groundbreaking initiatives for its citizens. For example, in 1999 the country launched a national program to prevent *mother-to-child transmission*,

followed two years later by nation-wide *antiretroviral* treatment for HIV-infected individuals meeting specific clinical criteria (including an AIDS-defining illness or *CD4+ T-cells* count below 200). In June 2003, Botswana became the first country in southern Africa to begin *clinical trials* of an experimental HIV vaccine.

Nearly two years before starting this vaccine trial, a *Community Advisory Board (CAB)* was established in Gaborone, Botswana's capital city. In March 2003, the CAB held its first ethics workshop to discuss issues concerning HIV vaccine trials in the country, amongst them the need to lower the legal age of consent (which stands at 21 years as of August 2004) so that younger people can participate in future trials. For our present trial we received permission to enroll participants starting at age 18. Looking towards the future, the National AIDS Council

Recognizing that many youth are sexually active well before age 16, it will be important to consider including younger participants in the long run.

has already recommended to the Ministry of Health that the legal age of consent for HIV testing should be lowered to 16 years of age. If this recommendation is adopted, it could support the case for doing the same in future vaccine trials. Recognizing that many youth are sexually active well before age 16, it will also be important to consider including younger participants in the long run.

The issue of adolescent involvement in HIV vaccine trials continues to be debated in Botswana and the region, within the Gaborone CAB, the National HIV Vaccine Committee and among trial researchers. The views presented here have evolved through extensive discussion among CAB members, community educators, investigators and clinicians involved in the current vaccine trial and vaccine-related research.

We see many reasons to include adolescents in HIV vaccine trials in Botswana. First and foremost is the need to protect this extremely vulnerable group, especially the females. Overwhelmingly, reports from Botswana (and several other countries in sub-Saharan Africa) suggest that young women's first sexual partners are older, more experienced men, and that this inter-generational sex is a major contributor to the epidemic. Given the burden of HIV/AIDS on the country's

young women, we must ensure that they are amongst the first group to access an HIV vaccine that's been proven to work.

For this to happen, the late stages of vaccine testing need to involve studies that can prove safety and effectiveness in young people. So if adolescents are not included in the relevant late-stage trials, their access to newly licensed vaccines is likely to be delayed. The UNAIDS guidance document on HIV vaccine research endorses the testing of HIV vaccines in children, including infants (who are at risk of infection via breast milk) and adolescents, once these vaccines have been tested for safety in adults. It also emphasizes the need to put the necessary ethical and legal structures in place.^②

the challenges

However, we also see the challenges raised by the enrollment of adolescents and have thought a great deal about how to address them. So far, people below the age of 18 have not been included in HIV vaccine trials anywhere in the world (except for two North American trials in babies, involving already-well-tested candidates). Since HIV vaccine trials are new to Botswana and the region, governments, regulatory agencies and community groups may hesitate to be first in allowing or advocating for the involvement of adolescents. Government officials may be accused of allowing their youth to be used as “guinea pigs” in an area of research where no precedent has been set, and communities may be inherently suspicious and fearful. For these reasons, a broader regional (and even global) movement in favor of adolescent participation could help garner support for such a decision, especially if it incorporates thoughtful communication strategies that explain the rationale and help dispel fears and myths about HIV vaccine research.

Another difficult set of issues is that enrolling adolescents would clash with widespread cultural taboos in discussing sex with young people and in acknowledging their sexual activity and risk of HIV infection. A recent assessment of needs in Botswana's schools^③ found that few parents were active in educating their children about AIDS, since they did not

consider it their responsibility. Nor did most of them attend meetings on this subject when invited—although they were comfortable with their children learning about sexuality and HIV/AIDS-related issues at school. Respondents felt that, while parents were concerned about increasing promiscuity among youth in general, they denied that their own children were sexually active.

Other new data add to this picture of widespread denial. For example, most sexually active 10–24 year olds in a recent Ministry of Health survey did not consider themselves at risk for sexually transmitted diseases (STDs), even though they generally used condoms inconsistently and 10% had experienced an STD in the past year. The survey also found that perception of pregnancy risk among 15–24-year old women participants was low, although a third of them had been pregnant at least once. These data show clearly that youth in Botswana *are* sexually active, but ill-informed about safe sex—which again emphasizes the urgent need for HIV/AIDS interventions targeting adolescents.^④

Informed consent for adolescents will also be a major issue in countries such as Botswana, which have a more “communitarian” ethic rather than an individualistic one.

Informed consent for adolescents will be a major issue in countries such as Botswana, which have a more “communitarian” ethic rather than an individualistic one.

Before deciding to volunteer for an HIV vaccine trial, potential (adult) participants usually consult with their partners and families, who may themselves consult others. But independent of how people reach their personal decision is the legal issue of parental permission for adolescents younger than 18 (or whatever the age of full consent may be in a given country). It also raises the question of confidentiality for adolescents concerning their sexual activity.

Ensuring full informed consent may also be challenging in this age group due to some adolescents’ lack of assertiveness in their lives in general, and to questions about their ability to weigh all the important factors relevant to participation. A recent study of children and adolescents participating in research in the USA found that they fully understood concrete issues such as the duration of the study

and any benefits to themselves, but had difficulty with more abstract concepts such as the purpose of the study and benefit to others—perhaps because their more limited life experience made it harder to see their trial participation in a broader context.^⑤

From a legal perspective, another issue that needs clarification is the definition of adolescents in a given population and their rights within that population—definitions that may vary even within a single country. For example, the Botswana Constitution defines a young person as age 21 and below; the National Youth Policy covers those aged 12–29;^⑥ the Children's Act covers those aged 0–18 and the Adoption Act covers 0–19 year olds.

recommendations

WHAT STEPS should be taken to facilitate participation of adolescents in vaccine trials in Botswana?

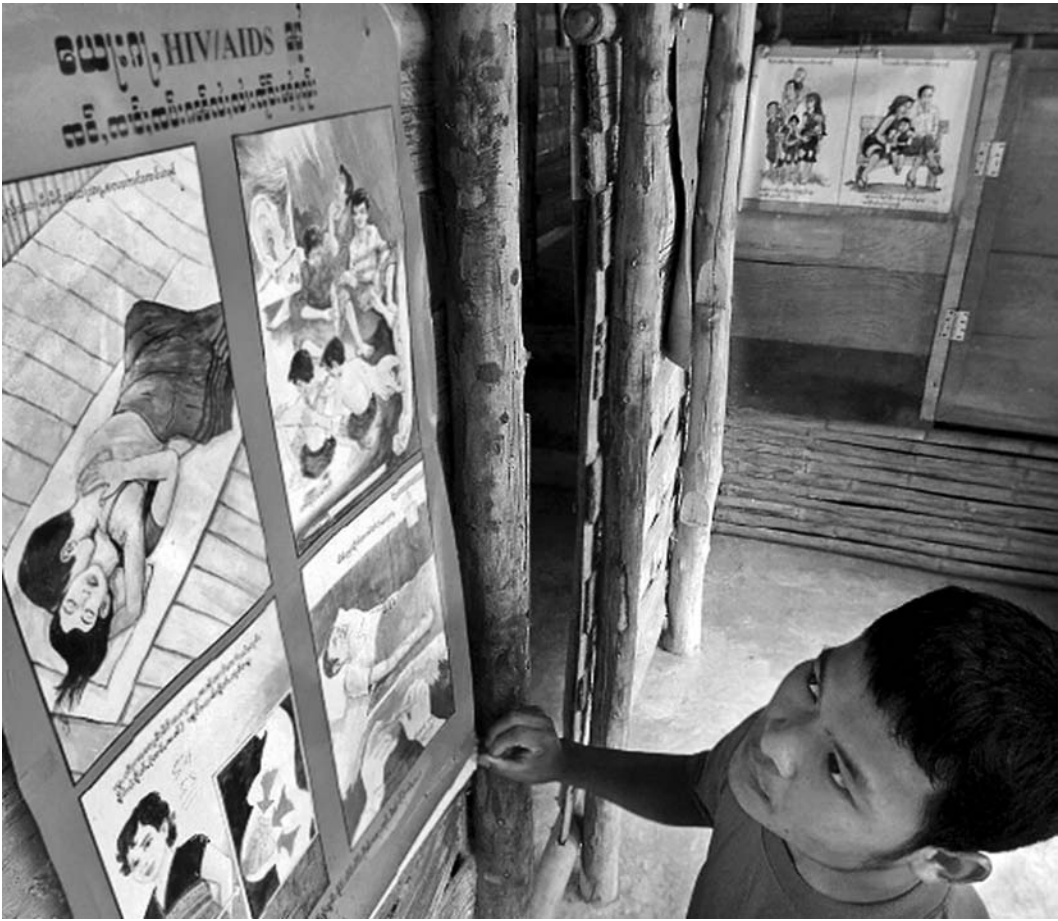
- › Public debate should be generated, with advocacy for adolescent participation led by key stakeholders such as the National HIV Vaccine Committee, CABs, people living with HIV/AIDS, and most importantly, Botswana youth and the organizations that represent them. The issue can also be debated at the National AIDS Council, a multi-sectoral committee chaired by Botswana's president; this group addresses HIV/AIDS in a comprehensive manner and includes representatives of youth organizations. Consensus building in this forum will also need to include national regulatory authorities.
- › Surveys should be conducted among youth and their parents to understand the degree of willingness to participate, and under what circumstances. This work should also survey attitudes and potential solutions to the adolescent-specific issues raised here, plus any new ones that might emerge from HIV vaccine research. Measures to implement solutions that are acceptable to the various stakeholders should be firmly in place before trials begin.

- › Only the most promising vaccines should be tested in youth, and only after safety data from adults show no sign of problems—with the caveat that uncommon side effects can emerge for *any* experimental product (or even newly-licensed vaccine) as more people are vaccinated. The trial must be set up to detect and treat any potential problems immediately.
- › All necessary legal structures should be in place, including clear guidelines on compensation for research-related injuries, particularly long-term injuries that have a greater potential impact on adolescents compared with adults.
- › Meetings should be held with the national regulatory agency to understand the requirements for conducting trials in young people and for eventually licensing a vaccine for use in adolescents. In addition, the national agency should consult with other regional authorities and WHO.

Daunting as these challenges may appear, they are not insurmountable—as demonstrated by the successful launch of international *efficacy* trials for vaccines against other sexually transmitted diseases, which involve participants as young as 10 years old (see chapter 30). Lessons learned from these experiences and greater collaboration among all stakeholders will help to ensure that HIV vaccine trials in adolescents can occur in an ethical, safe and efficient way.

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THAILAND

A young man looks at an HIV/AIDS prevention campaign poster at a refugee camp in northern Thailand.

testing STD vaccines in young people: how it's done

HUNTLY COLLINS

THE AIDS VACCINE field is now thinking hard about whether, when and how to test candidates in adolescents, and on working through the many challenges this would entail (as the previous two articles, chapters 28 and 29 describe). But surprisingly to many people, thousands of adolescents and pre-adolescents are already participating in international trials of promising vaccines against two common sexually transmitted diseases (STDs): cervical cancer and genital warts, which are caused by *human papilloma virus (HPV)* and the *herpes simplex virus (HSV)*, respectively. These studies are being done by the pharmaceutical giants that developed these vaccines—Merck & Co. and GlaxoSmithKline (GSK).

Whether or not these experimental products turn out to work, the experience gained in conducting the trials holds valuable lessons for the AIDS vaccine field. “Enrolling adolescents is not impossible,” says Susan Rosenthal, a psychologist who specializes in adolescent and behavioral health and advised both companies on their vaccine studies. “You just have to know how to do it.”

What's unique about *clinical trials* in adolescents is that two people must participate in the enrollment process for the study—the young person and the parent (or legal guardian). And with trials involving sexually transmitted diseases, the fact that the trial subjects are minors raises sticky ethical and legal issues.

What's unique about clinical trials in adolescents is that both the young person and a parent must participate in the enrollment process.

For example, *efficacy* studies—which test whether the vaccine actually protects people—enroll only people who are at high risk of a particular disease. That's because there have to be enough infections occurring over the course of a trial to tell whether the vaccine reduces the chances of infection when compared to a

placebo (dummy vaccine). Efficacy trials of an STD vaccine in adolescents would, in effect, require that adolescents be sexually active and therefore at risk for STDs.

But many teenagers could face punishment and ostracism by their families if they admitted they were sexually active. In places where there are laws forbidding people below a certain age to have sex, there could also be legal consequences.

Merck and GSK have both managed to deal with these and many other issues as they planned and launched international trials of their STD vaccines in recent years.

Merck began large international trials of its HPV vaccine, aimed at preventing cervical cancer, in 2001. Most of the 25,000 participants are adults over the age of 18. But 5,000 to 6,000 trial participants are adolescents and pre-adolescents, including children as young as 9. The reason, says Eliav Barr, the physician who oversees the trials in youth, is “our expectation that the best time to administer the vaccine [assuming it proves to work] is pre-adolescence, just prior to sexual debut.”

The youth studies enroll both girls and boys. While boys obviously don't get cervical cancer, they can get genital warts from HPV. They also transmit HPV to girls, even if boys themselves have no symptoms.

Merck is conducting two separate (and very different) trials: one for pre-adolescents, which includes youth between the ages of 9 and 15, and another which enrolls adolescents aged 16 to 18.

The study among the younger children is known as a *bridging* study. Rather than testing efficacy, bridging studies test the safety of the vaccine and its ability to induce *immune responses*. In effect they create a bridge to the adult efficacy studies: If the vaccine protects adults against HPV and stimulates similar immune responses in adults and youth, then it is assumed to work for youth as well. The advantages of this approach are that it is much smaller than an efficacy trial (that is, it involves fewer participants), and it avoids the need for participants to be at risk for the disease.

On the advice of experts in adolescent medicine, Merck decided that the study should not involve pelvic exams to diagnose HPV (done by Pap tests of cervical samples), since this would probably discourage participation. Consequently, they decided to enroll only virgins, who are HPV-negative. But to rule out HPV infection in participating girls, their blood was screened for *antibodies* to HPV both before and periodically during the trial, a test that detects exposure to the *virus* although it is not commercially licensed for diagnosis.

To identify potential participants, Merck developed a brochure that gave sexually active youth the chance to opt out of the study without explicitly saying they were sexually active—a strategy that allowed the company to avoid the ethical and legal dilemmas involved in asking (and finding out) whether a young person is having sex. The brochure, written at the fifth grade level, explained the study and clearly spelled out that participants had to be virgins. At the end, each person was asked to check one of two boxes—one that effectively said, “I do” want to participate, and another that said “I don’t.” It was the company’s version of a “Don’t ask, don’t tell” policy.

In addition to youth assent to participation, the company also got written parental permission, as required by law. The informational materials used in this process stressed that infection can lead to potentially fatal cervical cancer, rather than the fact that the virus is sexually transmitted (although this was clearly stated). “The key thing is to educate parents about the disease without emphasizing sexual transmission,” said Barr. “Parents will do the world for their children. They just don’t want to think about them having sex.”

Merck also told parents up front that they would have to leave the room when doctors discussed sexual activity with their child or did a physical exam. At the same time, the company told young people it could not guarantee that their parents would not be told if they became pregnant during the trial or developed an HPV infection.

The trial, which will end in 2005, has enrolled youth from more than 15 countries, some in the developing world. All are countries where Merck has subsidiaries, which helped with planning the trial and writing the educational materials. The sites showed wide cultural differences—such as those involving age level, the depth of information considered appropriate, and language—that had to be taken into account. In the end, the strongest recruitment was in developing countries, where cervical cancer is often the leading cancer among women.

Another issue was offering a direct return to participants. In Spain and Canada, local authorities wanted young people to get some health benefit in return for their participation. So in Spain, Merck gave them free hepatitis A vaccine; in Canada, free meningitis vaccine.

Merck's trial among older adolescents, ages 16–18 years, is an efficacy trial, and therefore has different entry criteria than the bridging study: Participants must be sexually active—or plan to be sexually active soon—and they must have five or fewer sexual partners. At entry, they are screened for HPV by pelvic exam. By focusing on older youth for this trial, Merck has been able to enroll young women based only on their own consent in some parts of the world. For example, in Europe, youth aged 16 and older do not need parental permission to get medical care related to reproductive health. So older youth seeking contraceptives at medical clinics, among other scenarios, could volunteer to join a trial without parental involvement. As in the US, this practice is based on the notion that young women who take the initiative to seek medical care on their own, where this is legally allowed, show a level of maturity that is also relevant to participation in clinical trials.

GSK's experience with its vaccine against HSV type 2, the virus that causes genital herpes, parallels that of Merck in many ways. In 2004, the company launched two trials in girls aged

10–17, and a third will begin in 2005—collectively enrolling 7,000 participants. Boys are not included because previous studies in adults suggested that this particular vaccine does not protect men—a surprising outcome that scientists are trying to confirm and understand. The trials are being conducted in the US, Canada, Australia and 15 countries in Europe.

The three HSV trials among youth are all designed as bridging studies, and are running in parallel with a US government-sponsored efficacy trial among 7,550 women (ages 18–30) in the US. By deciding to enroll youth only in bridging studies, GSK has avoided the problems involved with efficacy trials in young people. Like Merck, GSK consulted widely with experts in adolescent medicine before getting started, and it chose trial sites with extensive experience in adolescent medicine.

Such experience, experts say, can make a big difference. For example, if pelvic exams will be done, staff must know how to do them sensitively and quickly. Staff also need to truly like youth—and to understand that small gestures, such as birthday cards or baseball caps, can let young people know they are valued. “Kids can be incredibly needy for adult time and attention,” Rosenthal said. “It’s important to give them that. At the same time, study nurses need to be trained to set appropriate boundaries.” Other approaches tailored to these trials include age-appropriate written materials, directing youth to websites that cater to the sexual health of pre-teens, and limiting the number of clinic visits and blood draws.

Both GSK and Merck say that the US Food and Drug Administration (FDA) has been very understanding of the challenges in doing these trials. But while the agency has endorsed the bridging studies, it remains to be seen whether the data they generate will be considered adequate to get FDA approval for using the vaccines in adolescents.

Whatever the outcomes, the experience gained from these trials drives home the point that the AIDS vaccine field doesn’t have to start completely from scratch in designing trials for adolescents. Other people, says Rosenthal, “have been thinking about these issues for a long time.”

These trials drive home the point that the AIDS vaccine field doesn’t have to start completely from scratch in designing trials for adolescents.

RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men
in New York and California
—8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the diagnoses, mostly in New York City and the San Francisco Bay area, are alerting other physicians who treat large numbers of homosexual men to the problem in an effort to help identify more cases and to reduce the delay in offering chemotherapy treatment.

The sudden appearance of the cancer, called Kaposi's Sarcoma, has prompted a medical investigation that experts say could have as much scientific as public health importance because of what it may teach about determining the causes of more common types of cancer.

First Appears in Spots

Doctors have been taught in the past that the cancer usually appeared first in spots on the legs and that the disease took a slow course of up to 10 years. But these recent cases have shown that it appears in one or more violet-colored spots anywhere on the body. The spots generally do not itch or cause other symptoms, often can be mistaken for bruises, sometimes appear as lumps and can turn brown after a period of time. The cancer often causes swollen lymph glands, and then kills by spreading throughout the body.

USA

The New York Times
July 3, 1981

a queer eye on aids vaccine development

EDD LEE

GAY MEN have always had a major role in the story of HIV and AIDS. We had no choice. We were among the first to fall sick and to die. In the US it began in 1981 as otherwise healthy gay men fell ill and died of a mysterious illness that would later become known as AIDS. It was soon discovered that anyone, not just homosexuals, could develop AIDS. But gay men in the US were the first to mobilize in fighting this terrible disease.

AIDS vaccine development went down a different route—one that was more science-driven and less community-based. Yet in less visible ways, the gay community has also made important contributions to vaccine efforts, both as *clinical study* participants and pioneering vaccine advocates.

Perhaps most important, in their early, unwavering commitment to fight the disease—which quickly began appearing in many parts of the world—the gay community spawned a movement to fight AIDS globally, and still play a leading role today.

hiv/aids: the gay call to arms

Fear of the disease led to a new kind of prejudice: Prejudice against people with AIDS.

As AIDS started making newspaper headlines in the early 1980's, the growing prejudice was becoming obvious: While hemophiliacs were viewed as innocent victims, gay men and drug users were portrayed as having brought AIDS upon themselves. Fear of the disease led to a new kind of prejudice: Prejudice against people with AIDS.

Homophobia, AIDS-phobia and trauma from the deaths of so many gay men collided to spawn an explosive wave of activism

among gay men and lesbians in the US. Organizations like Gay Men's Health Crisis (GMHC), AIDS Coalition to Unleash Power (ACT UP), the KS Foundation (later renamed the San Francisco AIDS Foundation) and groups of people living with AIDS (PWAs) created the modern AIDS movement, calling for rapid development and access to AIDS treatments, prohibition of AIDS-related discrimination and public education. PWAs changed how they dealt with health care providers, becoming more active co-decision makers. They also demanded (and won) a seat at the table with scientists, policy makers and funders responsible for forging a national response to the new disease, and they injected a sense of urgency into the slow, business-as-usual pace of the medical research establishment and the regulatory agencies that approve drug trials and licensing.

Outside the US, gay men also mobilized to demand public education campaigns and care for people with AIDS—through actions like the *Grand Fury* and the *Grim Reaper* education in Australia, and the work of AIDS activists and non-governmental organizations in Brazil (see chapter 40), South Africa and many other countries. As in the US, they also pressured governments to address the growing social discrimination. In many of these settings, including the US, their success reflected the fact that most of the leading figures were Caucasian men (somewhat reflecting the modern-day ruling class) who knew how to work the political system.

aids vaccine research: is it queer as folk?

Yet when it came to vaccines, the gay community was initially uninvolved, even skeptical. Many worried that too much focus on a preventive vaccine would give homophobic policy makers a way to address the AIDS crisis while neglecting the needs of the socially unacceptable homosexuals—a reaction to the negative backlash AIDS had created for the gay civil rights movement in the US and the reluctance of then-President Reagan to even acknowledge a disease that was first called “Gay-Related Immune Disorder.” So gay activism stayed focused mostly on the development of treatments for those infected, with fears about vaccines subsiding only after the advent of *antiretroviral* (ARV) combination therapy.

While a few gay individuals joined the effort to develop an AIDS vaccine, the community overall did not take on the same leadership role as advocates that it had for AIDS early on. Instead gay men began to play a critical role as a key population for clinical studies. In the US and Europe gay men represent the largest and most easily accessible group at high risk for HIV infection. And they were highly motivated to participate—for example, in the “Jumpstart” and HIVNET vaccine preparedness studies in the early and mid-90’s, which collected epidemiological and behavioral information on high-risk communities, and “Project LinCS: Linking Communities and Scientist,” which identified key issues in working with these communities. The latter study found that social challenges such as trust of biomedical research, past experiences of discrimination and adequate *informed consent* had to be addressed before many people would consider volunteering for a vaccine trial.

More recently, the world’s first test of an AIDS vaccine (called *AIDSVAX*) for its ability to prevent HIV infection was carried out in a study population of nearly 5,000 gay men and about 400 high-risk women. Although the vaccine turned out to be ineffective, it did provide some key lessons for future clinical trials (see chapter 22). One is that it is possible to conduct large-scale trials involving thousands of high-risk, HIV-negative gay

men (and women at risk). Another is that risk behavior didn't increase in these volunteers, nor did they experience social discrimination as a result of their participation—concerns that had loomed large before this study.

is the future of aids vaccine research happy and gay?

The involvement of gay men in vaccine research will continue to be critical. Although a lot of attention now goes towards developing trial capacity in developing nations with severe AIDS epidemics, trials in the US will have to work with communities such as gay men, communities of color and injection drug users.

But volunteering for clinical trials is only part of the picture. Members of the gay community continue to be savvy AIDS advocates in the US and Europe, which contribute most of the funding for AIDS vaccine research. Their influence and experience gained over nearly 25 years of battling AIDS can bring enormous energy to the vaccine effort by helping to integrate it more closely into a comprehensive response to the pandemic and by setting higher standards for community involvement.

Yet keeping gay men invested in the hope of an AIDS vaccine is not without its challenges. The immediate need to address issues such as barebacking (the practice of intentionally seeking out unsafe sex), substance use and increased rates of sexually transmitted infections among gay men compete for the community's attention, especially since, at best, an effective vaccine won't be available for years. There's also a growing level of "AIDS fatigue" in the gay community, with some people simply losing interest in talking about HIV/AIDS—especially now that ARV therapy has drastically reduced the number of AIDS deaths in wealthy countries and gay marriage has become a headline-grabbing issue.

Involving a more diverse group of people in clinical studies is another high priority, as the VaxGen trial so glaringly showed. Discussions of "the gay community" often imply a monolithic

group, typically assumed to be white men. Efforts to engage this community that ignore racial, ethnic, cultural language differences and the needs of gay women further marginalizes minority gay men—even as the US epidemic shifts more and more toward minorities (and women), particularly African Americans and Latinos.

Adding to these challenges is the alarming resurgence of institutionalized homophobia in the US government. As reported in the *New York Times* (April 18, 2003) and elsewhere, one sign of this came when some scientists were unofficially advised by NIH project officers to remove certain words from the titles of their research proposals: If it looks like it's about gay men, sex workers or drug users, the scientists were told, it could cause problems for your funding. Other recent “shifts” in public health policy have “de-prioritized” the gay community in HIV prevention, which is particularly concerning given ominous signs that HIV rates may be rising in this group.

HOW CAN VACCINE ADVOCATES overcome these challenges? Several strategies come to mind.

- › AIDS advocates must be committed to challenging government policies that put political and religious agendas over sound public health policy.
- › Scientists and advocates must be committed to continued involvement of gay men, accepting the difficulties this presents along with the benefits. This means striking a balance between aggressive prevention strategies geared to the realities of gay life today and the long-term hope of an AIDS vaccine. It also demands new approaches to engaging gay men. Past methods which relied on fear of AIDS are clearly losing their ability to inspire action now that ARVs are perceived to have ended the AIDS crisis in the US. Interestingly, the AIDS VAX B/B trial found that altruism was the strongest motivator for trial participation—a finding that should be built on in devising new strategies.

- › Much greater effort is needed to engage minority communities, starting with providing the prevention and care services they need, and working hard to build a sense of trust and partnership.
- › In many parts of the developing world there is more hostility and secrecy about being homosexual, and even legal ramifications. Yet epidemics in those areas may very well have a gay component as well, whether it is acknowledged or not. The developing world needs to pay attention to this added dimension for international trials.

LIKE ANY COMMUNITY that has endured prejudice, involving gay men in the vaccine effort is far from easy. But gay men are in a unique position to advance the cause. With smart strategies and strong commitment, their contributions can make a huge difference.

aids prevention and african militaries: a conversation with colonel deborah birx

COLONEL DEBORAH BIRX with PATRICIA KAHN

Deborah Birx is a physician specialized in internal medicine and clinical immunology and a medical officer in the US Army for over 24 years. Since 1996, she has directed the US Military's HIV Research Program, which works primarily in Thailand and in a variety of African communities and militaries in partnership with the US National Institutes of Health (NIH) and the Division of AIDS (DAIDS). During these years she has been a pioneer in working towards community-wide prevention services, medical care and HIV treatment as an integral part of preparing for HIV vaccine trials. Here she speaks with Patricia Kahn about the challenges of confronting AIDS in African militaries.



LET'S START with an overview on the work you're doing among militaries.

We've worked with different militaries in the past, especially in the US and Thailand. Both have low infection rates, although in the early 1990's it was very high in Thailand—almost 10% among recruits. But the Thai Army really embraced testing and prevention programs full-force, and now their *incidence* is probably less than 0.5% a year.

Right now we're focusing on militaries with high *prevalence* rates, mostly in Africa, where the rates in different countries range between about 5% and 30%. In some countries we're also working with the national police force on vaccine research through other bilateral partnerships. These are forces similar to the US National Guard—they move around the country to places where they're needed. They also have their own barracks, hospitals and health care system. So together with other researchers we're looking at both military and national police groups—in Tanzania, Kenya, Nigeria, especially their police force in Dar es Salaam, and in Cameroon.

What do you mean by “looking at?”

Helping to set up their HIV testing system, their quality controls, their prevention messages. We start just like we do with any other group, with voluntary counseling and testing (VCT), prevention messages, figuring out prevalence.¹ Then, depending on what the prevalence is, we may go ahead and help develop the infrastructure to measure incidence² and set up the labs needed for vaccine trials. Tracking incidence is critical for the countries and the militaries as they expand their prevention interventions and evaluate impact of the interventions. Highly focused incidence studies married with evaluation of retention (*cohort* development) are expensive, so we only do them in areas where we really believe vaccine testing can be done.

But we also work with some of the smaller militaries. Most African militaries only have between 15,000 and 30,000 people. We also try to help militaries that have a lot of regional peacekeeping responsibilities, since they're at higher risk for infection through deployment-associated sexual contacts. That's not for full vaccine development; it will focus on setting up VCT and helping to develop deployment-specific prevention messages.

What types of messages do you use?

It's very different from other groups. It took us a decade to get the messages right in the US military. Usually we use messages that are consistent with the military training doctrine and builds on the sense of teamwork.

For example, there's the whole buddy system. A guy goes out drinking with his buddies. One of them doesn't drink and he makes sure that the others get home safely and don't go to a brothel and sleep with women without using condoms. So it's a very targeted message, because of course most of

¹ Prevalence measures the percentage of people in a population who are infected.

² Incidence measures the rate of new infections over a certain period of time, usually one year. For deciding where to do HIV vaccine trials and how to design them, incidence is the crucial number. But it is also much more difficult and expensive to measure (see chapter 11).

these militaries are 90-plus percent male. We also build messages around weapons and protecting themselves. The men understand self-protection when it comes to bullets, so the condom message is based on this same idea.

Are the militaries receptive to this?

Yes. A while back many of them were concerned that their high prevalence might restrict their freedom to move around different countries and participate in peacekeeping initiatives. The concern was that their AIDS programs would lead to disclosure of these high rates, and that entire militaries would then be stigmatized as having lots of HIV-infected soldiers, and be prevented from entering other countries. But this hasn't happened. People have really respected the military's use of HIV prevalence data only internally, to improve their prevention work. It's worked out in a very positive way.

The men understand self-protection when it comes to bullets, so the condom message is based on this same idea.

How is the uptake of VCT? Are people going to get tested?

It's excellent. Often we set this up in separate, anonymous areas so we're not seen as part of the military directive of health care. That means keeping it as a freestanding space away from the military hospitals and care, usually also accessible to the community. The reason is stigma. Being seen walking into a VCT center can be quite stigmatizing to a military career.

For soldiers who test positive, what then?

What care do they get?

I can speak best to the 12 African countries in the President's Emergency Plan for AIDS Relief.³ There's been a real push to make sure that the police, the prison guard and the military

³The program will invest \$15 billion over five years in AIDS prevention, ARV treatment, orphan care and building health capacity in 15 "focus" countries. They are: Botswana, Côte d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam and Zambia.

are all part of this rollout, which includes ARV treatment. Most healthcare delivery in these countries is done through the Ministry of Health, while the Ministry of Defense often has its own parallel system. So it's very important that the militaries are at the table, that they aren't left out of this emergency health plan rollout. This also really helps bring people in for testing. Now we need to make sure these programs continue to expand and embrace all the military sites.

How do you expand from prevention and care efforts like we've been talking about into vaccines?

Militaries have a lot of young men, sometimes a lot of young men with cash. So first of all, the emphasis on disease prevention has to be built around personal protection. You need to develop enough rapport with the command structure that they become invested in accurate testing and prevention messages. Then they may sign on to the research aspects—which means understanding that there will be a commitment to following people for long periods of time.

So the idea is to move from straightforward things everyone can agree on—we've got to test, we've got to get the prevention messages right—to the concept that experimental HIV vaccine

testing could limit some soldiers' deployments.

If there are four *immunizations* and volunteers are followed four times a year in a *Phase I* or *Phase II* trial, they could potentially lose six training days in a six-month period. These issues are very important to militaries.

But what's really changed the equation is bringing in treatment. If you had asked me a year ago about vaccine trials in military cohorts, I would have said it's a real problem to ask people to be tested and not have access to care.

What's really changed the equation is bringing in treatment.

What are some other issues specific to military cohorts in doing HIV vaccine trials?

Deployment is really one of the main hurdles. The first vaccine trial in Uganda, back in 1999 (see chapter 21), was very successful because the trial staff were able to follow volunteers up to the Sudan border and back. They had a very good working relationship with the military, and the government of Uganda really facilitated that trial. But I don't think this will happen in many countries. In most cases deployments and training will take precedence.

It's different for the national police forces—they're not as involved in deployments. And if they move, they go to a specific police region within a network, so you can usually reach them. This is a big advantage for vaccine work, or studies involving follow-up.

Another issue with military cohorts is that we also need data on HIV vaccines in women. So any male-only cohort has limitations. You need to have a group of women somewhere else to get the missing data.

Do you worry about whether a soldier's consent to participate in a trial can be truly voluntary within a military culture?

It's a sensitive issue. It's different for the officer level, the enlisted level and the recruit level (draftees). Most African militaries have recruits that do two years of mandatory service. We stay away from this group of draftees for vaccine trials—of course not for testing and prevention—because they didn't volunteer for the military, and there may be issues with voluntary consent for vaccine trials and ability to follow them over two or three years. And also because they might perceive being asked to enroll in a vaccine trial as part of their duty. We don't want that message ever to get out there, not even the slightest perception.

Do you think five years from now we'll be seeing HIV vaccine studies being done in militaries?

I think it's very important to give them the option. Vaccine trials bring a lot of investment in capacity building, infrastructure development and training of physicians and nurses.

To exclude the military would inhibit their ability to tap into scientific capability through development dollars, and would create a lower level of research and health care. So I think it's important to be sensitive to the military-specific issues—but not be so overwhelmed by the challenge that we just say, we're not working with the military.



global advocacy

COMMUNITY MATTERS: (RE)-DEFINING OUR ADVOCACY CHAPTER 33

FROM TRIAL VOLUNTEER TO VACCINE ADVOCATE CHAPTER 34

SPEED & EQUITY: WHY POLITICAL LEADERSHIP IS IMPORTANT CHAPTER 35

ENSURING RAPID GLOBAL ACCESS TO AIDS VACCINES CHAPTER 36

JUST 2 DROPS: POLIO ERADICATION IN PICTURES CHAPTER 37

PHOTO ©Jaime Razuri/AFP/Getty Images


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PERU / previous page

On World AIDS Day (December 1) in 2003, Peruvian AIDS organizations march for free access to antiretroviral drugs for all who need them.

community matters: (re)-defining our advocacy

SHAUN MELLORS / south africa



THE MOST RECENT International AIDS Conference (Bangkok, 2004) showcased an enormous diversity of communities around the world and how they are responding on the ground to the epidemic. It was also striking evidence that the battles we fought to find a place for community during the first two decades of this epidemic have largely been won. Communities, including people living with AIDS (PWAs), are part of almost every platform, sentence, project proposal, abstract and conference. And although we are sometimes still referred to as a principle (“We believe in the principle of community involvement”), we as community, together with our scientific colleagues, have a responsibility to define and transform this principle into reality.

Affected communities were the first to respond to the AIDS epidemic, out of a sense of fear, survival and compassion. Our voices have changed the nature of health care and doctor-patient relationships, and we all know from personal experience the invaluable contributions of community involvement on so many fronts.

But as community advocates, activists and representatives we have perhaps taken “community involvement” for granted, and may be in danger of losing our focus and direction. We are failing to ensure (or even to clearly define) an effective and accountable response to the epidemic—from our political leaders, our scientists and ourselves. Although communities are experienced and have expertise, we also have a lot more to learn, especially when it comes to preparing the public for vaccine trials. We cannot just simply pick up the cookie cutter that defined our approaches and programs at the beginning of the epidemic and reuse them in addressing today’s issues of vaccine preparedness. Instead, we need to assess what we’ve learned so far, and use these lessons to re-think our big-picture priorities and strategies.

We have learnt that large-scale human trials are possible, but demand much of us—especially when they take place in poor, highly affected communities. We know that better products need to be developed. We know that effective community involvement and trust are important for this research to succeed. We have known for a while that we need to act now to ensure equitable global access to AIDS vaccines and *microbicides*, once effective products become available.

As for strategies, it’s clear that success will require a far more coordinated, concerted effort over the coming years—which will depend on clearly defining roles, responsibilities, resources and mechanisms for accountability. It will also require broader public understanding and support.

But experience has shown that simply providing information will not automatically lead to broad public support. Political leaders, community and civil society are usually not instantly willing to step forward and embrace this research. The public is “AIDS fatigued,” and we are not being creative enough in placing the vaccine agenda within the public sector. To

do better, we will need to build new coalitions, partnerships and networks that work more effectively and efficiently on the ground than the cottage industry approach we now have.

The public is “AIDS fatigued,” and we are not being creative enough in placing the vaccine agenda within the public sector.

One aim of this revamped effort and alliance-building should be to improve national coordination amongst different stakeholders and partners. This is especially important in countries doing (or planning) trials of vaccines, microbicides and treatments, which usually involve different sets of national and international sponsors. Often each initiative has its “own” communities where trials, or trial preparations, are taking place. Each of them may be doing important research, but for the most part, coordination amongst them is almost non-existent. Besides establishing separate trial sites, the different microbicide and vaccine networks develop their own literature, community mapping activities, needs analyses, socio-behavioral studies, volunteer recruitment campaigns and standards of care for trial participants—even when these groups are working in the same province or district.

Having different initiatives that reinvent the wheel rather than work together is counterproductive. It unnecessarily drains limited financial and human resources. It squanders opportunities for *clinical trials* to do more to expand access to treatment and prevention in the community, and to fully involve communities in these studies. It also means that they often miss chances to learn important lessons from one another—for example, lessons that microbicide advocates can teach us about gender in clinical research, that vaccine advocates can teach about community mobilization and that treatment advocates can teach about community activism.

“It’s difficult to work as we are doing now, when one researcher comes along and wants to do community preparedness on vaccines, and then another one comes who works on microbicides,” says Dawn Cavanagh of the Gender AIDS Forum in South Africa. “Many of us are overstretched and battling with shrinking budgets...But we’re under pressure to take on these separate researcher/donor-driven needs.”

from lessons learned to an advocacy agenda

By drawing on what our experience is telling us, we can see some key areas for community action.

- › Ensure that trial sponsors work together at the national and community levels, especially in developing infrastructure for providing medical care, AIDS treatment and HIV prevention services—a big part of making sure that trials do in fact leave communities better off, and that this impact is sustained. [See chapter 20 for more on this issue.] And as vaccine, microbicides and treatment advocates, we must develop common agendas that all work for these goals.¹

- › Advocate for comprehensive national plans for countries engaged in AIDS vaccine development. These plans should cover strategies and timelines for pre-clinical and clinical research, regulatory review of clinical research studies and approval of vaccines and microbicides. They should also address public health use and accessibility, along with issues related to standards of care and treatment and developing the infrastructure needed to bring sustainable benefits to communities that participate in trials.

The national plans should form part of a broader national response, and the different interventions should not be seen as separate from each other, or competing for funds or attention. On the contrary, they offer opportunities to integrate the treatment, vaccine and microbicide agendas.

- › Support the acceleration of the clinical trial calendar and the strengthening of research infrastructure and capacity. This requires more investment from wealthy countries and other stakeholders, development of research staff and community representatives, and progress in understanding and grappling with preparedness work.

¹The US National Institutes of Health (NIH) has plans to interconnect its AIDS research networks by synchronizing their funding and requiring cross-network communication and some resource sharing, including a global Community Partners structure, by 2006.

- › Ensure that prevention efforts are culturally appropriate, in languages that people speak and understand, and that they are not biased against women. We also need to help focus prevention on value systems and not simply on practices, as it has done in the past and still does in many cases.

AS COMMUNITY ADVOCATES we also need to look beyond clinical trial implementation at the broader process of vaccine development and access. Vaccine preparedness encompasses public understanding of these issues, and public support and participation. Community advocates, especially from the South—where vaccine research is still relatively new—must become more effective, articulate vaccine and microbicide advocates. We also need to point out where the clinical research agenda fits in with other goals and agendas, such as reducing poverty, promoting development and strengthening women's rights. And we need to integrate the principles of benefit and justice into this research. If we do not, history will judge us harshly for failing to learn from our experience and capitalize on the lessons it offers us for fighting this epidemic.

We need to integrate the principles of benefit and justice into this research. If we do not, history will judge us harshly.

from trial volunteer to vaccine advocate

PAUL WETAKA / uganda

Since the first *clinical trial* of an AIDS vaccine back in 1988, nearly 24,000 people around the world have volunteered for AIDS vaccine trials—each of them, by definition, committed to the goal of finding an effective vaccine. But what do they do once the trial ends? Here one former volunteer describes how his experience as a study participant has shaped him into an advocate who speaks frequently in the media and among Uganda’s communities, emphasizing the need for the public to support—or, more accurately, to demand—the strongest possible effort to develop an AIDS vaccine.

Paul Wetaka, a professional soldier in the Ugandan military (and former member of the President of Uganda’s protection unit), began his involvement a decade ago when he volunteered for Africa’s first AIDS vaccine trial. That trial was initially controversial, but nowadays Uganda is preparing for its third AIDS vaccine study—amid a strongly supportive public. (For the story of how this came about, see chapter 21.) Today Wetaka works with the Army’s medical services unit responsible for care of soldiers with HIV/AIDS. The unit is now launching its own program to provide *antiretroviral drug* treatment.

I FIRST GOT INVOLVED with AIDS vaccines in 1995, when I was approached by the Joint Clinical Research Center in Kampala, where Uganda’s first trial was done. By then I had already traveled all over the country with the President of Uganda as one of his bodyguards, and listened to his speeches. We went to many towns and villages, and he spoke about AIDS and how to guard against it. At the same time, I was seeing my commanders and friends die of AIDS. Back then we called it ‘slim’ disease. I spent a lot of time visiting friends in the hospital, going to funerals, trying to help the orphans they left behind, so they could pay their school fees and get the things they needed.

To be in the trial I had to have an HIV test. This worried me, but finally I did it and I was HIV-negative. This made me decide I wanted to do more about AIDS than just try to help my friends, so I made the final decision to go ahead with the trial. I had many questions about possible risks of participating, but the trial staff explained everything and answered all my questions.

The trial didn't start for two more years. During that time the volunteers learned a lot about science and research, things like *informed consent*, *placebos*, HIV transmission, and how to know if a vaccine works. And about safer sex, and modes of HIV transmission. But we had two years of just focus groups. We said, please, give us the vaccine. We are ready.

During the trial a *Community Advisory Board (CAB)* was started, and I became a representative for the volunteers. Most of the volunteers were military men, and there were also a few civilian women. The other CAB members included religious leaders, HIV-positive activists, community leaders. We were told that after this trial, there will be more trials, and that one day we would need to test the effectiveness of some vaccines, and it will take many people to do this. So I wanted to continue doing something about AIDS, especially for the AIDS vaccine movement.

The CAB couldn't continue after the trial ended, so we started our own group, called the Uganda Pioneers for Vaccine Research. Most of our activities were aimed at raising awareness of HIV/AIDS and vaccine trials in the community. We didn't have any assistance or support to move around as a group, so we each did what we could on an individual basis. I used my access to military leaders, who gave me the chance to speak with my fellow soldiers about HIV/AIDS and vaccine development in Uganda.

During that time—it was 1999—I also started speaking about AIDS on radio, TV, and at workshops. I still do this, usually about once a week. This means talking with a lot of people and hearing their questions, and what they think about HIV/AIDS and vaccines.

Distrust of clinical research is a big problem in our communities. When vaccine trials first came here, where traditional culture is observed, the new idea wasn't always welcomed quickly. And HIV/AIDS is often regarded as a public shame or disgrace.

People often ask whether I'm HIV-positive and whether the vaccine can cause HIV. There were a lot of rumors at the time of the first trial that the volunteers are HIV positive. AIDS patients were treated in the same place where the trial

was carried out, which made many people think we had AIDS. We faced a lot of stigma, and spent a lot of time explaining to people what was really going on.

When the second trial came up, I continued to talk about the need for an AIDS vaccine. Helping the community see the need and demand for a vaccine. And that we shouldn't wait a decade or longer to get a vaccine after it's been licensed for use in industrialized nations. I also speak about the importance of vaccines we already have. In some communities in Uganda, and in other parts of Africa, there's still a problem of accepting vaccines that have proven effective, like for polio and measles. But the public response to the second trial was very positive.

I was allowed to work with this trial to share my experiences as a former participant. I got involved with the CAB, and we helped with some of the preparation—looking at the language used in the *protocol*, informed consent documents and educational materials. We also started a newsletter with IAVI [the International AIDS Vaccine Initiative], who sponsor the trial.^① But the trial came to an end in February 2005.

There will be another study starting soon at Makerere University with the Walter Reed Army Institute from the US, and I hope to play the same role. But I will find ways to stay involved even if all trials end. Somehow the vaccine movement will go on until we find a vaccine for HIV/AIDS. If the present products don't go forward, we shall try others. I hope scientists are having sleepless nights to find the best product for us to try. So we will still need to prepare communities for more trials.

A big challenge is that many people in Uganda don't realize that the AIDS vaccine movement needs support from the public—this is a new idea to them. All the vaccines and drugs we depend on come from industrialized countries in the Western world. So people don't know that the scientific research to make them goes beyond the laboratory and involves people. We need people to understand that developing an AIDS vaccine which can save lives and economies will be one of the world's greatest achievements. And that not to do so would be one of its greatest failures.

Many people don't realize that the AIDS vaccine movement needs support from the public.

reference

- ① www.iavi.org/uganda
Website of the Uganda Virus Research Institute/IAVI AIDS vaccine program, with the quarterly newsletter published by the site's CAB; information on volunteering for trials and frequently asked questions.

speed and equity:
why political leadership is important

CHRIS COLLINS

THERE IS A LOT OF ANGUISH in being a US citizen these days if you care about public health. It means watching your country use global health policy to advance the causes of gargantuan profit and religious conservatism at the expense of treatment access and scientific knowledge.

Of course, many governments fall terribly short in addressing health priorities, not just the US. That was part of the initial appeal of the AIDS vaccine movement for me. It seemed that an AIDS vaccine might be able to circumvent political limitations because, like the polio vaccine, it could be delivered universally, including to marginalized groups. A vaccine might overcome social obstacles to effective HIV prevention, like the unequal status of women, intolerance for sexual diversity, and the rights of drug users.

I was wrong. Politics is as important in AIDS vaccines as it is in other areas of health. Political leaders help determine the pace of scientific discovery and the ethics of *clinical trials*, and they will be crucial in determining who gets a vaccine quickly when one is developed. Fortunately, there are examples of political leadership on AIDS vaccines, and they should serve as models for policy makers around the world.

It's rare that the leader of a nation shows up to launch an AIDS vaccine trial. But by November 2003, when President Paul Kagame of Rwanda came to inaugurate AIDS vaccine research in his country, he had done much more than make speeches about the epidemic. He had created a climate in which AIDS could be talked about with increasing openness, and where AIDS vaccine development was treated as a high priority.

This leadership produced tangible results. Administrative aspects of the country's first vaccine trial were handled efficiently. The Health Minister made sure research supplies were imported duty-free to the trial site. A local ethics committee was formed, asked hard questions, and then decided to approve the trial.

Six years earlier, then-US President Bill Clinton came to Morgan State University in Baltimore and issued a challenge to the nation. "If this is the Age of Biology," Clinton declared, "let an AIDS vaccine be its first great triumph." That day he announced plans to build a new Vaccine Research Center (which opened in 2000 and is now an important contributor to AIDS vaccine development), and soon he would propose incentives to spur development and delivery of AIDS vaccines globally.

Governments play an essential role in mobilizing resources, determining how effectively they're used and in creating an enabling environment.

Every country brings different resources to the AIDS vaccine effort. Governments play an essential role in mobilizing these resources, determining how effectively they are used to address the country's needs, and creating an "enabling environment" that allows AIDS vaccine development work to flourish.

Achieving this involves a wide range of activities. On the most basic level, government leaders can marshal support for AIDS vaccine research and define how it fits into broader national goals—as, for example, Thai leaders did when they included vaccines as part of the country's early, aggressive response to the epidemic, a prescient decision that has made Thailand a key player in the field today. Governments can also influence this research through their policies and laws. For example, many countries, including Brazil, Canada, Ethiopia, Tanzania, and Uganda, have signaled their political



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Former US President Bill Clinton speaking at a conference for HIV/AIDS researchers (Boston, February 2003). Since leaving office in early 2000, he has made HIV/AIDS one of his main priorities. In 1997, while still President, he called for the world to develop an AIDS vaccine within the decade.

commitment by incorporating vaccines into their national plans for combating the AIDS epidemic, which in turn helps in establishing infrastructure and momentum for vaccine work. In October 2003, parliamentarians from around Asia issued a joint declaration pledging stepped-up efforts on behalf of vaccine research, placed within a context of legislative activities on HIV prevention and treatment, human rights, and anti-stigma efforts. And most recently, the G8 countries have endorsed—and will hopefully help finance—a “Global HIV Vaccine Enterprise,” a coordinated plan to tackle scientific and infrastructural obstacles to a vaccine, under the auspices of the Bill & Melinda Gates Foundation.

accelerating research

But how can a government actually speed up the pace of scientific discovery? How does it make sure that health-related research truly meets the needs of its population?

Financial support for targeted research is one answer. For example, although the South African government has been widely criticized for its overall response to HIV/AIDS, it has demonstrated strong leadership in the area of vaccines, founding and supporting the South African AIDS Vaccine Initiative (SAAVI) to fund what is now a robust pre-clinical and clinical research program on vaccines suited to the country's epidemic.

Another approach is to support multilateral organizations involved in AIDS vaccine development. Eight governments provide direct funding to the International AIDS Vaccine Initiative (IAVI), a public-private partnership that supports work on vaccines for use in the developing world. As another example, numerous African countries (plus the World Health Organization) fund the African AIDS Vaccine Programme, which advocates and builds local capacity for accelerated research on AIDS vaccines. Countries can also band together: In July 2004, Brazil, Thailand, China, the Russian Federation, Nigeria and Ukraine signed a Joint Declaration to work more closely with one another to produce AIDS treatments and develop AIDS vaccines and *microbicides*.

By far the largest financial commitment to AIDS vaccine research has come from the United States, which will spend well over \$400 million on this research in fiscal year 2004 through its National Institutes of Health (NIH). And in the 1990s, with lagging interest in AIDS vaccines from pharmaceutical companies (where most of the world's expertise in vaccine development is found), NIH moved beyond its traditional basic-science approach to provide more funding for product development.

But governments are still struggling to find additional ways of filling the gap left by industry's relatively minimal engagement in the search for an AIDS vaccine. Some funding

agencies (including NIH and IAVI) are attempting to harness private sector know-how by providing direct support to companies doing AIDS vaccine research. More indirect measures have been used as well: for example, in 2002 the United Kingdom introduced a tax credit for companies working on drugs or vaccines targeting AIDS and other infectious diseases primarily affecting people in developing countries.

In the late 1990s, proposals in the US Congress would have created similar incentives (for work on microbicides and vaccines against malaria, tuberculosis and HIV). These proposals were never enacted. But when governments are sufficiently motivated they *can* act decisively. The threat of bioterrorism inspired the US Congress, in 2004, to pass a package of incentives aimed at encouraging industry to develop bioterror “countermeasures,” such as anthrax and smallpox vaccines. Those incentives, which include not only direct funding for research but also liability protections, accelerated regulatory review and guaranteed purchase of new products once they are licensed, could all be extended to vaccines against AIDS and other major infectious diseases.

US government incentives to develop vaccines against bioterror diseases could be extended to vaccines against AIDS and other major infectious killers.

promoting clinical trials

When an AIDS vaccine candidate moves out of the lab and into humans, it enters the collective (and political) sphere. Clinical trials of these products are expensive, they can present ethical conundrums, and they often receive intense media scrutiny. Their success depends on public trust. For these reasons, government support is also crucial to their success—especially in countries new to such research, or where past clinical trials helped identify effective products which then took many years (or even decades) to become widely available locally.

Again, Thailand provides an example of how government can lead the way. The Kingdom has made AIDS vaccine research a high priority, partnering with industry, academics and government researchers from several countries to conduct

more than a dozen *Phase I and II* trials and launch two *efficacy* trials (one completed, one continuing through 2009). Thailand has also used this research to enhance the country's overall response to HIV and the broader health problems facing its population. Its ongoing AIDS vaccine efficacy trial is helping the country expand prevention and treatment services, build health care and research infrastructure, and achieve a new level of community involvement in research. Increasingly, other developing countries are joining in the effort: In the last five years, nearly two dozen countries in Africa, Asia and Latin America have launched, or are preparing for, AIDS vaccine trials (see appendix 2).



SOUTH AFRICA

©SAAVI

Nelson Mandela, South Africa's former president, visited the vaccine trial site in Soweto shortly before it began the country's first AIDS vaccine trial. Mandela has devoted much of his time since leaving office to the battle against AIDS. From left to right: researchers Glenda Gray, Carolyn Williamson, Atom Dilraj; Nelson Mandela, Community Advisory Board (CAB) member Winnie Serobe, former SAAVI head Tim Tucker and researcher Andrew Robinson.

These trials require extensive preparation of laboratories, clinics and participating communities (see chapters in Clinical Trials, section 3), and one of the most important roles for rich countries is to support the buildup of this capacity in the developing world. The HIV Vaccine Trials Network (through the US National Institutes of Health), the US Military Program, the International AIDS Vaccine Initiative and the European and Developing Countries Clinical Trials Partnership are all important examples of agencies involved in this effort.

Many challenges are involved, such as expanding the genuine involvement of local researchers, sharing data and lessons learned across clinical trial sites, and maintaining these sites between trials. Another challenge is to foster local expertise in evaluating the safety, scientific and ethical aspects of these studies, efforts in which countries with established regulatory agencies, plus the World Health Organization, can play a crucial role.

ensuring access

Ensuring that an effective vaccine will rapidly reach the populations in greatest need (and avoiding a repetition of the catastrophic inequalities in access to *antiretroviral drugs*) is largely an issue of political will. But that does not mean the challenges are any less complex. For example, there are no detailed answers to the deceptively simple question of how much vaccine will be needed worldwide, since this will vary greatly according to vaccine dosage, type, effectiveness, price, peoples' willingness to be vaccinated, their access to health care facilities and other factors.

Ensuring that an effective vaccine will rapidly reach the populations in greatest need is largely an issue of political will. But that does not mean the challenges are any less complex.

Nevertheless, to achieve nearly simultaneous distribution of AIDS vaccines in wealthy and poor countries, governments and international organizations will need to take a variety of actions, such as:

- › Vaccine manufacturers must be poised to produce hundreds of millions of doses very quickly once a vaccine is licensed, and governments should be ready to help—for example, by providing incentives for technology transfer to vaccine manufacturers in the South, who can help meet global demand.
- › The world must be ready to pay for this large-scale manufacture, such as through pre-commitments to purchase vaccine for global use. Vaccines must be available to all, regardless of ability to pay.
- › Health care infrastructure must be expanded so that vaccines can be delivered quickly to adolescents and adults, not only to infants.
- › Anti-stigma efforts should be launched so that an effective vaccine will be widely accepted by marginalized and highly vulnerable people around the world.

(These and other issues related to access are discussed more fully in chapter 36.)

PUBLIC LEADERS AND VACCINE ADVOCATES can build on their AIDS vaccine work by addressing other prevention technology priorities. For example, infrastructure created for AIDS vaccine research might be used to deliver existing vaccines and treatments, such as Hepatitis B vaccine. Vaccine advocates could also help develop an agenda for global access to tenofovir, an antiretroviral product that shows promise as a prevention tool.

An AIDS vaccine will not eliminate the need for behavioral prevention, since at least the first licensed product may be only partially effective (see chapter 9), and even with the best preparation it will take time to vaccinate hundreds of millions of people around the world. So the need for behavioral prevention will persist, as will the familiar political obstacles to providing evidence-based interventions—a reminder that the quest to produce and deliver a vaccine which can end the epidemic will continue presenting new challenges to political leaders and policy advocates for a long time to come.

resources

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ensuring rapid global access to aids vaccines

DAVID GOLD

IT WOULD BE morally unthinkable to have a safe and effective AIDS vaccine without the capacity to deliver it quickly to those most at risk of HIV infection. Yet there are enormous challenges to making a new vaccine available in developing countries at the same time as in industrialized countries—in fact, it's never been done before.

Advocates and policymakers are beginning to think about how these challenges can be overcome. As they do, they must also consider the amount of time, resources and political capital to invest in the access issue, when a safe and effective AIDS vaccine may still be at least a decade away.

At first glance, it might seem unnecessary (or even wasteful) to start planning now for delivering a vaccine that doesn't yet exist. But the world's experience with licensed vaccines demonstrates the terrible consequences of failing to tackle access issues early. Poor countries still wait an average of 20 years after a vaccine is licensed in industrialized nations before it starts reaching their own populations.

This unconscionable delay has several causes, including:

- › Too little money to buy the vaccines. This is true even with the creation of new organizations dedicated to closing this gap, such as the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund.
- › The slow pace at which companies scale up capacity to manufacture large enough amounts of new vaccines to meet global needs.
- › Needlessly long regulatory approvals processes.
- › Too few effective systems for distributing new vaccines in poor countries.

Poor countries wait an average of 20 years before new vaccines start reaching their populations.

Access to AIDS vaccines first captured global attention at the 2000 International AIDS Conference in Durban, which was dominated by the issue of access to *antiretroviral* therapy in developing countries. Citing this glaring example of public health disaster stemming from early failure to plan for treatment access, a small number of advocates began urging

policymakers to start thinking about vaccine access in advance of having a product. The meeting also featured the release of “A Blueprint for Ensuring Rapid Access to AIDS Vaccines” by IAVI and the distribution of buttons and posters calling for “An AIDS Vaccine for ALL.”

One year later, at the United Nations General Assembly Special Session on AIDS (UNGASS), advocates from several countries succeeded in getting a statement on AIDS vaccines included in the final “UNGASS Declaration of Commitment.” In this document, nations of the world agreed to:

Encourage investment in HIV/AIDS-related research, in particular for sustainable and affordable prevention technologies, such as vaccines and *microbicides*, and encourage the proactive preparation of financial and logistic plans to facilitate rapid access to vaccines when they become available.

key challenges to aids vaccine access

MOST PEOPLE IN THE FIELD agree on the main challenges to ensuring rapid, broad access to AIDS vaccines. These include:

Estimating demand

Demand for an effective AIDS vaccine is likely to be very high. Yet precise estimates of how high (and therefore how much vaccine will be needed) don't exist. That's partly because demand will depend a lot on the specific properties of the vaccine, such as its level of effectiveness, its cost and ease of use. For example, there will be much more demand for an inexpensive product that protects 80% of all vaccinated people after one dose, compared with a more expensive vaccine that gives only 40% protection and requires three injections. In the latter case, different countries will probably make different decisions about vaccinating their populations, depending on the severity of their epidemic. (See chapter 6 for more discussion of these issues).

But difficult as it is to come up with comprehensive estimates of demand, this information is crucial for planning how to finance, produce and deliver a successful vaccine. A broad group of stakeholders therefore needs to work together on demand estimates for a range of different AIDS vaccines. Vaccine manufacturers, who do not usually collaborate, must make a special effort to tackle this problem together.

Manufacturing

Building a large vaccine production plant that meets the requirements of regulatory agencies typically takes 4–5 years and costs hundreds of millions of dollars. This long time scale and high cost creates a dilemma. If building begins only after *Phase III* trials show a vaccine to be safe and effective, the result will be a 4–5 year delay until the new facility can produce large amounts of vaccine. If it starts early enough to avoid this delay—that is, several years before a vaccine has

been shown to work—it risks the entire investment should the product prove ineffective.

But there are ways to begin scaling up manufacturing capacity before a vaccine's *efficacy* is proven, yet without requiring manufacturers to assume the full financial risk. These include:

- › Sharing the risk between the public and private sectors.
- › Building production plants with the flexibility to shift into making other vaccines by other technologies, if the candidate AIDS vaccine turns out to not to work.
- › Engaging manufacturers who already produce licensed vaccines in developing countries, to see whether they have potential for large-scale production of AIDS vaccines.

Not even the most advanced regulatory agencies have clear guidelines on what properties an AIDS vaccine needs for licensure.

Regulatory approval

Regulatory agencies, particularly those in developing countries, are often not well set up to review new products such as AIDS vaccines quickly. But not even the most advanced agencies have outlined clear guidelines on what properties an AIDS vaccine will need to show to be granted a license. Nor is it clear whether countries will require a vaccine that has proven effective in one (or several) regions to be tested again in local populations and/or against locally circulating HIV *strains*. Also, since each country or region has its own licensing authority with its own requirements, it will be impossible for vaccine producers to apply for a single license that's valid everywhere; instead, many different regulatory applications will be needed.

Authorities in developing countries may look to industrialized nations for guidance in licensing a particular AIDS vaccine, but ultimately they will want and need to reach their own conclusions. Those with established regulatory capacity (such as Brazil, India and South Africa) will need to play a leading role. But many others will desperately need technical assistance to strengthen their capacity for making these regulatory decisions.

Delivering AIDS vaccines

The infrastructure for delivering vaccines in poor countries is focused almost entirely on infants and children. But an AIDS vaccine, at least initially, will be targeted to adolescents and adults—groups that are not effectively reached through existing infrastructure, even in wealthy countries.

Developing sustainable systems for getting vaccines to people is expensive, even for childhood *immunization*. The six basic vaccines given to infants in most countries cost less than US\$1 per dose, but delivering them costs 10 to 20 times more—due to the price of transporting them, sometimes to remote locations, while keeping them cold (depending on the type of vaccine), developing local infrastructure and training personnel to immunize people, and a range of other steps. It is crucial that funds to help developing countries pay for AIDS vaccines cover the cost of both purchasing and delivering them.

Financing vaccine purchase

A highly effective AIDS vaccine is likely to be cost-effective at any reasonable price (although this may not be true for low-efficacy vaccines, especially in countries where HIV infection rates are relatively low). But even cost-effectiveness does not guarantee that enough money will be available to buy AIDS vaccines for poor countries. Although childhood vaccines are among the most cost-effective health interventions ever developed, more than 2 million unvaccinated children a year still die from the diseases these vaccines prevent (see table 5.1, following page).

The cost of purchasing hundreds of millions of vaccine doses over many years will be significant, even if prices are heavily tiered (meaning that they are much lower in developing countries than in industrialized ones). Some advocates have called for donor countries to set aside funds to buy large amounts of vaccine, even before one is developed. Their reasoning: this step would give the pharmaceutical industry and international funders more confidence to invest in AIDS vaccine development and manufacturing capacity, since it

would guarantee buyers for the product. Others question these proposals, citing the desperate need for funds and commitments targeting health interventions that already exist but are under-used. (For example, much more money is needed to avoid falling even farther behind with childhood immunization coverage.) But public health advocates agree that donor organizations and governments must do more to improve vaccine coverage in poor countries—both to save millions of lives and to help build confidence in the world's willingness to buy a future AIDS vaccine and deliver it where it is desperately needed.

Table 5.1 Annual deaths from vaccine-preventable diseases (2002)

Disease	Number of deaths
Diphtheria	5,000
Measles	612,000
Polio	1,000
Tetanus	215,000
Pertussis	294,000
Hepatitis B	600,000
Heamophilus influenzae b	413,000
Yellow Fever	30,000
Total	2,169,000

Source: World Health Organization

conclusion

THE CHALLENGE of getting an AIDS vaccine quickly to people in poor, hard-hit regions of the world will be enormous, but not impossible—if steps are taken well in advance of having a vaccine ready for delivery. This will also require resources and political will. AIDS vaccine advocates must continue to pressure policymakers, governments in the North and South, multilateral agencies and vaccine manufacturers to work together on access issues. We must also continue to aggressively push the research and development effort, because a safe and effective product is still the bottom line.

resources

www.vaccinealliance.org

Global Alliance on Vaccines and Immunizations (GAVI) and the Vaccine Fund. Information on the levels of vaccine coverage and funding for childhood vaccines globally, plus news and updates about global immunization programs and policies.

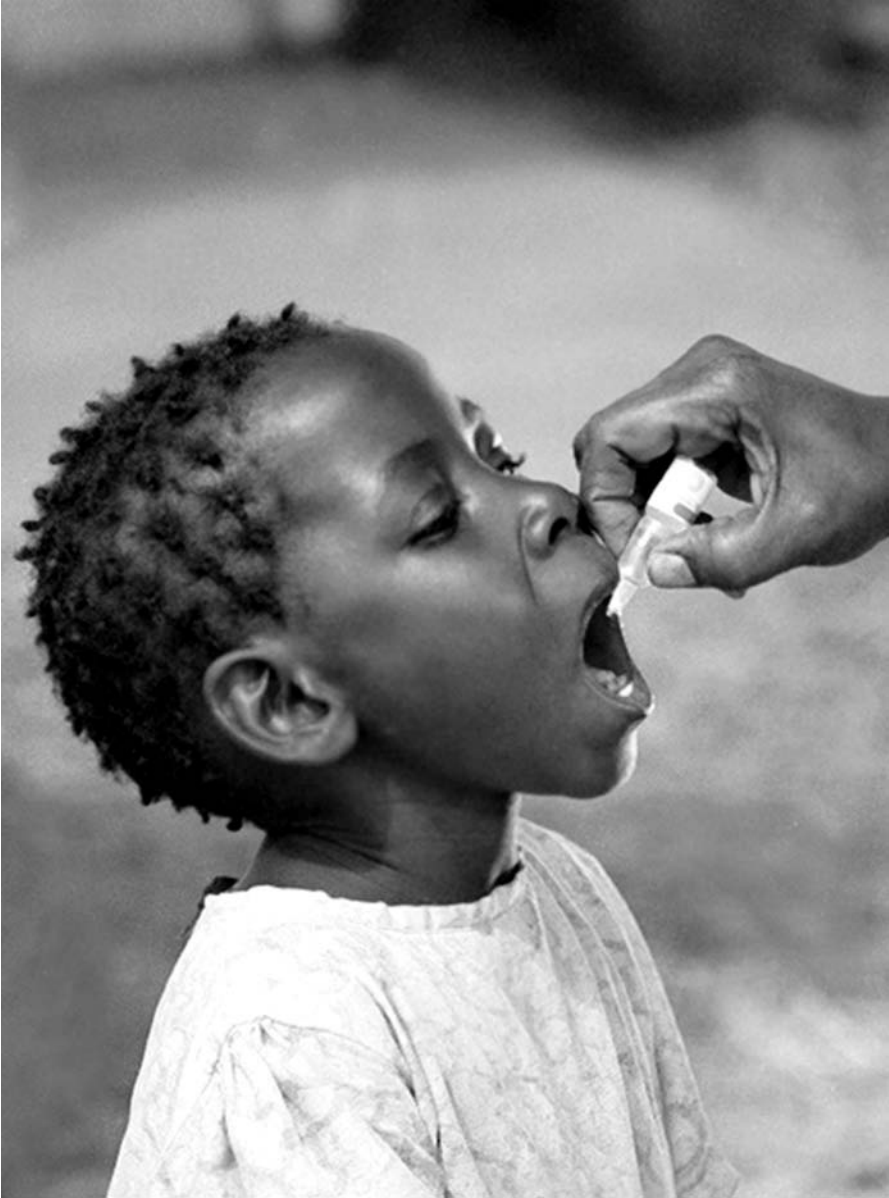
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International AIDS Vaccine Initiative (IAVI). Two papers analyzing the policy challenges and making recommendations on how to ensure global access to an AIDS vaccine.



©The World Health Organization (WHO)

JUST 2 DROPS

Two drops of an oral vaccine (given multiple times) gives lifelong protection against polio to almost all immunized children.

just 2 drops: polio eradication in pictures

text by PATRICIA KAHN /

photos from the WORLD HEALTH ORGANIZATION archives

In the last century, polio epidemics killed or paralyzed millions of people around the world, mostly children. Today, nearly 20 million people live with disabilities caused by their past infection.

The development of vaccines against polio was therefore a monumental public health achievement. When the first one was licensed in 1955, its developer, Jonas Salk, became an instant international hero. A few years later, Albert Sabin developed an oral vaccine (one that can be given by mouth rather than injected). By eliminating the need for sterile injecting equipment and highly trained medical staff, an oral vaccine simplifies mass immunization programs, especially in countries without strong health care systems.

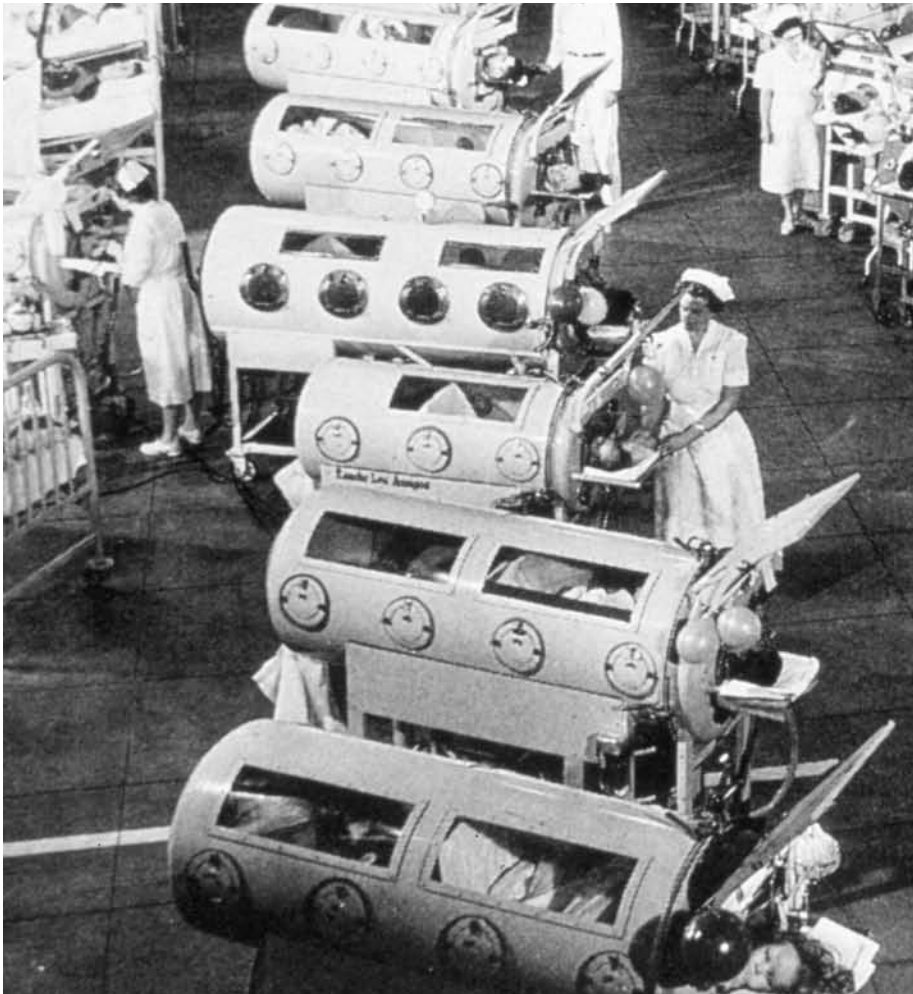
Yet it still took decades for effective mass vaccination to reach most parts of the developing world. In 1988—the year the World Health Organization (WHO), UNICEF and other international partners launched a global campaign to eradicate polio—the disease was still established in 125 countries and paralyzed 350,000 children.

Since then, the eradication campaign has immunized over two billion children and is on the verge of wiping out polio completely: in 2003, there were fewer than 800 cases recorded worldwide, and transmission had been eliminated in all but six countries. But 2004 brought a backslide, when war and other disruptions in vaccination programs caused outbreaks in areas of west and central Africa that had been polio-free. Still, WHO is hopeful that it can end polio transmission everywhere in 2005.

Polio and AIDS are obviously very different diseases, and they pose different scientific challenges for vaccines. Yet the story behind polio vaccines offers us valuable lessons today—especially about the crucial role of strong leadership and public support, and about the formidable challenges of bridging the immunization gap between wealthy and poor countries once an effective vaccine becomes available. The pages that follow portray some highlights of the polio story, from the 1920's until today.

IN THE PERIOD just before the Salk vaccine became available, about 45,000 people in the US were newly infected with polio each year.

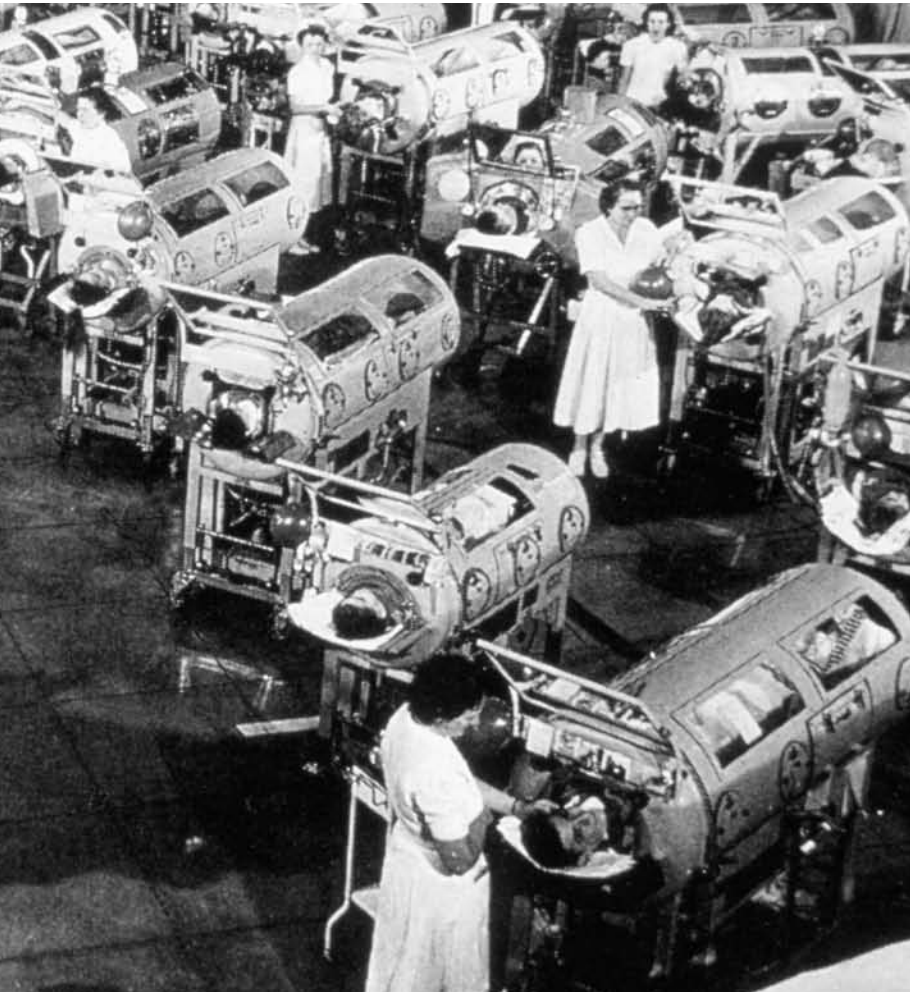
Between 5 and 10% of people contracting polio became paralyzed not only in their legs but also in their breathing muscles, putting them at risk of death through suffocation. To keep them alive, a machine called the “iron lung” was developed in the 1930’s.



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WHERE WE WERE - THE TROUBLING LANDSCAPE OF THE POLIO EPIDEMIC

Wards filled with iron lungs became a common feature of hospitals in North America.



IN 1921, Franklin Delano Roosevelt, Governor of New York State, was struck with polio, leading to partial paralysis. Over the following years he established a treatment center in Warm Springs, Georgia for young people rehabilitating from the effects of polio and launched a series of fundraising activities to support it.

STRONG LEADERSHIP

Roosevelt, who spearheaded the development of a polio vaccine, visits with two youngsters at the Warm Springs Foundation treatment center.



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IN 1938, Roosevelt (by then President of the US) and his ex-law partner, Basil O'Connor, founded the National Foundation for Infantile Paralysis, which focused on developing a vaccine. The Foundation later became known as the March of Dimes, thanks to the practice of asking the public to support its work by sending dimes to the White House.



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COMMUNITY MATTERS

The March of Dimes prioritized and funded research that led to the first effective polio vaccine, and mobilized massive public support.

The enormous public fear that came with each summer's wave of polio, combined with Roosevelt's and O'Connor's strong leadership, rallied the country behind the vaccine cause and the March of Dimes. In 1948, the March of Dimes began funding Dr. Jonas Salk's efforts to make a killed polio vaccine.

BY 1952, Salk had a candidate vaccine made from all three strains of polio *virus*. After initial tests in people found that it was safe and induced antibodies to the virus, Salk and the March of Dimes launched an *efficacy trial* in nearly two million schoolchildren—the largest peace-time mobilization of volunteers in US history.

PIONEERING RESEARCH

In 1954, Salk's vaccine was tested for efficacy in schoolchildren, who were dubbed the "Polio Pioneers."



©March of Dimes

ON 22 APRIL 1955, the long-awaited results of the trial were announced: The vaccine was safe, and it protected over 60% of the immunized children against polio.



©March of Dimes

VACCINE TRIUMPHS

Headlines celebrated the vaccine breakthrough, but it has taken 50 years and massive (ongoing) efforts to nearly conquer polio worldwide.

IMMUNIZATION DRIVES

Rock-and-roll icon Elvis Presley, shown here getting a polio vaccination, brought his star power to the immunization drive in the US.



©March of Dimes

WITHIN SIX YEARS, the Salk vaccine had essentially eliminated polio in the US. In 1962, the number of new polio cases in the US was below 1000.

During the 1960's, Sabin's oral vaccine—which is less expensive, easier to use and more effective in preventing transmission (not just infection)—gradually replaced the Salk vaccine. In 1988 it became the vaccine of choice for the global eradication campaign.

THE GLOBAL POLIO ERADICATION CAMPAIGN, the largest public health project ever undertaken, remains in high gear as it works to eliminate polio from its last strongholds. One important strategy is to reach more children in remote areas. That's a tall order, especially since the vaccine must be kept cold at all times or it loses effectiveness. Some examples of the challenging logistics:

GLOBAL CHALLENGES / CENTRAL AFRICA

Vaccination teams cross rivers, mountain passes and deserts in an effort not to miss any villages.



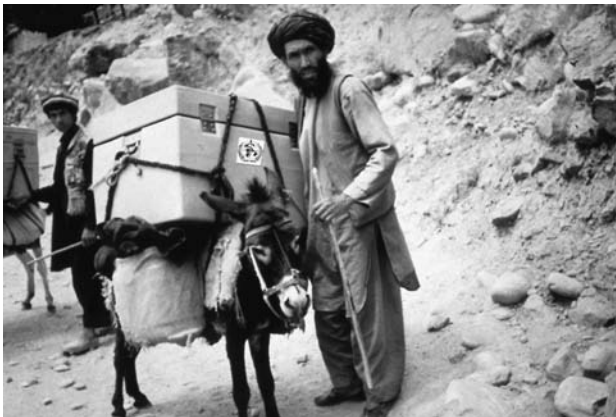
©WHO



NEPAL

©WHO

A porter treks polio vaccine into the Himalayas.



PAKISTAN

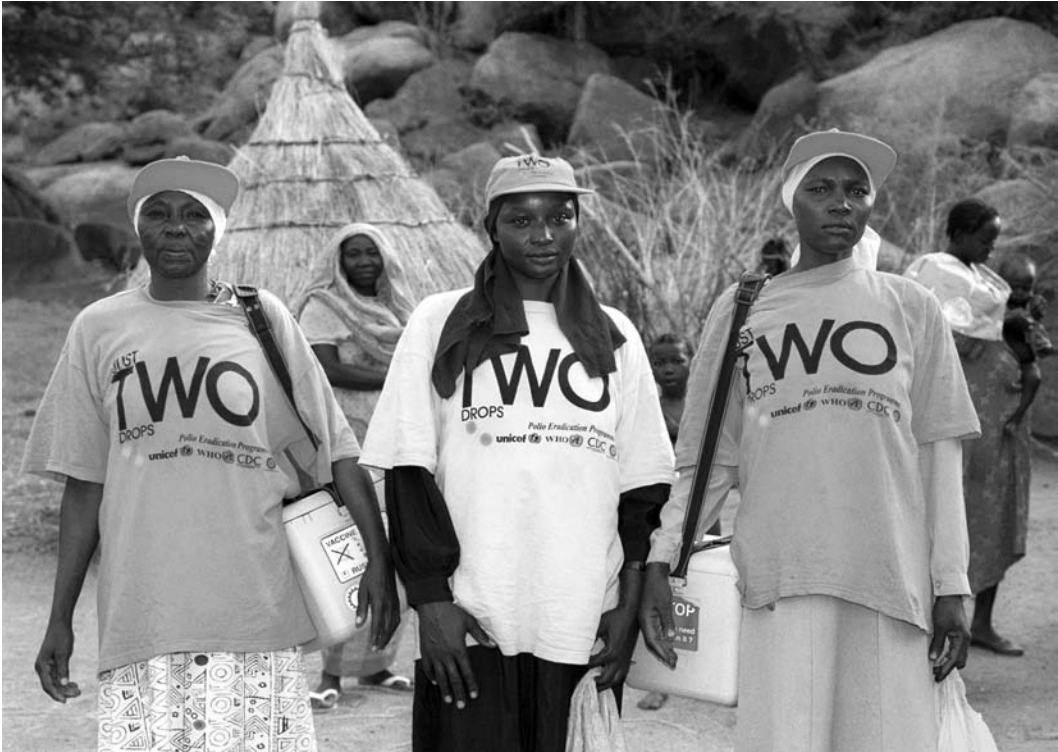
Donkeys can carry the vaccine through rugged mountain terrain in areas which are otherwise impassable.

©WHO

ANOTHER IMPORTANT PART of the eradication strategy is to supplement routine vaccination with National Immunization Days (NIDs). On these days, teams of vaccinators fan out in synchronized mass campaigns to immunize every child under 5 years old, regardless of their prior vaccination status.

GLOBAL STRATEGIES / SUDAN

These women are local vaccinators selected by WHO from villages around western Nuba. Colorful T-shirts printed with the words “Just Two Drops!” clearly identify the vaccination staff and the reason for their presence.



©WHO/Philippe Blanc

IN 2003, 415 million children were immunized during NIDs in 55 countries. Because the oral polio vaccine does not require a needle and syringe, volunteers with minimal training can serve as vaccinators.



©WHO/Jean-Marc Giboux

PAKISTAN

Vaccinators in Nasir Bagh Afghan refugee camp.

INDIA

A recent NID in India deployed 2 million volunteers to immunize over 150 million children in just a few days.



©WHO

THE YEARS 2005 AND 2006 are crucial as the world teeters on the edge of eliminating polio completely.

Two key challenges:

- › Combating the polio resurgence in west and central Africa amid the region's armed conflicts.
- › Filling the funding gap of \$75 million for 2005 and \$200 million for 2006.

Once again, success will demand strong political will and leadership, and public pressure.

resources

www.polioeradication.org

The official website of the Global Polio Eradication Initiative.

www.unicef.org/immunization/index_polio.html

Website of the United Nations Children's Fund (UNICEF), which plays a major role in the polio eradication effort.



voices

WORKING WITH COMMUNITIES: 1991 CHAPTER 38
COMING OF AGE AMID GRIEF, DEATH AND AIDS CHAPTER 39
TERMS OF ENGAGEMENT: SHAPING BRAZIL'S VACCINE AGENDA CHAPTER 40
AIDS, SOUTH AFRICA, STIGMA, VACCINES: JUSTICE CAMERON CHAPTER 41
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GOING FIRST: MDU NKOSI CHAPTER 43

My dream for the future?
To have a baby who grows up in a country free of HIV/AIDS.

—Mdu Nkosi, AIDS vaccine trial volunteer

PHOTO ©Josephine Cox

6

TANZANIA / previous page

Schoolchildren in Bagamoyo, Tanzania, who joined a group of researchers attending a workshop on AIDS vaccine development for their early morning jog.

working with communities: 1991

BILL SNOW

This speech was an early effort by a community representative in the US to convince researchers and government research program officers that community input is important for the AIDS vaccine field. (Snow was representing ACT UP New York, one of the first AIDS activist organizations, at an October, 1991 workshop of the National Cooperative Vaccine Development Groups for AIDS.) We have included it here as a testament to how far community involvement has come in some places, and as encouragement to other communities that are only now beginning to take their rightful seat at the table to participate in researchers' deliberations and decisions. It's also telling that the high-priority issues facing the field back then, which Snow discusses, have hardly changed.

MY NAME IS BILL SNOW. For the last few years, I've followed and reported on vaccine research and development for ACT UP New York's Treatment and Data Committee.

Last year, after we convinced the AIDS Clinical Trials Group (ACTG) to open its meetings, someone here realized we were useful, or that it was polite to include us, and we were invited to attend this conference. This year we've been asked to talk to you about "constituency" priorities.

"Constituency" is the safe government name for AIDS activists, patient advocates, community service groups, and people with HIV themselves, though of course we haven't chosen you and you haven't chosen us, as constituents do.

As scientists or businesspeople, and only amateur politicians, you may not have thought about having a constituency before. You probably don't think of yourselves as representing us except in the most general, vague ways. Many of you work in laboratories with specimens or animals and never interact with us. Even those of you involved in *clinical trials* work primarily with HIV-negative patients.

Our advice about your constituency is this: Everyone needs a vaccine for AIDS, but “everyone” isn’t a constituency. It is people known to be at high risk, those with the same demographics as the epidemic, who will benefit most immediately and most directly from your vaccine if they will take it, and if they can get it.

Our advice about your constituency is this: Everyone needs a vaccine for AIDS, but “everyone” isn’t a constituency.

Let me remind you who they are: gay men, intravenous drug users and their sexual partners, Blacks and Hispanics, certain unborn babies, prisoners, bisexual men and their sexual partners, and whole populations in Africa.

Let me tell you who they also are: adolescents, prostitutes and their clients, sexually active heterosexuals, and whole

populations in Asia.

And they are also your colleagues: laboratory workers and medical personnel who care for AIDS patients.

As activists, we have consistently pressed for participation in decision-making and access from all affected groups, no matter how uncomfortable that may be. In the AIDS Clinical Trials Group (ACTG), representation has taken the following forms:

- › open meetings,
- › a Community Constituency Group whose members vote on ACTG committees, and
- › *Community Advisory Boards* at each ACTG trial site.

Through our insistence and hard work, government, scientists, and the AIDS communities are getting to know each other well enough so that valuable informal communication channels have also developed to exchange information and opinions.

These mechanisms haven’t been in place long enough to prove themselves effective. Activists are divided on whether or not to support them. Some see them as co-optation, others as an opportunity to make changes from within. Certainly they’ve changed the tone and flavor of ACTG and introduced a realistic, patient-oriented point of view as well as a certain amount of healthy discomfort and open disagreement.

I believe that many potential problems can be identified earlier and addressed through these mechanisms and that we all benefit from open discussion and the urgency of our viewpoint. Yet, I don't believe these mechanisms will remove the need for ACT UP's kind of activism.

It is essential for you to move now and make the same provisions for community participation in the vaccine development effort:

1. Leaders of the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research and Development Branch should set up a community advisory group that participates in decision-making, as soon as possible.
2. The AIDS Vaccine Evaluation Units should all have active Community Advisory Boards.
3. Outreach should be used to publicize your meetings in affected communities.

Focus on populations with a high *incidence* of infection. We are educated and experienced from our drug development battles and are learning the specifics of vaccine development very quickly. We are also the ones who will be essential for vaccine *efficacy* trials. Wherever public funds are being spent or human experimentation is taking place, you have an ethical obligation to let us in.

It's not news that we live in a country where we can't educate freely about safe sex, or give out condoms or clean needles without a fight. There is no reason to believe you'll be able to give your vaccine freely either, if those in political power think it will promote promiscuous sex, homosexuality, freer drug use, or teenage sexuality. We have experience, a perspective, and a kind of moral authority that could ultimately help the vaccine development effort succeed, provided we can really work together.

LAST YEAR we heard three priorities from the National Cooperative Vaccine Development Groups:

One: Given the urgency of the epidemic, basic research is "irrelevant."

Yet we've heard all week that knowledge of *immunity* is far from complete. From the patient standpoint, a most obvious and urgent need is for the animal researchers who have demonstrated some immunity to characterize the immunological effect on every part of the immune system. These results could then be used as a basis to determine efficacy and trial endpoints that don't depend solely on *CD4+ T-cells* or clinical events that seldom occur in the patients with healthy immune systems you've been choosing for your trials. Especially with many potential agents, this will reduce the need for too many and too large efficacy trials.

Two: Highest priority will be given to large-scale SIV evaluation of vaccines.

A key idea should be to coordinate early animal and human experimentation. Instead, developers fall into one camp or the other, often due to their interpretation of the logistics and economics of vaccine development.

Animal and human experimenters must work together better. Ideally, animal experiments would provide guidelines and data for similar human experiments, perhaps conducted nearly in parallel. In the animal trials, you would look for immunology that could be used to determine progress in human trials, and you could do *challenge* experiments, and compare in vitro results.

Three: Empirical research is not the best strategy, but conduct as many Phase I and II trials as possible, as soon as possible.

Is this a logical approach? Are these trials asking and answering key questions? Are they as safe, as important, and as good for subjects as possible?

I'm a patient in the only AIDS Clinical Trials Group vaccine treatment trial. It has 52 patients, and it took almost a year for the *protocol* to be revised and vaccine made available. I almost wasn't included because my *T-cells* declined during the delay; I have two friends who weren't. It took seven more months to complete enrollment.

Now, after ten months and five shots of vaccine or *placebo*, nobody seems to know precisely what they've got. *In vitro*, my blood proliferates to *gp160* and *gp120*; it didn't before. There have been no dramatic changes in T-cells. I'm still feeling fearful but fine.

I recognize that I took a personal risk, but I've also started asking myself if the investigators know what they're looking for in these human trials. No clinical outcomes have ever been projected. Are they only looking for *in vitro* results? Is it a fishing expedition? Treatment activists are knowledgeable about sites, enrollment, fairness, willingness of patients to participate, avoidance of risk behavior, and trial speed. There are many AIDS activists from high-risk groups who are HIV-negative themselves. Risk populations have strong reasons to participate if approached correctly and responsibly. Their participation will also give us all the most reliable and relevant information.

Vaccine research and development have been changed. You make regular small strides. You report at the end of conferences to close them on an upbeat note. You get good press because the press and the public love the idea of a happy ending to end the AIDS crisis; ready to forget millions already infected. AIDS activists aren't breathing down your neck yet.

Still, you haven't had to produce anything but hopes, prospects and the bits of science that are important to us all. There are no timelines yet, no commitments, not even particular vaccines or cocktails of vaccines decided upon, just projections that are—comfortably for you, uncomfortably for us—far away.

A fraction of AIDS spending goes to you, but that could change in an instant. As you work towards academic-industry-government cooperation, as you plan and work together, you must include us, your “constituents.”

Thank you.



USA

Poster designed by a group of gay activists in 1987, to protest and raise awareness about the slow US government response to the burgeoning AIDS epidemic. The logo was later given to ACT UP New York, which has used it widely. The original posters also included the words: "Turn anger, fear, grief into action."

coming of age amid grief, death and aids

GARANCE FRANKE-RUTA

THERE ARE CHOICES one makes in life, and then there are experiences one doesn't so much choose as simply have. I became a member of ACT UP New York in 1988, when I was 17 years old, because I lived in a part of the world—gay Greenwich Village in the mid-to-late 1980s—that was a kind of ground zero for the AIDS epidemic in the US. Today, I live in straight and straight-laced Washington, D.C., where I work as a political journalist, and am as distant from the ongoing struggle for an AIDS vaccine and better treatments as the average member of the American public, though somewhat better informed about the history of these efforts.

I cannot claim that my own experiences represent anything in particular—in fact, I am certain that they don't—but in retrospect, my youth at the time I was involved with ACT UP was unusual. And in my memory of those years, perhaps, can be found some insight into how a person who knows little about life confronts a world that seems only full of death.

As AIDS continues to devastate nations around the world, millions of young people struggle in far different circumstances with a similar conundrum: How to live and build a life when

the world around you seems to have been upended before you arrived in it. More than a dozen years after I left ACT UP in 1991, the memories of those early years and battles remain strong. But the only take-home lesson I can offer should come as no surprise: AIDS messes with young people's heads.

What I remember most about those years was not the anger that fueled our work, or the camaraderie that gave us strength, or the hours upon hours of work we did—staying up all night writing reports and painting signs and banners and emerging into the early New York morning feeling virtuous and purposeful. What I remember most is the grief. “We are all people living with AIDS,” went one of the slogans of the day. And it was true. In gay communities where 40 to 50 percent of men were infected, people lived with loss as a constant background presence, a grief so shared as to seem somehow unworthy of acknowledgement, and yet deeply affecting each of us.

Larry Kramer asked people to live each day as if they might die tomorrow. It was a powerful rhetorical exercise for conveying the sense of urgency he had about the epidemic. And for many who were HIV-infected in that early medical era—when AZT was the only approved medication and there were not yet any particularly good treatments for opportunistic infections—it was not too far removed from being a realistic worry. But it was also not a particularly good framework for thinking about life as a young person. The natural trajectories of social development got broken and contorted by AIDS. I was moving into the world while too many people I knew were moving out of it—including many not much older than myself.

I recall Phil Zwickler telling me, when he was diagnosed with CMV and going blind, as if he'd just realized another thing he was going to miss by dying young: “I'll never get to see another Democratic president.” George H.W. Bush was still in office, and before that we'd had only the Carter interlude to break up the Republican grip on the presidency that stretched from 1968 to 1992.

I recall Jerry Jontz in the hospital in the awful summer of 1991, the streets of New York so hot you could smell the *E. coli* in the gutters, the sidewalks full of girls in mini-skirts

and platform sandals. Myself, still not college-educated and so broke I subsisted on 35-cent cheese sandwiches from a Puerto Rican bakery. The city was in the grip of the Bush recession, full of “Going out of Business” signs in storefronts and the sounds of Naughty by Nature blasting out of car windows. By August, the whole city seemed to have reached some desperate, sweltering pitch. And Jerry lay dying in St. Vincent’s Hospital. In 2001, that facility became the designated center for trauma victims on September 11, then spent weeks shrouded by a thin blanket of “Missing” posters, one decade’s tragedy overwriting another’s. AIDS had decimated far more of that hospital’s community in the 80’s and 90’s, but no nations then rallied to show their support. What we went through in New York in those years we went through alone.

One day Jerry could no longer recognize me. He could no longer see properly, or speak. He’d reach for an imaginary something just above and in front of his face. Swelling of the brain, the doctors said. Then came a short series of days when he did nothing but moan.

Sometimes the group held open casket funerals. Jon Greenberg wanted a political funeral; I said good-bye by bending over to touch his still, cold arm in Thompkins Square Park. By making the grieving public, a spectacle, his friends tried to include the world in their sorrows, and demand that its members involve themselves in the project of helping do something to alleviate them. I was 19 that year.

When I finally went to college at age 21, I met 19 year-olds who might as well have been raised on a different planet. I tried joining one of the college AIDS counseling groups, for continuity’s sake, but gave it up after I found myself having difficulty taking the worries of my sheltered fellow students seriously. Their troubles seemed so minor. Nor did the world I’d seen do anything but frighten them. I learned not to talk about the past.

AIDS is no longer a part of the world I experience. It seems strange that this is possible, but in the US, AIDS is so concentrated in certain communities that if you leave those

By making the grieving public, a spectacle, his friends tried to include the world in their sorrows, and demand that its members involve themselves in the project of helping do something to alleviate them.

circles you can go years without ever coming across more than a few people who are infected. And the advent of combination therapies in the late 1990's really did change AIDS from a death sentence into a chronic, largely manageable—though still incredibly difficult—medical condition for many in the world's wealthy countries. Even many infected individuals who once lived as if they might die tomorrow began thinking about how to live again—I mean really live, and not just survive.

My introductory experiences with the world are not something I would wish on another generation. And yet, they are decades—and a vaccine—away from being the kind of thing no one will ever know again.

terms of engagement: how communities helped shape brazil's aids vaccine agenda

ALEX MENEZES / brazil

IN LATE 1996, BRAZIL took the extraordinary step of making *antiretroviral* combination therapy available without cost to anyone who needs it. By combining the best treatments with aggressive prevention programs, the country has built a national AIDS strategy that's now hailed internationally as a model for how developing countries can effectively respond to the epidemic.

Non-governmental organizations (NGOs) have been an important part of this story by helping to build and sustain this national response. That's not been easy—behind this remarkable success story, it's a constant struggle to run a state-of-the-art program within a public health system riddled with problems. Both the government and civil society organizations wrestle daily with issues of quality, capacity, competing needs, bureaucracy and political commitment. What from a distance looks like a model for other countries, up-close is a work in progress.

But with the world's attention focused mostly on Brazil's treatment program, one thing that's gone unnoticed is that the national response (and the advocacy agenda) also embraced

vaccines as far back as 1992, well before effective treatments were available. By making vaccine issues part of their mandate, AIDS organizations took the lead in building public support for Brazil's involvement in the global effort.

This didn't come overnight; it's taken a long time for AIDS vaccine research to gear up in Brazil. So far there have been only three early-stage *clinical trials*—the first one in 1995, and two others launched in 2001 and 2004. And despite the high levels of support and mobilization, much more still needs to be done to get the country engaged to its full capacity, especially in preparing for future large-scale trials.

Once again, communities have a decisive role in this process. And they have valuable lessons to guide them, drawn from the broad mix of treatment, prevention and early vaccine efforts, and the experience gained in sustaining complex programs against long odds. As someone who's been involved in this process for over a decade, here's my perspective on where we've been, where we're going, and what defines the "Brazilian way" of community engagement with AIDS vaccines.

setting an advocacy agenda: the early 90's

When discussions about AIDS vaccine trials began in Brazil, the government's response to the epidemic was under heavy criticism. Most community groups felt that the national AIDS policies were ineffective and misguided, and there was constant friction (and little dialog) between government and activists. So at first, AIDS advocates were skeptical of plans to add vaccine research onto what they saw as a badly flawed program. Their initial mistrust, combined with a desire to closely monitor the process, became the key motivation for NGOs to get involved.

To ensure that the research agenda being proposed was justified, ethical, and appropriate to Brazil, advocates first sought the knowledge they needed to follow the scientific discussions. But rather than simply following the research from the sidelines, a core group of five NGOs began to develop its own vaccine agenda. They decided to focus on public awareness and vaccine education, starting with communities that were most affected by the epidemic. The skills and activities needed

to do this were already familiar to them: providing clear, simple information, raising issues publicly and building support around difficult questions. And the need for more informed communities was acute, since Brazil's first vaccine trial, which began in 1995, aroused huge public debate—mostly revolving around misconceptions and fear.

The NGOs began by putting together a series of publications about the state of vaccine research and the issues it raised. Beyond their information content, these materials—which later became a regular newsletter—sent an important message of support for vaccines from independent, broadly respected organizations. And they helped affirm that AIDS vaccines are a community matter, not just a scientific one. As interest grew, vaccines quickly became part of all main national AIDS events, and vaccine-specific meetings organized by and for community advocates drew hundreds of participants.

NGOs helped affirm that AIDS vaccines are a community matter, not just a scientific one.

an early legacy: combining treatment and vaccines

An important result of early community engagement—one that's especially important at this moment in the epidemic's history—is that it established vaccine work in Brazil as part of the overall response to HIV. The organizations that embraced the issue all had broader missions which blended treatment, prevention, advocacy and human rights. Vaccine advocacy and education were seen as additional roles, which NGOs had to play, especially in cities with trials planned, or ongoing. There was also a practical rationale: staff and funding shortages among AIDS organizations made this “comprehensive approach” a necessity, not a choice.

The result was that the leading spokespeople for vaccines were also advocating for the rights of people with AIDS and, in many cases, living with HIV themselves. To most of them, participation in vaccine research was a way of empowering affected communities to have a stake in using science to combat AIDS. At the same time, lessons learned from vaccine discussions helped NGOs improve their monitoring of clinical

studies on treatment and to earn a seat at the table with the scientific community and the government.

Brazil still has a serious epidemic, especially among its poorest people—so NGOs continue to face enormous demand for their support and services. But even now, organizations that have taken the lead on AIDS vaccine issues haven't dropped the ball on prevention or care.

advocacy without trials: 1996-2000

By the end of 1995, Brazil had a broad base of community organizations that were well informed about AIDS vaccines and supportive of research efforts. But it was six more years until the launch of the next vaccine trial. During this time, advocates and scientists worked mostly to prepare for future clinical research on vaccines—for example, three cities with plans for future vaccine trials conducted *cohort* studies, which follow volunteers from potential trial populations over time and gather data such as HIV infection rates and behavioral risks.

The NGOs that spearheaded mobilization around AIDS vaccines continued to organize skills-building workshops and updates on the global vaccine effort for the broader AIDS community. But with no new products moving into the clinics and uncertainty about when planned trials of older products would get launched, there weren't many opportunities for a new generation of advocates to get more involved.

What was not apparent at the time is that the site preparation work, despite the frustrations of long timelines and changes in research priorities, was important in sustaining interest around vaccines beyond a particular trial. And for communities, work on vaccine issues was never interrupted, regardless of the gap in running trials.

reinventing communities' role: 2000-2004

Once preparations for a second trial began in 1999, community interest in AIDS vaccines quickly intensified. The country's

first *Community Advisory Board (CAB)* for any kind of *clinical study* was formed. And the early engagement of community groups paid off nicely. Many of the doubts and fears that had surfaced around the first trial were barely heard of—because there was now a solid base of understanding on the issues that provoked the earlier controversy. The tide of public opinion had turned, and the 2001 trial (and a third one in 2004) received broad support.

New efforts to get these studies off the ground gave community work on vaccines a clear sense of purpose. Several new NGOs became involved with helping to develop research infrastructure, integrate vaccine messages in their daily work, and advocate for research or work with CABs. There are now three sites in Brazil doing HIV prevention trials, and at least two of them expect to start testing other products soon.

The “old guard” of vaccine advocates is still active, and is often called on to help build skills among the new generation. The vaccine community meetings and newsletter have continued. But the context is changing fast, and many organizations interested or active in the vaccine field are updating their agendas.

One recent example of this renewed enthusiasm for vaccines comes from a new clinical site in the south of Brazil. In 2002 news circulated that the National AIDS Program was thinking about developing clinical trial sites in this region. Its epidemic has some important differences to the rest of Brazil: a higher infection rate, a different mix of circulating HIV *strains*, and a significant IDU population. Local activists, galvanized by the prospect of a new trial site, have hosted regional vaccine workshops and organized a CAB to support efforts for bringing trials to the State of Rio Grande do Sul, becoming a driving force in this effort.

In another example, in October 2004 a grassroots organization in the northeastern region of Brazil gathered its peers from several neighboring states to develop a vaccine agenda. At the end of the meeting, participants issued a declaration supporting AIDS vaccine development and highlighting how community groups can contribute to the process, regardless of whether they are geographically close to a trial site.

Table 6.1 Milestones for community involvement with AIDS vaccines in Brazil

2004	Phase II trial (adenovirus-5-based vaccine) starts at 3 sites (one in Rio de Janeiro, two in São Paulo).
	Regional meeting of vaccine advocates in Northeast of Brazil (Pernambuco) issues Call to Action for accelerating vaccine development.
2002	Second update of National AIDS Vaccine Plan.
	Regional meeting of advocates in Southern Region of Brazil gathers support for local vaccine research; formation of local CABs.
2001	First Latin American Meeting on AIDS Vaccines for community advocates, held in São Paulo.
	Second CAB starts activities in São Paulo.
	Phase II trial starts in Rio de Janeiro (gp120 and canarypox-based vaccines).
2000	National AIDS Vaccine Plan revised.
	National training workshop for NGOs interested in AIDS vaccines.
1999	First CAB created at Rio de Janeiro trial site.
1996	Vaccine preparedness study starts in Rio de Janeiro.
1995	First clinical trial of an AIDS vaccine (based on peptides) starts in Rio de Janeiro, Belo Horizonte.
1994	First national community meeting on AIDS vaccines, attended by 400 NGO representatives.
1992	First NGO publication on AIDS vaccines; later became regular community newsletter.
	Creation of National AIDS Vaccine Committee, with 5 community representatives.
	National AIDS Vaccine Plan created.
1991	Meeting on vaccines with World Health Organization, Brazil's National AIDS Program and 22 Brazilian NGOs.

what have we learned?

ONE OF THE KEY LESSONS from Brazil's experience in AIDS vaccines is that it's never too soon to mobilize communities. Early engagement gave communities a sense of investment in the process. This, in turn, helped to build a strong constituency for AIDS vaccines and to sustain the effort over the years. On the other hand, the long lag time between trials in the 90's taught us that when there are no products to test, community mobilization can only do so much in advancing the research agenda. During these gaps, communities' watchdog role is especially important for avoiding unnecessary delays in moving the clinical research forward, whether from bureaucracy or from unfounded fears among the general public.

Advocacy for AIDS vaccines in Brazil has been guided by a long-term vision—the hope for a vaccine—grounded in the need to ensure that actual clinical research is ethical and appropriate. While an effective vaccine can seem like a far-off goal, trials are very concrete and require a lot of work to ensure that the local communities ultimately benefit from them.

Brazil's advocates have learned the importance of developing their own models for engagement, taking the country's epidemic, social systems, limits and priorities into account.

At the same time, though, it was also important to coordinate with peers in other regions, both to learn from one another and for more access to knowledge of international experience. And they learned that communities can speed progress by making the vaccine agenda their own—and then being ready to adapt it as the field progresses.

Advocacy for AIDS vaccines in Brazil has been guided by a long-term vision—the hope for a vaccine—grounded in the need to ensure that actual clinical research is ethical and appropriate.

resources

www.aids.gov.br/plano_nac_vacinas_ingles.pdf
Brazil's National AIDS Vaccine Plan, in English.

www.giv.org.br
Grupo de Incentivo à Vida's Portuguese-language website. The website has a comprehensive searchable archive of all articles ever published in the national vaccine newsletter, *Boletim Vacinas Anti-HIV/AIDS*.

www.praçaonze.ufrj.br
Projeto Praça Onze. The website of this clinical research unit in Rio de Janeiro has information about their CAB, their current trials, etc.

www.vacinashiv.unifesp.br
Universidade Federal de São Paulo (UNIFESP). São Paulo State University's vaccine research unit. This Portuguese-language website has comprehensive information about AIDS vaccines.

aids, south africa, stigma, vaccines: a conversation with justice edwin cameron

JUSTICE EDWIN CAMERON with PATRICIA KAHN / south africa

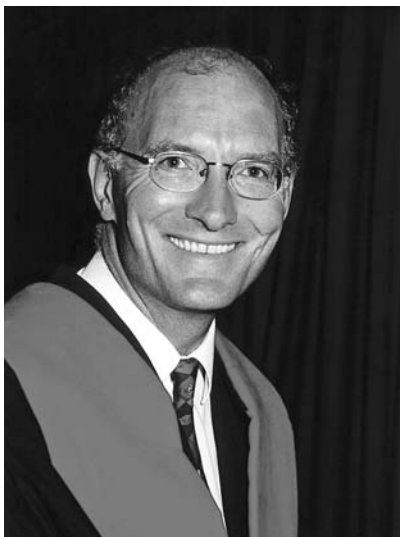
Justice Edwin Cameron, a judge on South Africa's Supreme Court of Appeal, first made headlines around the world in 1999, when he publicly declared his HIV-positive status. The next year he electrified the audience of the 13th International AIDS Conference in Durban with a keynote speech that was a searing indictment of his country's (and the world's) neglect of the epidemic, and a rallying call for commitment to providing *antiretroviral* treatment for the millions of infected people unable to pay for it. In June 2004, Patricia Kahn caught up with Justice Cameron to discuss his country's progress since Durban and its growing role in HIV vaccine development.

LET'S BEGIN by talking about stigma and AIDS. It was a groundbreaking act when you first publicly declared that you're HIV-positive. Have things changed since then?

Yes, definitely. That was five years ago, in April 1999. I was at an AIDS candlelight memorial recently where a well-known radio personality was the emcee, and she's living openly with HIV. There's been quite a fundamental shift just in the last few months, in terms of people willing to go public with their status.

What about at the village level, among people who aren't well off or prominent? Aren't stigma and fear still very engrained—even though HIV affects so many people?

The experience in central Africa is that there are high levels of stigma until AIDS starts affecting *every* household, *every* family, every workplace, church and community organization. South Africa is where Uganda was 12 or 15 years ago. The remarkable thing is that stigma is now reducing here, for this reason.



JUSTICE EDWIN CAMERON

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On an informal level there's a much greater willingness amongst people with HIV to speak out.

But perhaps things are a bit different here in South Africa, because we have a very developed AIDS activist community. And before that we had a very developed anti-apartheid resistance. In democratic, post-apartheid South Africa the country's strongest activist group is an AIDS organization, the Treatment Action Campaign (TAC). Within TAC there's always been a very high level of visibility and openness for people living with HIV and AIDS.

Yet outside these activist circles, stigma continues to be a problem. The brute reason is that sexually transmitted diseases

are so attended with overtones of closeting, privacy, taboo, shame, guilt. As for why stigma is still so high, I think it's because we haven't reached the peak of AIDS deaths. As that happens, things will change.

Has stigma found its way into the law, or are there strong legal protections for people living with HIV?

The legal framework has always been outstanding. The one thing we got right as far back as 1994 is good principles and good legislation. I won't go through the details, but we've got an unparalleled legislative framework protecting people from discrimination. But of course legal rights depend on people's willingness to be assertive. And there we go back to the issue of stigma, and the bind it creates.

As for why stigma is still so high, I think it's because we haven't reached the peak of AIDS deaths. As that happens, things will change.

How do you see the government's progress on responding to the epidemic?

I feel it's very promising. In April 2002 the government released a Cabinet statement which for the first time envisioned antiretrovirals as part of an overall national AIDS strategy.

I welcomed it then as being revolutionary. I've always talked up rather than talking down the government initiatives. I continue to be determinedly optimistic, despite some troubling evidence of government foot-dragging. Still, I think the initiative in August 2003, which was the first commitment to provide treatment in the public sector, and then the Cabinet plan approved in November, are enormous breakthroughs.

At least we have gotten to the point where we're dealing with the real problems—which are toxicity, monitoring, access, availability, compliance. This is an enormous relief. And I would draw your attention to the fact that President Mbeki actually mentioned the commitment to a treatment target in his State of the Nation speech [in May 2004] when he addressed Parliament after his re-election. That has enormous symbolic importance.

Let's move to AIDS vaccines. The South African government has been a strong supporter of vaccine research—even back in 1999-2000, when President Mbeki was openly embracing the “HIV dissident” view which denied that HIV causes AIDS. This seems like such a paradox.

Our government has always been willing to countenance a quick-fix solution to AIDS. You'll remember the Virodene debacle of 1995–1996. This was a quack remedy which received Cabinet endorsement, huge amounts of publicity, government funding—and was proven to be virtually a hoax. But a quick fix not only cuts medical corners but also ideological corners.

In a way the vaccine option takes the sting not only out of treatment and the whole epidemic, but also skirts ideology. That's why I think there's been such a ready embrace of it.

What does this have to do with vaccines?

If a vaccine is safe and harmless, it doesn't matter how many people you give it to. But if HIV doesn't cause AIDS, and treatment is complicated and long, has to be sustained and monitored, and is potentially toxic, then you need to investigate whether this is a conspiracy perpetuated by Western governments and drug companies to poison Africans, which is what the Denialist stance amounts to. So in a way the

vaccine option takes the sting not only out of treatment and the whole epidemic, but also skirts ideology. That's why I think there's been such a ready embrace of it.

You might remember that President Mbeki toured the US in 2001, where he visited a vaccine facility in Virginia. This was just three months after he sent a letter to heads of Western governments, including President Clinton, comparing the AIDS dissidents to Galileo.

Speaking of paradoxes, during the review process for the vaccine trials now going on in South Africa, the regulatory agencies required that sponsors guarantee access to ARVs for volunteers who became infected through their risk behavior while the trial was going on. But at that time the government itself wouldn't commit to providing treatment. How do you explain this?

It depends who in the government you're speaking of. Within the AIDS directorate and the Medical Research Council, there's always been acceptance of HIV as the cause of AIDS. The Denialist hypothesis was never widely accepted outside the presidency itself and a few Cabinet members. The rest of the government still functioned on the conventional premise, although with massive inhibitions.

As the country begins to roll out a national program for treatment, can vaccine trials contribute to the treatment agenda?

Yes, as pilot programs, very much so. Vaccines add to the rationality process, by offering a de-stressed, non-ideological way forward. If treatment is an adjunct to a trial, even for a relatively small number of vaccine volunteers, then it's acceptable. So I think it has helped.

Although the vaccine trials going on now in South Africa have only small numbers of the lowest-risk volunteers, larger trials coming up will draw participants from high-risk populations. Going back to the issue of stigma, do you think people will be willing to come forward?

No doubt whatsoever. But I'll give a long answer, since this ties in with something we haven't spoken about. We need to radically rethink the activists'/human rights community's requirements on testing [that testing should be done only on request]. I support the Botswana government's position, which is that patients at public health facilities are tested for HIV by default. They get the choice to opt out, but it's got to be opt out, rather than opt in. My human rights comrades didn't always support that.

I bring this up to make the point that as treatment becomes accessible, human rights norms must change because peoples' attitudes will change. As vaccine trials move into high-risk populations, the availability of treatment is definitely going to change peoples' attitudes towards getting tested, and to come forward for vaccine studies as well. It's a whole beneficent circle you want to get going.

Looking ahead to the issue of vaccine access, do you see any ways to avoid that access to vaccines goes the same route as ARVs, in the sense that a successful vaccine is available first, or only, to those who can pay?

I don't, unless there's a commitment to make it available through activist organizations, or with their assistance. This is the sort of governmental/NGO cooperation that our Constitutional Court pleaded for when it issued its judgment requiring the government to make perinatal treatment available. Unfortunately, though, we're dealing with a skewed world, and this skewedness reflected within each poor society—India, Thailand, South Africa, Nigeria. You've got a microcosmic First World/Third World gulf between people who live like I do, in warmth and affluence, mobility and international connection, internet connection, and people who don't. Unless you make a very real commitment to avoid privileging the same people with a vaccine rollout, you're going to replicate those problems within the society. The activist organizations like TAC, which has been *very* savvy about building bridges with community organizations and trade unions, would be one way to avoid that.

resources


www.aidsinfonyc.org/tag/tagines/2000/cameron.html
Justice Cameron's speech at the XIIIth AIDS Conference, Durban (2000).

www.tac.org.za
Treatment Action Campaign. Information on TAC's campaign to broaden access to affordable treatment in South Africa.

going first: a conversation with anthony morris

ANTHONY MORRIS with PATRICIA KAHN / usa

On July 15, 2003, Anthony Morris became the first person to be *immunized* in a trial of a new type of AIDS vaccine. Born and bred in a low-income Baltimore neighborhood that's been hard-hit hard by the AIDS epidemic, Morris, a young African American man, bucked the extreme skepticism of his family and friends when he became a trial volunteer. The vaccine in this study uses a new technology (based on a harmless version of a horse virus called *VEE*) and contains a single gene from an HIV *strain* isolated in South Africa. Morris spoke with Patricia Kahn shortly after he finished his study visits for the one-year trial. (Chapter 43, which follows, is a conversation with one of the first volunteers to test this same vaccine in South Africa several months later.)



TELL ME a little bit about yourself and your background.

I'm 34 years old, which I say reluctantly. I was born in Baltimore, Maryland, raised mostly with members of my mother's side of the family, since my mother died when I was 17. I went through two years of college doing criminal justice and then was injured. I had a long recovery and am still disabled.

What happened?

I was working as a security guard and got a gunshot wound in the back. I was in the hospital for three years. I sometimes joke that I'm more metal than man—they had to reconstruct my spinal column and replace some of it with metal rods. I can walk, even though they told me I wouldn't, and there is still lots of pain. But now I'm back in college finishing my degree.

What got you interested in the vaccine trial?

I happened to come across an ad in a newspaper, looking for volunteers for the vaccine study. I was always interested in finding out more about AIDS because there seems to be so much wrong information, and because some of my friends and family members have died of AIDS. So when the vaccine study came up, I thought maybe I can do something.

Some of my friends and family members have died of AIDS. So when the vaccine study came up, I thought maybe I can do something.

How did those deaths affect you?

A lot of my friends who died were into drugs, for some others it was unprotected sex. My uncle who died got infected from using drugs. That stunned me more than any other death, because when I was a kid, he was a mountain of a man. With a bad attitude. He and my father, they were tough, and they taught us to be the same way.

To go into the hospital and see a man who used to be really muscular and weigh 200 pounds—he was down to 120 pounds, just skin and bones. It was really frightening.

This was in the late 80's, and people around me were still in denial about AIDS. We thought it was just a gay white man's disease, and that heterosexuals couldn't get it. But since then, even a lot of female friends of mine have died of AIDS. And we hear more about the down low life, about more African American men who have unprotected sex with other men, sometimes in clubs and parties, and then bring HIV home to their wives and girlfriends. They don't consider themselves gay—that doesn't jibe with their sense of masculinity. But for AIDS, what really matters is being open, living without deception, so you can protect yourself and other people.

What happened when you first contacted the trial site?

They sat me down and talked with me about how the trial process works. But I didn't get into the first study because I came in too late. Then they called me back later and told me about another study, the one I'm in now. This one was a completely new vaccine.

How did your family and friends react when you told them you were going to be a volunteer in the trial?

“Crazy man,” mostly. Some of them said, “What, are you out of your mind? You’re actually going to in there and get shot with AIDS?” I explained everything to them, and after all that they said again, “OK, so you’re going to go get shot up with AIDS?” I said no again, and it went back and forth.

Why didn’t they hear you?

The reasons were mixed. Some just didn’t trust the government, some brought up white man, black man and so on. They said, “well, you know back in the days of Tuskegee they did terrible experiments and they always used the black man.” I said OK, I know this, and the trial staff told me this. I understand it. But I just don’t think this will happen now. This is the 21st century. Government restrictions are very tight and I don’t believe they’d be foolish enough to do something terrible that could be exposed so easily. Something like that would rock the nation. If I had any thought it would be that way, I would have turned against them and tried to expose it.

Did any of your friends and family change their minds over time, or do they still think you were crazy to participate?

Some were so close-minded that they didn’t understand, and they still don’t. They still walk around saying to me, “you got AIDS.” For other people, once they knew more, they were disappointed that what we’re testing isn’t a cure. I would love it to be a cure. Then no one would have to worry about AIDS in their life. Unfortunately we’re not on that road.

What made you willing to trust the medical system, especially when most people around you didn’t? You said before that you spent three years in the hospital and almost didn’t walk again—did that make a difference?

Absolutely, that was part of it. But there was also something else. The time of my shooting was just after it came out in the news that there were cases of people getting AIDS from blood transfusions. I was having lots of surgery, so I was pretty scared. I was definitely checking what type of blood was being used, that it was being tested thoroughly. And my family was checking and asking questions during my surgery. But I got through that, too.

Were you scared when you got vaccinated?

No, it never really occurred to me to be scared, once they explained that I couldn't get HIV from the vaccine. They explained that the vaccine had only a part of the HIV and that they would test for the *immune reactions* in my bloodstream. They said if the vaccine worked it wouldn't cure the disease, which I thought at first, but could make it take a very long time until people got sick, or make the disease more manageable for people who get infected after they're vaccinated.

It never really occurred to me to be scared, once they explained that I couldn't get HIV from the vaccine.

What about being the very first person to get this vaccine?

Like I said, I'm the type of person who's just gung ho. I had the information I needed, let's just do this. I was pretty positive of the outcome and the procedure. My biggest fear was about getting jabbed, that maybe they wouldn't stick me right. Nothing about the vaccine itself.

What do you see now in the community around you?

Are things getting better or worse?

In the low-income society that I experience, I know a lot of people who have changed their ways. But society itself hasn't really changed. There's easy access to street drugs. The economic situations of a lot of people, especially in the African-American community, mean a high level of depression, which leads people to try to self-medicate. That can put them at risk

for HIV/AIDS, in a whole deadly circle. A lot of people without income, black, white, whatever, without income—there's a state of mind. People try to lead their lives by any means possible, even if it involves self-medicating with drinking and drugs—any way they can escape, even for a short time.

Now that the trial is over, what stays with you the most when you think back on it?

I'm happy to see a lot of people really investing time and energy to confront AIDS. I'm positive we'll see a dramatic change in conquering this disease, hopefully in my lifetime. At least in time for those nieces and nephews of mine. These studies at least give us hope that AIDS will go away. Someday.



MDUZI SABATH NKOSI

©Liz Clarke

going first: a conversation with mdu nkosi

MDU NKOSI with LIZ CLARKE / south africa

Five months after Anthony Morris was vaccinated in Baltimore in *clinical trials* of a new type of AIDS vaccine (see chapter 42), the study expanded to trial sites in Durban and Johannesburg. The vaccine was the first one based on *clade C strains* of HIV (the most common family of strains circulating in South Africa) to enter clinical trials. And it was the first AIDS vaccine study to be launched in South Africa, followed in quick succession by two others.

Mduduzi Sabath Nkosi, age 28, was the first South African to be vaccinated in Durban. Nkosi, nicknamed Mdu, calls himself “a proud Zulu” and was born and raised in the northeastern region of the country, close to the Swaziland border. Here he speaks with journalist Liz Clarke, AIDS writer for Independent Newspapers in South Africa, about his experience as a trial volunteer.



TELL ME about yourself.

My home is in the rural area of Mpumulanga. My mother and father are simple farming people in their 60's, and I have a large extended family. I am Zulu speaking. In 1998 I came to KwaZulu-Natal to study electrical engineering. At the moment I am working part-time to earn enough money to finish my studies.

How did you hear about the vaccine trial?

One day I was listening to the Ukhozi Radio station when I heard staff from the Medical Research Council (MRC) invite people to their offices in Durban to learn about AIDS vaccine research. They gave a telephone number so I contacted the lady. That was in December 2002. I spent a full day there with others who had also heard the program. [The staff] explained everything about the *virus* and the importance of a vaccine that could one day help millions of people.

At that point, what did you know about HIV/AIDS?

I had read about this disease in magazines and how dangerous it was to have unprotected sex, but at that stage I did not know the science or what the virus did inside the body. None of my family is infected and I don't know a single person [living openly] with HIV. But this maybe is because people don't like to talk about it and wouldn't admit they have it. I know people who are ill, and yes, they could have the symptoms. But they haven't been tested for HIV, so it is difficult to say.

What do your friends think of this disease?

People are very frightened. They don't talk about it or call it by its real name. They sometimes call it "*Egameni Likayisa Nelendodana Nelikamoya Oyingcwele*," which means "In the name of God, the Son and the Holy Ghost." Because I have a lot of information I try to tell young people to take advice from nurses and doctors about prevention. I ask them if they are aware of the devastating things that can happen, and that there is no cure. It is very disappointing when they don't listen. Even when they start to lose weight and cough a lot, or have diarrhoea or sores in their mouths, they would not say anything. They are ashamed and know that people will look down on them if they are positive. Their families could also turn their backs on them.

Are you also frightened of getting HIV?

I am aware of the problem, but I have always been a very responsible person, and don't believe in having a lot of girlfriends. I always use condoms and will only be with someone I intend to marry. In the Zulu tradition the rules are very strict. If you meet a girl and it is serious, you take her home where *lobola* [money the man's family pays for the wife] is discussed. Sleeping around with one girl after another if you don't intend marriage is not acceptable in Zulu culture. If young people followed that rule there would be fewer people getting sick. When you have playboys there is no commitment, and that is where the problems start.

What do you see as the value of a vaccine and your role in the process?

If our people are going to survive we need something that will prevent this disease. If there comes a time when every baby born in the world is vaccinated against HIV/AIDS, this would be a good thing. I decided to join the study because I wanted to help prevent our children from becoming infected.

If our people are going to survive we need something that will prevent this disease. If there comes a time when every baby born in the world is vaccinated against HIV/AIDS, this would be a good thing.

What happened after you agreed to participate in the trial?

It took about 11 months between joining up and having the first injection. There were many meetings. It was explained what was expected of us during the trial period, and how the vaccine might work. We were told that the only people eligible were those between ages 18 and 60 who were HIV-negative and had no other diseases. But we would have to undergo an AIDS test and other blood tests. They told us that there were some risks of side effects from the vaccine, but this would be watched carefully. [Although there is no risk of infection from the vaccine,] if we became infected during the trial we would be offered treatment.

We didn't say yes or no right away. First we went back to our families and people close to us and talked with them about it.

What did your family say when you told them you were going to volunteer for an AIDS vaccine trial?

I didn't discuss it much with my father because it wouldn't really mean much to him. He is illiterate, so he has not read anything about it. My mother is also illiterate, but she is much more knowledgeable about everything and takes an interest. She knows about HIV from people explaining it to her. She said I was doing the right thing and I must continue. She was proud I had made this decision.

How did you feel on the day when you knew you would be making history as the first South African volunteer?

It's difficult to describe. When I got up that morning I was a bit nervous because I knew that this was a very important day for my country, my community and really for the whole world. I wanted to tell everybody what was in my heart, but there wasn't anybody who would really understand. On my way to the MRC I wondered about the injection. Would it hurt? Would I feel any different afterwards? But I trusted the staff, and they had prepared us well for this occasion.

At the clinic, everybody was very excited. It was a nice feeling knowing that this could make a big difference to people's lives one day. I know it is still going to be many years, but you have to take a first step. After the injection, everybody shook my hand. It was a strange feeling knowing that this vaccine was making its way through my body. I tried to imagine where it was and what it was doing. I also hoped my body would do the right thing.

One day when I have children and grandchildren I will tell them about this day. I think it will always be important in my family, maybe not now but in 10 years. I have also learned a lot from this experience about my own health and my body and also about research and vaccines.

Have you had any bad reactions to the vaccine?

No. I have been very well. I have had several blood checks and everything was fine.

Would you encourage other people to become volunteers?

Of course. But that is very difficult. The disappointing thing is that people are so afraid to be tested, which is the first problem in volunteering. I say to my friends that if they are HIV-positive it would be much better to know early on, when more can be done to help them. They shake their heads and don't want to talk about it. But I will go on trying.

What were the reactions when it became known you were the first volunteer?

After my picture appeared in the newspaper there was a lot of talk about it. A 15-year-old friend rushed back to her mother with the newspaper and said to her, “Look what my friend has done—one day I would like to do the same thing.” Her mother said I was a “good guy.” So it is important that more people read about the vaccine. Then they won’t be suspicious and think it is something bad.

What lessons have you gained from this experience?

It is that we must be in a partnership like brothers. The government must make sure that *antiretroviral* treatment is available at all the hospitals and clinics in our country. But we must also try [harder] to prevent [infections from] happening in the first place. Often I hear people saying there is not enough money for AIDS medicine, but when those same people get sick they don’t want to be tested or take any advice.

The only way to find solutions is to participate in the future. We can’t all be heroes, but we can make a difference.

[I also learned that] the only way to find solutions is to participate in the future. We can’t all be heroes, but we can make a difference.

What is your dream for the future?

To have a baby who grows up in a country free of HIV/AIDS. But perhaps that will be for my grandchildren.



Since AVAC published the first edition of this book just five years ago, 25 million more people have become infected with HIV and almost 15 million have died. Almost 5 million people became infected in 2003 and nearly 3 million were killed by AIDS. Over 20 million people have died since the first cases of AIDS were identified in 1981. The number of people living with HIV continues to grow and now approaches 40 million worldwide. Each day 14,000 men, women and children get infected — people in the most productive years of their lives, or with their whole lives still ahead of them. Shocking, numbing, sobering — the tragic testament to an epidemic that rages on.

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BIOGRAPHIES

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has been involved in HIV advocacy and education for over a decade, through organizations such as The Gay Men's Health Collective of The Berkeley Free Clinic in California, the Whitman-Walker Clinic in Washington, DC and AVAC. He has also served on Community Advisory Boards (CABs) for HIV vaccine trials on both coasts of the US. He now does HIV prevention work in Southern Mexico and Belize.

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LIZ CLARKE

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CHRIS COLLINS

is a co-founder of AVAC and was its Executive Director in 2002-2003. As an aide to US Congressional Representative Nancy Pelosi he helped develop the first national legislation to provide incentives for private companies to work on developing microbicides and on vaccines against HIV, TB, and malaria. He has written widely about HIV prevention, research and policy issues and is currently a consultant in health policy and communications, as well as a member of the AVAC Board of Directors.

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is a senior editor at *American Prospect*, a Washington, DC-based magazine that covers US politics. Before joining the Prospect staff, she worked as a writer for *The Washington City Paper*, the District of Columbia’s alternative weekly newspaper. During the early years of ACT UP New York, from 1988–1991, she volunteered with the Treatment and Data Committee to promote research and development of new AIDS treatments. Garance is a co-founder of AVAC, along with Bill Snow, David Gold and Chris Collins.

DAVID GOLD

began his work in AIDS as a volunteer lawyer at Gay Men’s Health Crisis (GMHC) and a treatment activist with ACT UP New York. From 1991–1995 he headed the medical information program at GMHC and edited its newsletter, *Treatment Issues*. He then moved to the International AIDS Vaccine Initiative, where he founded and edited the *IAVI Report* newsletter for several years before becoming IAVI’s first vice president for policy and public support. He is now a principal at Global Health Strategies, a consulting company specializing in public health issues.

RUPERT HAMBIRA

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RICHARD JEFFERYS

is Basic Science Project Director at the Treatment Action Group (TAG), a non-profit AIDS research advocacy organization in New York. He started in the HIV/AIDS field in 1993 at the AIDS Treatment Data Network, working on treatment and treatment access-related issues, and moved into writing full-time about AIDS vaccines and immunology as a staff writer for the *IAVI Report* newsletter in 2001. He has also written on these topics for *HIVPlus*, *GMHC Treatment Issues*, *CRIA Update*, *POZ Magazine* and *TAGLine*.

PATRICIA KAHN

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is Gender Advisor to the International AIDS Vaccine Initiative, where she focuses on identifying and removing obstacles to women's participation in AIDS vaccine trials. Before joining IAVI in 2002 she worked for the United Nations Children's Fund (UNICEF) and the United Nations Development Fund for Women (UNIFEM) in New York.

EDD LEE

is the AVAC Director of Community Education and Outreach. Edd grew up in the Twin Cities area in Minnesota, where he was involved with various health and human rights group, including the American Cancer Society, District 202, the Minnesota LGBT Educational Fund, The Queer Street Patrol, Minnesota Men of Color and the Dim Sum Club. Before joining AVAC he was Associate Director of Prevention Services for the Asian & Pacific Islander Wellness Center in San Francisco and served as community co-chair for the San Francisco HIV Prevention Planning Council.

GRAHAM LINDEGGER

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JOSEPH MAKHEMA

is a physician and co-investigator on various vaccine research protocols in Botswana. He has extensive experience caring for AIDS patients and is a key player in preparing the country for vaccine trials. Joe is a former member of the National HIV Vaccine Committee and continues to advise the Committee on many issues.

MICHAEL MARTIN

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SHAUN MELLORS

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ALEXANDRE MENEZES

has been involved in AIDS advocacy since 1992. From 1993–2001 he worked with Grupo Pela Vidda in Rio de Janeiro, helping to organize community meetings and skills-building workshops and representing them at Brazil's National AIDS Vaccine Committee. He was also an active member of the Rio de Janeiro vaccine trial site's Community Advisory Board. Alexandre currently works for the International AIDS Vaccine Initiative in New York and is on the AVAC Board of Directors.

NTHABISENG PHALADZE

is a lecturer in the Department of Nursing Education at the University of Botswana. She has been a member of the Maiteko a Tshireletso HIV Vaccine Initiative Community Advisory Board since its inception in September 2001 and is currently co-chair of the Gaborone-based CAB and the global CAB of the US HIV Vaccine Trials Network (HVTN). Nthabi is also a member of several community-based groups focused on the AIDS epidemic.

AUDREY SMITH ROGERS

is an epidemiologist with the Pediatric, Adolescent and Maternal AIDS Branch at the National Institute for Child Health and Human Development, a unit within the US National Institutes of Health (NIH). In 1994–2001 she was Science Officer for the REACH Project, a study which followed a population of medically managed HIV-positive youth, and is now Science Officer for the Adolescent Medicine Trials Network for HIV/AIDS Interventions. She is also a member of the Adolescent Scientific Committee of the Pediatric AIDS Clinical Trials Group (ACTG) and is active in the Society for Adolescent Medicine, especially in helping to develop guidelines for the ethical conduct of research involving adolescents.

BILL SNOW

has been an advocate for AIDS vaccines since 1990, first through ACT UP New York and then through ACT UP Golden Gate/Survive AIDS. He was instrumental in establishing national and local Community Advisory Boards in three US government vaccine clinical trials groups—the AIDS Vaccine Evaluation Group (AVEG), HIV Network for Prevention Trials (HIVNET) and HVTN—and served as a community representative on each of their scientific steering committees. Bill is currently a member of the Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise and an Emeritus member of the AVAC Board of Directors.

CHRISTINE STEGLING

is Director of the Botswana Network on Ethics, Law and HIV/AIDS, an organization that addresses human rights and legal issues in the context of Botswana's HIV epidemic. Her background is in social anthropology and development studies, and she was formerly a lecturer in sociology at the University of Botswana. Christine has been a member of the Maiteko a Tshireletso HIV Vaccine Initiative Community Advisory Board since its inception and has served as its Secretary since early 2003.

PRAVAN SUNTHARASAMAI

is a physician specialized in clinical tropical medicine and vaccinology. He is now a consultant of the Clinical Infectious Research Unit within the Faculty of Tropical Medicine at Mahidol University in Bangkok and Deputy Chief of Clinic Coordinating Component of the Bangkok Tenofovir Study Group.

JORDAN TAPPERO

is a physician and Director of the Thailand/US collaboration between the Thai Ministry of Public Health and the US Centers for Disease Control, and Public Health Attaché to the US Embassy in Thailand. Before coming to Thailand he led the CDC's epidemiology section for the Meningitis and Special Pathogens Branch, which focuses on bacterial meningitis and bioterrorism preparedness. From July 1995–May 1998 Jordan served as CDC's first medical epidemiologist assigned to its field station in Botswana, where he did research and worked to strengthen activities on HIV and tuberculosis.

PENINAH THUMBI

is the clinical trials manager responsible for the daily management of participants in Botswana's HIV vaccine study clinic, and for adherence to the trial protocols and to Good Clinical Practice (GCP) and source documentation.

FRITS VAN GRIENSVEN

is a behavioral epidemiologist and the Associate Director for Research of the collaboration between Thailand's Ministry of Public Health and the US Centers for Disease Control Collaboration. He was trained in The Netherlands and the US in medicine and public health, following his studies of sociological theory and social research methods. His main interest is behavioral and biomedical HIV prevention research.

SUPHAK VANICHSENI

is a physician who has worked on issues of injection drug use and HIV/AIDS in Thailand for over two decades. She coordinated follow-up of incarcerated participants in Thailand's first Phase III trial of an AIDS vaccine (VaxGen's AIDSVAX candidate), and of the preparatory study leading up to the trial. She is now Chief Clinic Coordinator for The Bangkok Tenofovir Study.

TONYA VILLAFANA

is the site Director for the HIV Vaccine Initiative in Botswana and an investigator on several vaccine research studies in the country. She was responsible for establishing two HIV vaccine clinical trial sites in Botswana and has worked closely with the Ministry of Health on initiatives to build in-country capacity for conducting these trials, including strengthening of national regulatory bodies and advising the National Vaccine Committee on the development of a national vaccine plan.

SABINA WAKASIKA

is a licensed nurse with expertise in public health and has spent the last six years as an STI/HIV trainer for middle level medical training colleges in Kenya and as a tutor for nurses. She began working with the Kenyan AIDS Vaccine Initiative in 2001, with a focus on integrating and educating communities about vaccine development and on counseling AIDS vaccine trial participants. She is also a community advisor to the Nairobi office of the International AIDS Vaccine Initiative, helping to build vaccine literacy (through building capacity at community-based organizations) in five provinces.

STEVE WAKEFIELD

is a health care advocate with over 25 years of involvement in projects to increase community participation, particularly among African-Americans. He is currently the Associate Director for Community Relations and Education for the NIH-sponsored HIV Vaccine Trials Network. Steve also serves on the AIDS Vaccine Research Working Group of the US National Institute of Allergy and Infectious Diseases and on the AVAC Board of Directors.

MITCHELL WARREN

became the Executive Director of AVAC in April 2004. Before moving to AVAC he led efforts at the International AIDS Vaccine Initiative to increase community understanding and national involvement in AIDS vaccine trials in parts of Africa, Asia and Latin America. Prior to joining IAVI Mitchell spent over a decade working on public and reproductive health issues in developing countries, as Vice President and Director of International Affairs for The Female Health Company, the manufacturer of the female condom, and with Population Services International in South Africa.

PAUL WETAKA

is a soldier in the Ugandan military and has been involved with AIDS vaccines since the mid-1990's, when he volunteered for the country's (and Africa's) first AIDS vaccine trial. He was also a member of that study's Community Advisory Board, and of the CAB for Uganda's second trial in 2003-2005. He currently works with the Army unit that provides medical care for soldiers with HIV/AIDS and speaks frequently on radio, television and at workshops about HIV prevention and vaccine research.

Fig. 7.1 Countries conducting AIDS vaccine trials (February 2005)



trial sites around the world

source: adapted from International AIDS Vaccine Initiative (IAVI)

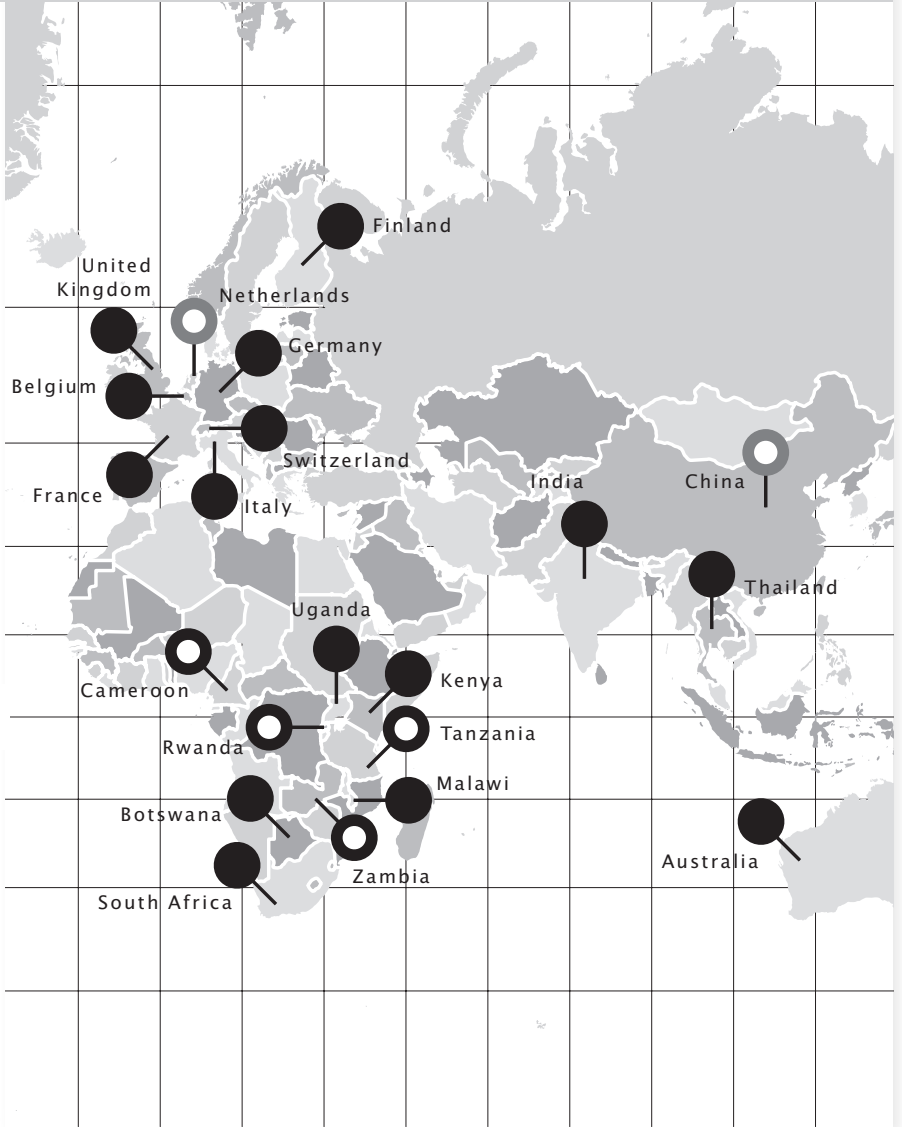


Table 7.2 Preventive AIDS vaccines in clinical trials (February 2005)

Two-vaccine combinations			
Sponsor¹	Developer¹	Trial site(s)	Phase
USMHRP, MoPH	Aventis, VaxGen	Thailand	III
DAIDS/HVTN, ANRS	Aventis	USA	I/II
IAVI, MRC	U. Oxford, KAVI	Kenya, Uganda, UK	I, I/II
DAIDS	Australian/Thai HIV Vaccine Consortium	Australia	I/II
DAIDS/HVTN	VRC USMHRP, Makerere U.	Uganda, USA	I
DAIDS/HVTN	Therion	USA	I
U. Mass. Med., ABL		USA	I
DAIDS/HVTN	Chiron	USA	I
DNA vaccines			
FIT Biotech		Finland	I/II
DAIDS/HVTN	VRC	USA	I
IAVI	ADARC	USA	I
ISS		Italy	I
DAIDS/HVTN	Epimmune	USA, Botswana	I

(table continued on following pages)

¹ Abbreviations and contact information for these organizations are listed in Appendix 4.

² Clade A/E is an older but still often-used designation for HIV strains that were later found to be recombinants between two clades, rather than a pure clade. It is now called CRF01_AE. (CRF= circulating recombinant form.)

ongoing clinical trials

source: data from IAVI^① NIH^② and HVTN/UCSF's Pipeline Project^③

Vaccine design	Clade
PRIME canarypox viral vector with <i>env</i> and <i>gag-pol</i> BOOST Env protein (gp120 subunits)	B, A/E ²
PRIME canarypox vector with <i>env, gag, pro, RT, nef</i> BOOST 5 lipopeptides with CTL epitopes from <i>gag, pol, nef</i>	B
PRIME DNA vaccine with <i>gag</i> + CTL epitopes from <i>gag, pol, nef, env</i> BOOST MVA with <i>gag</i> + same CTL epitopes	A
PRIME DNA vaccine with <i>gag, RT, rev, tat, vpu, env</i> BOOST fowlpox viral vector with same genes as prime	B
PRIME DNA vaccine with <i>gag, pol, nef</i> + <i>env</i> BOOST adenovirus vector with <i>gag-pol</i> + <i>env</i>	B + A, B, C
PRIME MVA viral vector with <i>env, gag, tat, rev, nef, pol</i> BOOST fowlpox viral vector with same genes as prime	B
PRIME DNA vaccine with <i>gag</i> + 5 different <i>env</i> genes BOOST 5 Env proteins (gp120) in adjuvant (QS21)	A, B, C, A/E ²
PRIME DNA vaccine with <i>gag, env</i> attached to microparticles BOOST Env protein (oligomeric gp140) + adjuvant (MF59)	B
<i>nef, rev, tat, gag, pol, env</i> , CTL epitopes	B
<i>gag, pol, nef</i> + <i>env</i> One trial testing vaccine with or without cytokine (IL-2)	B + A, B, C
<i>gag, env, pol, nef, tat</i>	C
<i>tat</i>	
21 conserved CTL epitopes from <i>gag, pol, env, nef, rev, vpr</i> and T-helper epitope	

references

- ① www.iavireport.org/trialsdb
Clinical trials database at the International AIDS Vaccine Initiative (IAVI).
- ② <http://clinicaltrials.gov>
Database of trials sponsored by the US National Institutes of Health (NIH).
- ③ <http://chi.ucsf.edu/vaccines/vaccines?page=vc-03-00>
Table of trials conducted by the US HIV Vaccine Trials Network (HVTN).

Table 7.2 Preventive AIDS vaccines in clinical trials (February 2005) *continued*

Viral vector vaccines			
Sponsor¹	Developer¹	Trial site(s)	Phase
DAIDS/HVTN	Merck	US, Dominican Republic, Haiti, Peru, Canada, Australia	IIb
		US, Puerto Rico, Brazil, Haiti, Malawi, South Africa, Peru, Thailand	I
DAIDS/HVTN	VRC	US	I
DAIDS/HVTN, SAAVI	AlphaVax	US, South Africa, Botswana	I
IAVI, ICMR, NACO	Targeted Genetics	Belgium, Germany, India	I
EU, Imperial College London, UK MRC Clinical Trials Unit	EuroVacc	UK, Switzerland	I
IAVI	ADARK	US	I
IAVI, MRC, SAAVI	U. Oxford, KAVI	UK, Switzerland, Kenya, South Africa	I
DAIDS/HPTN	Aventis	Uganda	I infants
Peptide vaccines			
ANRS	Aventis	France	II
DAIDS/HVTN	Wyeth	US	I
ANRS	Aventis	France	I
ANRS	Biovector SA	France	I
Protein subunit vaccines			
USMHRP	AVANT, Harvard U.	US	I
ANRS	Aventis	France	I

Vaccine design	Clade
adenovirus vector with <i>gag, pol, nef</i>	B
adenovirus vector with <i>gag</i>	B
adenovirus vector with <i>gag-pol</i> or <i>gag, pol, nef</i> + <i>env</i>	B + A, B, C
VEE (venezuelan equine encephalitis) vector with <i>gag</i>	C
AAV (adeno-associated virus) vector with <i>gag, pro, RT</i>	C
NYVAC-HIV-C (vaccinia vector) with <i>gag, pol, nef, env</i>	C
MVA vector with <i>gag, env, pol, nef, tat</i>	C
MVA vector with <i>gag</i> + CTL epitopes from <i>gag, pol, nef, env</i>	C
canarypox viral vector with <i>env</i> and <i>gag/pol</i>	A/E ²
5 lipopeptides with CTL epitopes from <i>gag, nef, pol</i>	B
Conserved CTL epitopes from <i>gag, nef</i> and helper T epitopes from <i>env, gag</i> in adjuvant (RC329-SE), with or without cytokine (GM-CSF)	B
5 lipopeptides with CTL epitopes from <i>gag, pol, nef</i> + helper epitope from non-HIV protein (tetanus toxoid)	B
4 lipopeptides with CTL epitopes ⁴ from <i>gag, pol-RT, pol, nef</i> and helper epitope from a non-HIV protein (tetanus toxoid)	B
Portion of Gag protein (p24) fused to anthrax-derived protein (minus toxin)	
Env proteins gp120 and gp41 given mucosally (nasally or vaginally) with or without adjuvant (DC-chol)	B

organizations

involved with AIDS VACCINE DEVELOPMENT and/or ADVOCACY¹

KEY
 telephone number **T**
 facsimile number **F**
 email address **E**
 internet website address **I**

GOVERNMENT AGENCIES and NON-PROFIT ORGANIZATIONS SUPPORTING AIDS VACCINE DEVELOPMENT

ANRS

Agence Nationale de Recherche sur le SIDA

National Agency for AIDS Research

France's funding agency for research on HIV/AIDS basic science, treatment, vaccine development and clinical testing, with six international clinical sites: Africa (3 sites), Asia (2) and South America (1).

101, rue de Tolbiac
 75013 Paris
 France

T +33 (1) 53.94.60.00
F +33 (1) 53.94.60.01
E information@anrs.fr
I www.anrs.fr

DAIDS

Division of AIDS

of the US National Institute of Allergy and Infectious Diseases (NIAID)

Supports basic research, pre-clinical development and clinical testing of AIDS vaccines through a variety of programs, including the HIV Vaccine Trials Network and the US Military HIV Research Program (see listings below).

NIAID Office of Communications & Public Liaison
 6610 Rockledge Drive, MSC6612
 Bethesda, MD 20892-6612
 USA

T +1(800) 772-5464
I www.niaid.nih.gov/daids/vaccine/default.htm

¹ Some of the organizations listed work in areas in addition to AIDS and AIDS vaccines. Descriptions included here focus only on AIDS-related activities.

EDCTP

European and Developing Countries Clinical Trials Partnership

Works to integrate European research and coordinate with African researchers in developing medicines and vaccines against HIV/AIDS, malaria and vaccines, through funding of clinical trials, infrastructure and networking.

Laan van Nieuw Oost Indië 334
The Hague, The Netherlands
T +31 (70) 344 0880 [or]
+31 (70) 344 0899
E info@edctp.org
I www.edctp.org

EU

European Union

Supports AIDS vaccine research and testing (including EuroVacc, see listing), development of clinical trial site infrastructure, and policy work.

Research Directorate-General
B-1049 Brussels
Belgium
T +32 (2) 299 11 11
E research@ced.eu.int

Sixth Framework Research
Programme:

I http://europa.eu.int/comm/research/fp6/index_en.html

EUROVACC

EuroVacc Foundation

Supports collaborations among European laboratories to develop and test AIDS vaccines and build clinical trials infrastructure in developing countries.

EuroVacc Foundation Secretariat
c/o IATEC, Rm 03-02
Pietersbergweg 9
1105 BM Amsterdam
The Netherlands
T +31 (20) 314 93 27
F +31 (20) 314 93 99
I www.eurovacc.org

HVTN

HIV Vaccine Trials Network

International collaboration of scientists conducting clinical trials of AIDS vaccine candidates. HVTN supports sites in Africa (6 sites), Asia (3), Caribbean (5), South America (4) and the US (12). (listed in the next section)

1100 Fairview Avenue North, LE-500
Seattle, WA 98109-1024
USA
T +1 (206) 667-6705
E info@hvtn.org
I www.hvtn.org

IAVI

International AIDS Vaccine Initiative

Carries out pre-clinical and clinical development of AIDS vaccine candidates, along with policy and advocacy work.

New York office:
110 William Street, Floor 27
New York, NY 10038-3901
USA
T +1 (212) 847-1111
F +1 (212) 847-1112
I www.iavi.org

ICMR

Indian Council of Medical Research

Funds health-related research, including AIDS care, treatment, vaccine development and surveillance.

V. Ramalingaswami Bhawan,
Ansari Nagar,
New Delhi - 110029
India
T +91 (11) 26588895, 26588980
E icmrhqds@sansad.nic.in
I www.icmr.nic.in

MOPH

**Ministry of Public Health
(Thailand)**

Builds and supports infrastructure for large-scale AIDS vaccine trials.

E eng-webmaster@health.moph.go.th
I <http://eng.moph.go.th>

MRC

Medical Research Council (UK)

Funds basic research, pre-clinical and clinical vaccine development. Its Clinical Trials Centre provides central support for EuroVacc trials (see next section, United Kingdom).

20 Park Crescent,
London W1B 1AL
UK

T +44 (20) 7636 5422
F +44 (20) 7436 6179
I www.mrc.ac.uk

NACO

**National AIDS Control
Organisation (India)**

Coordinates national response to HIV/AIDS, including prevention and care in context of AIDS vaccine trials.

Ministry of Health & Family Welfare
Government of India
9th floor, Chandralok Building
36, Janpath
New Delhi 110001
India

T +91 (11) 23325343 [or]
23731774 [or] 23731778
F +91 (11) 23731746
E info@nacoonline.org
I www.naco.nic.in

OAR

Office of AIDS Research

within the Office of the Director of NIH
Responsible for the scientific, budgetary, legislative and policy elements of the NIH AIDS research program.

National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
USA

E oardtemp1@od31em1.od.nih.gov
I www.nih.gov/od/oar

SAAVI

**South African AIDS Vaccine
Initiative**

Coordinates research, development and testing of AIDS vaccines in South Africa.

MRC Cape Town
Francie van Zijl Drive
Parowvallei, Cape;
PO Box 19070
7505 Tygerberg
South Africa

T +27 (21) 938 0525
E saavi@mrc.ac.za
I www.saavi.org.za

USMHRP

US Military HIV Research Program

Develops and tests candidate AIDS vaccines; builds clinical trials infrastructure (3 trial sites in Africa; 4 in Thailand). Cooperative effort of two organizations: Walter Reed Army Institute of Research and Henry M. Jackson Foundation.

US Military HIV Research Program
1600 East Gude Drive
Rockville, Maryland 20850
USA

T +1 (301) 251-5000
F +1 (301) 762-7460
I www.hivresearch.org

AIDS VACCINE CLINICAL TRIAL SITES (and prospective sites)

BRAZIL

Hospital Escola Sao Francisco de Assis
Projeto Praca Onze
Av. Presidente Vargas, 2863 - Cidade Nova
20210-030
T +55 (21) 2273-9073
I www.pracaonze.ufrj.br

Centro de Fefrencia e Treinamento - DST/AIDS
HVTU Vila Mariana
Centro de Referência e Treinamento em DST/Aids
Secretaria de Estado da Saúde de São Paulo
Rua Santa Cruz, 81
CEP 04119-000
T +55 (11) 5081-5052

BOTSWANA

Jwaneng Mine Hospital
T + 267 5882-004

Botswana-Harvard Partnership for HIV Research & Education
Vaccine Initiative
Princess Marina Hospital
Private Bag BO 320
Gaborone
T +267 302-671

CAMEROON

Walter Reed Johns Hopkins Cameroon Program
BP 7039
Rue Ceper
Yaoundé
T +237 (221) 33-82 [or]
+237 (950) 46-72
E info@wrjhcp.org

CHINA

Guangxi Health and Anti-Epidemic Center
80 Taoyuan Road
Nanning 530021
Guangxi P.R.
T +86 (771) 5327-110

DOMINICAN REPUBLIC

IDCP
C / Federico Velasquez
esq. Albert Thomas
Santo Domingo
T +809 684-6265 [or]
+809 684-3257 ext. 342

HAITI

Cornell-GHESKIO
Institut National de Laboratoire et de Recherches
33 Boulevard Harry Truman
Cit  de l'Exposition
Port-au-Prince
T +509 222-0031 [or]
+509 222-2241

INDIA

Indian Council of Medical Research
PO Box 1895, Plot #73, G Block
MIDC Bhosari
Pune 411 026
T +91 (20) 7121072

ITALY

Spallanzani Hospital (IRCCS)
Rome

San Raffaele Hospital (IRCCS)
Milan

Dept. of Infectious Diseases
University of Rome "La Sapienza"

San Gallicano Hospital (IRCCS)
Rome

IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) are Institutes for Clinical Care and Research.

JAMAICA

**Epidemiology Research
Training Unit**

Jamaica Ministry of Health
55 Slipe Pen Road
Kingston 5
T +876 922-2513

KENYA

KAVI

Kenyan AIDS Vaccine Initiative
HIV/AIDS Vaccine Evaluation Unit
University of Nairobi
Dept. of Medical Microbiology
Kenyatta National Hospital
PO Box 20723
Nairobi
T +254 (2) 717694 or 714613
E info@kaviuon.org [or]
kavi@kaviuon.org
I www.kaviuon.org

Walter Reed Project – Kenya
United States Army Medical Research
Unit
Kenya Medical Research Institute
Clinical Research Center
Walter Reed Project
Hospital Road
Kericho District Hospital
T (254-361) 21733/31138
I www.usamrukenya.org

MALAWI

**College of Medicine
Johns Hopkins Project**
Kachere Rehabilitation Centre
Chipatala Avenue
PO Box 1131
Blantyre
T +265 (1) 670132

PERU

Asociación Civil Selva Amazonica
450 Fanning
Iquitos
T +51 (65) 23-6277
I www.impactaperu.org

IMPACTA

Affiliated Unit of FHCRC/University of
Washington
Grimaldo del Solar 805
Miraflores, Lima 18
T +51 (1) 242-3072 [or] 800-17432
I www.impactaperu.org

PUERTO RICO

University of Puerto Rico
Maternal Infant Studies Center
Biomedical Building 2
1st Floor
Rio Piedras 00935
T +1 (888) VACUNAS or +787 753-5913

RWANDA

Projet San Francisco
BP 780
Kigali

Home office:

Rwanda-Zambia HIV Research Group
Emory University
Rollins School of Public Health
Dept. of International Health
1518 Clifton Road NE, Suite 764
Atlanta, GA 30322
T +1 (404) 727-7883
F +1 (404) 727-4590
E sallen5@sph.emory.edu

SOUTH AFRICA

Medical Research Council

491 Ridge Road
Overport
Durban 4001
T +27 (31) 203-4828
I www.mrc.ac.za

Perinatal HIV Research Unit

Chris Hani Baragwanath Hospital
PO Bertsham
Soweto 2013
T +27 (11) 989-9822
I www.chrisanibaragwanathhospital.co.za/bararesearch_summaries.jsp#perinatal

Desmond Tutu HIV Centre

University of Cape Town
Anzio Road
PO Box 13801
Mowbray 7705
T +27 (21) 650-6960

SWITZERLAND

Centre Hospitalier Universitaire Vaudois (CHUV)

Rue du Bugnon 46
1011 Lausanne
T +41 (21) 314 11 11
E info@chuv.ch
I www.chuv.ch

TANZANIA

Mbeya Medical Research Programme

Mbeya Referral Hospital
Hospital Hill
PO Box 2410
Mbeya
T +255 (25) 2503364
F +255 (25) 2503134
E MMRP.TZ@lrz.uni-muenchen.de
I www.mmrp.org

THAILAND

Armed Forces Research Institute of Medical Sciences

Department of Retrovirology
315-6 Rajvithi Road
Bangkok
T +66 (2) 644-4888
F + 66 (2) 644-4824
I www.afrims.org

Information about ongoing efficacy
trial/trial sites in southern Thailand:
I www.primeboost3.org

Research Institute for Health Sciences

Chiang Mai University
110 Intavaroros Road, Amphur Muang
Chiang Mai 50202
T +66 (53) 05389-4792-3

TRINIDAD AND TOBAGO

Medical Research Foundation of Trinidad & Tobago

Affiliated Unit of University of
Maryland at Baltimore
7 Queens Park East
Port of Spain
T +868 622-4917

UGANDA

Makerere University/Walter Reed Project

Makerere Univ Medical School, A10-A14
Mulago Hill Road
Kampala, 16524
T +256 (41) 534588
F +256-41-534586
I www.muwrp.org

UVRI

Uganda Virus Research Institute

PO Box 49
Entebbe Uganda
T +256 (41) 320776
F +256 (41) 321457
E information@iavi.or.ug
I www.health.go.ug/other_inst.htm

Trial site and CAB newsletter:
I www.iavi.org/uganda

UNITED KINGDOM

Clinical Trials Centre
 St. Mary's Hospital
 Imperial College of Science,
 Technology and Medicine
 Praed Street
 London W2 1NY

Johns Hopkins University
 Center for Immunization Research
 Hampton House, Room 117
 624 North Broadway
 Baltimore, MD 21205-1996
 T +1 (877) 863-1374 or 955-7283
 I www.projectsave.jhsph.edu

UNITED STATES

Alabama Vaccine Research Clinic
 University of Alabama at Birmingham
 Department of Medicine
 Division of Infectious Diseases
 908 20th Street South, CCB 310
 Birmingham, AL 35294-2050
 T +1 (205) 975-2839
 I <http://main.uab.edu/show.asp?durki=29787>

University of Maryland at Baltimore
 Institute of Human Virology
 Medical Biotechnology Center N449
 725 West Lombard St.
 Baltimore, MD 21201-1192
 T +1 (866) 448-4448
 I www.ihv.org

San Francisco Department of Public Health
 AIDS Office
 25 Van Ness Avenue, Suite 500
 San Francisco, CA 94102-6033
 T +1 (415) 554-9068
 I www.sfairsresearch.org

Saint Louis University School of Medicine
 HIV Vaccine Trials Unit
 3691 Rutger, Suite 103
 St. Louis, MO 63110
 T +1 (800) 268-5880 ext.5448 [or]
 +1 (314) 977-9644
 I <http://medschool.slu.edu/hvtu>

University of Illinois at Chicago
 Division of Infectious Disease
 UIC Department of Medicine
 808 S. Wood St., Room 874
 Chicago, IL 60612
 T +1 (312) 413-9794

Aaron Diamond AIDS Research Center
 455 First Avenue, 7th Floor
 New York, NY 10016
 T +1 (212) 448-5125
 E aidsvaccine@adarc.org
 I www.adarc.org

Brigham and Women's Hospital
 Infectious Disease, Clinical Trials
 Center PBB-A457
 75 Francis Street
 Boston, MA 02115
 T +1 (617) 525-7327
 I www.partners.org/bwh

Columbia University
 Division of Infectious Diseases
 PH8-101
 630 West 168th Street
 New York, NY 10032
 T +1 (212) 305-2201

Fenway Community Health
 7 Haviland Street
 Boston, MA 02115
 T +1 (617) 927-6450
 I www.fenwayhealth.org

Project Achieve - Bronx
 391 East 149th Street
 Suite #405
 Bronx, NY 10455
 T +1 (800) 973-3312 or
 +1 (718) 402-0743
 I www.projectachieve.org

UNITED STATES (continued)

Project Achieve - Union Square
853 Broadway, Suite 1111
New York, NY 10003
T +1 (212) 388-0008
I www.projectachieve.org

**University of Rochester -
Medical Center**
Infectious Diseases, Box 689
601 Elmwood Avenue
Rochester, NY 14642-0002
T +1 (585) 756-2DAY
E hvtu_cer@urmc.rochester.edu
I [www.stronghealth.com/services/
medicine/infectiousdiseases/
hivtrials/index.cfm](http://www.stronghealth.com/services/medicine/infectiousdiseases/hivtrials/index.cfm)

Miriam Hospital
164 Summit Avenue
Fain Building, Room 389
Providence, RI 02906
T +1 (866) STOP-HIV [or]
+1 (401) 793-4932
I www.lifespan.org/partners/tmh

Vanderbilt University
Room AA0232B MCN
1161 - 21st Avenue South
Nashville, TN 37232-2582
T +1 (615) 322-HOPE [or]
+1 (888) 559-HOPE
I www.hivvaccineresearch.com

**Fred Hutchinson
Cancer Research Center**
University of Washington Vaccine
Trials Unit
Cabrini Medical Tower
901 Boren Avenue, Suite 1320
Seattle, WA 98104
T +1 (206) 667-2300
I www.seattlehivvaccines.org

ZAMBIA

**Zambia-Emory HIV Research
Project (ZERHRP)**
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P/Bag 891
Lusaka

ZEHRP-Copperbelt
75 Kuomboka Drive
Kitwe

22 Lupili Road
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**PHARMACEUTICAL and BIOTECHNOLOGY COMPANIES
DEVELOPING, TESTING and/or MANUFACTURING AIDS VACCINES**

ABL

**Advanced BioScience
Laboratories, Inc.**
5510 Nicholson Lane
Kensington, Maryland 20895-1078
USA
T +1 (301) 816-5225
I www.ablinc.com

ALPHAVAX

AlphaVax Human Vaccines Inc.
PO Box 110307
2 Triangle Drive
Research Triangle Park, NC 27709-
0307
USA
T +1 (919) 595-0400
F +1 (919) 595-0401
I www.alphavax.com

AVANT

AVANT Immunotherapeutics, Inc.
119 Fourth Avenue
Needham, Massachusetts 02494-2725
USA
T +1 (781) 433-0771
F +1 (781) 433-0262
I www.avantimmune.com

AVENTIS

see **Sanofi Pasteur**
(formerly Aventis Pasteur)

CHIRON

Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916
USA
T +1 (510) 655-8730
F +1 (510) 655-9910
I www.chiron.com

COBRA

COBRA Biomufacturing Plc
Stephenson Building
The Science Park
Keele
ST5 5SP
UK
T +44 (17) 8271 4181
F +44 (17) 8271 4168
I www.cobrabio.com

EPIMMUNE

Epimmune, Inc.
5820 Nancy Ridge Drive
San Diego, California 92121
USA
T +1 (858) 860-2500
F +1 (858) 860-2600
I www.epimmune.com/templates/home.cfm

EXCELL

Excell Biotech
15 Morgan
USA
T +1 (800) 424-6101
F +1 (949) 421-2539 or 2675
E info@qbiogene.com
I www.qbiogene.com/business/divisions/excell.shtml

GENVEC

GenVec, Inc.
65 West Watkins Mill Road
Gaithersburg, MD 20878
USA
T +1 (240) 632-0740
F +1 (240) 632-0735
I www.genvec.com

GEOVAX

GeoVax

1256 Briarcliff Road
Atlanta, Georgia 30306
USA
T +1 (404) 727-0971

GSK

GlaxoSmithKline plc

980 Great West Road
Brentford
Middlesex
TW8 9GS
UK
T +44 (20) 8990 9000

GlaxoSmithKline plc

5 Moore Drive
PO Box 13398
Research Triangle Park, NC 27709
USA
T +1 (888) 825-5249
I <http://us.gsk.com>

IDT

Impfstoffwerk Dessau-Tornau GmbH

Streetzer Weg 15a
D-06862 Rodleben/Tornau
Germany
T +49 (3 49 01) 885-0
F +49 (3 49 01) 885-323
I www.idt-direct.de

MERCK

Merck Research Laboratories

Merck & Co., Inc.
One Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100
USA
T +1 (908) 423-1000
I www.merck.com

SANOFI

Sanofi-Pasteur SA

(formerly Aventis Pasteur)
World Headquarters
2, Avenue Pont Pasteur
F-69367 Lyon CÃ©dex 7
France
T +33 (4) 37.37.01.00
I www.sanofipasteur.us

TARGETED GENETICS

Targeted Genetics Corporation

1100 Olive Way; Suite 100
Seattle, WA 98101
USA
T +1 (206) 623-7612
F +1 (206) 223-0288
I www.targetedgenetics.com

THERION

Therion Biologics Corporation

76 Rogers Street
Cambridge, MA 02142-1119
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T +1 (617) 475-7500
F +1 (617) 475-7501
I www.therionbio.com

VICAL

Vical Inc.

10390 Pacific Center Court
San Diego, California 92121-4340
USA
T +1 (858) 646-1100
F +1 (858) 646-1150
I www.vical.com

WYETH

Wyeth Worldwide Headquarters

5 Giralda Farms
Madison, NJ 07940
USA
I www.wyeth.com

ADVOCACY, EDUCATION and RESEARCH SUPPORT

AFAO

Australian Federation of AIDS Organisations

Main nongovernmental organization representing Australia's community-based response to HIV/AIDS. Emphasizes education, policy, advocacy and international projects in treatment and prevention (including vaccines).

PO Box 51
Newtown NSW 2042
Australia
T +61 (2) 9557 9399
F +61 (2) 9557 9867
E aquan@afao.org.au
I www.afao.org.au

AEGIS

AIDS Education Global Information System

A comprehensive online knowledge base covering the history, prevention and treatment of HIV/AIDS; searchable by keyword. Also available: HIV/AIDS-specific publications, HIV/AIDS news from sources around the world (including daily summaries of AIDS coverage) and reference materials.

E help@aegis.com [or] comments@aegis.com
I www.aegis.com

AIDES

One of Europe's largest community-based organizations against HIV/AIDS, with a focus on support for HIV-positive people, education and advocacy (including vaccine issues) and community mobilization. Publishes a French language quarterly newsletter.

Tour Essor
14, rue Scandicci
93508 Panitn Cedex
France
T +33 (1) 41.83.46.46
F +33 (1) 41.83.46.49
E communications@aides.org [or] aides@aides.org
I www.aides.org (French)

English:

I www.aides.org/sites/aides/?cmd=indep&num_alpha=introducing

AVAC

AIDS Vaccine Advocacy Coalition

Community organization focused on accelerating vaccine development and delivery through independent analysis, policy advocacy, public education and community mobilization. Maintains the AIDS Vaccine Clearinghouse, a collection of information on AIDS vaccines. (For more, see page 343).

101 West 23rd St. #2227
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USA
T +1 (212) 367-1279
F +1 (646) 365-3452
E avac@avac.org
I www.avac.org

AIDS Vaccine Clearinghouse:

I www.aidsvaccineclearinghouse.org

AAVP

African AIDS Vaccine Programme

Advocates for and supports African contributions to global AIDS vaccine development effort, through work in science, policy, ethics and resource mobilization.

Interim Secretariat:
WHO-UNAIDS HIV Vaccine Initiative
Vaccines and Biologicals
World Health Organization (WHO)
20 Avenue Appia
1211 Geneva 27
Switzerland
T +41 (22) 791 43 95
F +41 (22) 791 48 60
I www.who.int/vaccine_research/diseases/hiv/aavp/en

BMGF

Bill & Melinda Gates Foundation

Supports AIDS vaccine development work; provides interim home base and support for the Global HIV/AIDS Vaccine Enterprise.

PO Box 23350
Seattle, WA 98102
USA
T +1 (206) 709-3100
E info@gatesfoundation.org
I www.gatesfoundation.org

CDC

Centers for Disease Control and Prevention HIV Vaccine Unit (US)

Epidemiological, social/behavioral research relevant to AIDS vaccine development and testing; clinical trials, building infrastructure.

HIV Vaccine Unit
Epidemiology Branch
Div. of HIV/AIDS Prevention
National Center for HIV, STD and TB Prevention
Centers for Disease Control and Prevention
Mail Stop E-49
Atlanta, Georgia 30333
USA
T +1 (301) 519-0459
I www.cdc.gov/hiv/vaccine/hivvu.htm

GIV

Grupo de Incentivo

Helps affected communities establish and maintain treatment and prevention services; advocacy. Publishes a Portuguese-language newsletter (Boletim Vacinas) on AIDS vaccines, with a searchable archive on its website.

Rua Capitão Cavalcante
145 - Vila Mariana
São Paulo
CEP 04017-000
Brazil
T/F 5084-6397 [or] 5084-0255
I www.giv.org.br

gTt

Grupo de Trabajo sobre Tratamientos del VIH

Spain's main HIV/AIDS NGO (non-governmental organization). Provides news and medical information on HIV/AIDS and AIDS vaccine information in Spanish; works in advocacy and education and publishes Lo+Positivo, a bi-monthly newsletter.

GTT
c/Sardenya, 259 3^o 4^a
08013 Barcelona
Spain
T +34 (93) 208 08 45
F +34 (93) 207 00 63
E contact@gtt-vih.org
I www.gtt-vih.org

HVTN

HIV Vaccine Trials Network

As part of clinical trials work, supports CABs at domestic and international trial sites; publishes the CAB Bulletin newsletter and maintains information on HVTN-supported clinical trials.

HIV Vaccine Trials Network
1100 Fairview Avenue North, LE-500
Seattle, WA 98109-1024
USA
T +1 (206) 667-6705
E info@hvtn.org
I www.hvtn.org

HVTN newsletter:
I www.hvtn.org/community/bulletin.html

Bimonthly newsletter on community activities at HVTN sites and trial-related issues relevant to CABs.

The Pipeline Project:
I <http://chi.ucsf.edu/vaccines>
Collaboration of the UCSF Center for HIV Information and the HIV Vaccine Trials Network. Information on preventive AIDS vaccine trials sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS (DAIDS).

IAVI

International AIDS Vaccine Initiative

Works in vaccine development, policy and advocacy; publishes two newsletters on AIDS vaccines and maintains a searchable database of vaccine clinical trials.

New York office:
110 William Street, Floor 27
New York, NY 10038-3901
USA
T +1 (212) 847-1111
F +1 (212) 847-1112
I www.iavi.org

IAVI Report and VAX newsletters:
I www.iavireportonline.org
The IAVI Report, published bimonthly, covers research and development, clinical trials and policy. VAX, published monthly, has less technical articles on the same areas; available in English, French, Spanish, German and Portuguese.

AIDS vaccine clinical trials database:
I www.iavireport.org/trialsdb

ICASO

International Council of AIDS Service Organizations

Global network of non-governmental and community-based organizations (CBOs). Works to mobilize and advocate for communities affected by HIV/AIDS, and to help strengthen local CBOs. Secretariats in five geographic regions and a central secretariat in Canada.

65 Wellesley St. E., Suite 403
Toronto, Ontario
Canada M4Y 1G7
T +1 (416) 921-0018
F +1 (416) 921-9979
I www.icaso.org

KFF

The Henry J. Kaiser Foundation

Non-profit foundation focused on health care. Information and daily news bulletin summarizing press coverage of HIV/AIDS global issues.

2400 Sand Hill Road
Menlo Park, CA 94025
USA
T +1 (650) 854-9400
F +1 (650) 854-4800
I www.kff.org

NAT

National AIDS Trust (UK)

UK's leading HIV/AIDS policy development and advocacy organization. Works domestically and internationally for policies to enhance prevention efforts, improve access to treatment, challenge HIV stigma and discrimination and engage political leaders in fighting AIDS.

New City Cloisters
196 Old Street
London
EC1V 9FR
UK
T +44 (20) 7814 6767
F +44 (20) 7216 0111
I www.nat.org.uk

TAG

Treatment Action Group

Non-profit AIDS organization advocating for research and helping people living with HIV/AIDS get treatment, care, and information. Publishes TAGline, a monthly newsletter that includes coverage of HIV immunology and vaccine issues.

Treatment Action Group
611 Broadway, Ste. 612
New York, NY 10012-2608
USA
T +1 (212) 253-7922
F +1 (212) 253-7923
I www.aidsinfonyc.org/tag

WHO-UNAIDS

WHO-UNAIDS

HIV Vaccine Initiative (HVI)

Joint activity of the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Promotes development, facilitates evaluation and addresses future access to preventive HIV vaccines, focused on developing countries.

WHO-UNAIDS HIV Vaccine Initiative
Vaccines and Biologicals
World Health Organization
20 Avenue Appia
1211 Geneva 27

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E VaccineResearch@who.int
I www.who.int/vaccine_research/diseases/hiv/en

about avac

the AIDS VACCINE ADVOCACY COALITION

AVAC Founded in 1995, the AIDS Vaccine Advocacy Coalition (AVAC) is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of vaccines against HIV/AIDS.

AVAC's AIDS Vaccine Clearinghouse is an on-line compendium of materials on AIDS vaccine research and a link to other people and organizations concerned about AIDS vaccine advocacy, research, and global delivery. The Clearinghouse welcomes submissions of documents, translations, announcements and events.

The *AIDS Vaccine Handbook*, AIDS Vaccine Clearinghouse, and our continuous policy analysis, advocacy, education and outreach work are made possible by the dedicated labor of AVAC advocates and support from the Bill & Melinda Gates Foundation, Broadway Cares/Equity Fights AIDS, the Ford Foundation, the Gill Foundation, the International AIDS Vaccine Initiative, the Overbrook Foundation, Until There's a Cure Foundation, the WHO/UNAIDS HIV Vaccine Initiative, and many generous individuals who have become AVAC Members.

AVAC is an IRS-certified 501(c)3 tax exempt organization and your donations are tax deductible. For more information, or to contribute to the work of AVAC, please contact:

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AIDS Vaccine Clearinghouse:

I www.aidsvaccineclearinghouse.org

glossary

of AIDS VACCINE-RELATED TERMS

Adapted from glossaries compiled by the AIDS Education Global Information System (AEGIS) and the US National Institute of Allergy and Infectious Diseases (NIAID) and from articles in this volume.

adenovirus

A family of viruses that causes the common cold. Researchers are using weakened versions of certain adenovirus strains to make vectors that carry HIV genes into cells, as a way of developing a live vector vaccine against AIDS.

adenovirus-associated vector

AAV

A harmless virus which is different than adenovirus but is also being used to make live vector vaccines against AIDS.

adjuvant

A substance sometimes included in a vaccine formulation to enhance or modify its immune-stimulating properties.

adverse event

adverse reaction

An undesirable change in the body of a clinical trial participant. Follow-up work is needed to determine whether or not an adverse event is due to the study vaccine or drug. Adverse events most commonly associated with vaccines include a sore arm after injection or a slight fever.

AIDSVAX

The experimental AIDS vaccine made from the HIV envelope (specifically, the gp120 subunit) by VaxGen, a California-based biotechnology company. It was the first AIDS vaccine to be tested for efficacy (in two separate trials), but was found not to work.

antibody

Infection-fighting protein in the blood, which recognizes and helps destroy pathogens such as bacteria and viruses. Antibodies are made by white blood cells called B-cells in response to stimulation by foreign molecules (antigens). Each antibody binds only to the specific antigen that stimulated its production.

antigen

Any substance recognized by the cells or antibodies of the immune system.

antigen-presenting cell

A cell (such as a macrophage) that “presents” foreign antigens to the immune system, thereby alerting the body to the presence of an invader. It does this by chopping the antigens into small pieces, which it then displays on its cell surface.

arm

In a clinical trial, a group of participants who receive the same treatment. For example, vaccine trials usually have a vaccine arm and a placebo (control) arm.

antiretroviral therapy

ARV

Treatment for HIV infection that uses medicines which work by killing or suppressing the virus.

attenuated

Weakened. Attenuated viruses are often used as vaccines because they no longer cause disease but may still stimulate a strong immune response. Examples include vaccines against measles, mumps and rubella, as well as oral vaccines against polio.

b

B-cell

B-lymphocyte

A subset of white blood cells in the immune system, derived from bone marrow and spleen. B-cells develop into plasma cells, which produce antibodies.

binding antibody

An antibody that attaches to some part of a pathogen, such as HIV. Binding antibodies may or may not lead to elimination of the pathogen.

blinded study

Clinical trial in which the participants do not know until the study ends whether they received the experimental product or a placebo. Blinding is done to reduce bias in clinical trials. (see also **double-blinded study**)

booster

A second or subsequent vaccine dose given after the primary dose, to enhance immune responses. A booster vaccine may or may not be the same as the primary vaccine. (see **prime-boost**)

bridging study

A clinical trial that tests the safety of a vaccine and its ability to induce specific types of immune responses in a particular population, often as an indirect way of gathering information about efficacy. For example, if a vaccine is shown to protect adults against a certain disease and bridging studies show that it induces similar immune responses in adults and adolescents, then the vaccine may be assumed to work for adolescents as well.

C canarypox

A virus that infects birds but is harmless and unable to grow in people. It was one of the first vectors used to make live vector AIDS vaccines, several of which have been tested in clinical trials. An efficacy trial that combines a canarypox-based vaccine and a protein subunit vaccine against AIDS is taking place in Thailand.

CD4+ T-cell**CD4+ T-lymphocyte; helper T-cell**

Immune cell that carries a protein called CD4 on its surface. CD4+ T-cells help orchestrate the activities of the immune system, such as turning antibody production on and off and activating killer T-cells. They are also the main targets of HIV infection. In HIV-infected people, the number of CD4+ T-cells in a blood sample is often used as a measure of the health of the immune system.

CD8+ T-cell**CD8+ T-lymphocyte**

Immune cell that carries a protein called CD8 on its surface. One important class of CD8+ T-cells, called cytotoxic T-cells (CTLs) or killer T-cells, destroys host cells that are infected with viruses or bacteria. CTLs are thought to play an important role in immunity to HIV.

cell-mediated immunityalso **cellular immunity**

Branch of the immune system consisting mainly of T-cells (such as helper T-cells and killer T-cells) and macrophages. Its role is to recognize and destroy cells infected with pathogens so that the pathogen cannot multiply and then spread to other cells.

cell membrane

The envelope surrounding a cell and enclosing its contents.

challenge experiment

The deliberate exposure of an immunized animal to an infectious agent. Challenge experiments are never done in humans in HIV vaccine research.

circulating recombinant form

CRF

In HIV, a mosaic virus that contains pieces from HIV of at least two different clades and has entered the pool of HIV strains circulating in a population.

clade

also **subtype**

A group of genetically related HIV isolates. There are two major groups of HIV-1 isolates, called M and O. Group M consists of nine clades, A through K (with no E or I).

clinical trial

clinical study

A highly organized procedure for determining the safety and/or effectiveness of a new medicine, vaccine or therapy, by giving the new agent to participants under strictly controlled conditions. In many clinical trials, new agents are tested against older ones and/or an inactive substance (placebo). The clinical trials process includes Phase I, II and III studies and Phase IV post-marketing evaluation.

cocktail vaccine

A vaccine produced from two or more viral (or bacterial) strains.

cohort

A group of individuals who share certain characteristics and are followed over time in a research study. For example, a Phase I vaccine trial typically enrolls a cohort at low risk for HIV.

Community Advisory Board

CAB

A group of community members (e.g., people with HIV/AIDS, care providers, advocates) who provide recommendations regarding the conduct of clinical research in their community.

conserved sequence

A genetic sequence which changes very little from one individual (or HIV isolate) to another.

control

see **placebo** and **placebo-controlled clinical trial**

correlates of protection**correlates of immunity**

The specific immune responses that are associated with protection from a certain infection. The precise correlates of immunity for HIV are unknown.

cross-reaction

Immune response to an antigen other than that which originally stimulated the response.

CTL**cytotoxic T-lymphocyte;****killer T-cell**

see **CD8+ T-cell**

cytokine

A group of proteins produced by different subsets of white blood cells and that act as messengers between cells. A cytokine can stimulate or inhibit the activity of a specific type of immune cell. Some are being tested as immune modulators in vaccine formulations.

d

diversity

see **genetic diversity**

DNA**deoxyribonucleic acid**

The genetic material of all living things except for RNA-carrying viruses, such as HIV. DNA is a double-stranded, twisted molecular chain found within each cell and is made from four chemical building blocks. It contains the information needed for cells to produce proteins, which in turn enable cells to reproduce and carry out their functions.

DNA vaccine

An experimental vaccine technology in which one or more genes encoding specific antigen(s) are injected into the body, where they hopefully produce these antigen(s) in the recipient and trigger immune responses. The technology is potentially promising for producing simple, inexpensive and heat-stable vaccines.

double-blinded study

Clinical trial in which neither the study staff nor the participants know which participants received the experimental product and which ones received placebo. Double-blind studies are thought to produce the most objective results.

efficacy

In vaccine research, the ability of a vaccine to protect people against a specific infection or disease as measured in a clinical trial. A vaccine can be tested for efficacy in Phase III (or Phase IIb) trials once Phase I and II trials show it to be safe and to induce immune responses.

env (gene)

Env (protein)

HIV gene encoding gp160, a glycoprotein molecule that gets split into the Env proteins gp120 and gp41.

envelope

The outer surface of a virus, also called the coat. Not all viruses have an envelope. In the case of HIV, the envelope contains two viral proteins (gp120 and gp41), which are initially produced as a single, larger protein (gp160) that is then cleaved in two.

enzyme

A protein that accelerates the rate of a specific chemical reaction, without itself being altered. For example, HIV makes an enzyme called reverse transcriptase, which copies the viral genetic material (RNA) into DNA during the HIV replication cycle.

epitope

Within an antigen, a specific site that stimulates an immune response.

exposed seronegative

ESN

A rare individual who remains uninfected despite being repeatedly exposed to HIV. Researchers have found ESNs among sex workers, uninfected partners of HIV-infected people and breastfed infants of HIV-positive mothers.

fowlpox

A virus belonging to the same bird virus family as MVA and canarypox, and which has also been used to make live vector vaccines against AIDS.

gag (gene)

Gag (protein)

HIV gene encoding p55, a protein which is then cleaved into several smaller Gag proteins (called p17, p24, p7 and p6) that form the inner (viral) core surrounding the genetic material.

genetic diversity

also **genetic variation**

The degree of difference in DNA sequence among individual organisms, groups, or members of a population. HIV is the most genetically diverse viral pathogen known.

genetic engineering

The set of laboratory methods for isolating a specific gene from the genome of an organism and splicing it to other pieces of DNA so it can be propagated in the laboratory and made to produce protein—for example, insulin (for use as a medication), or an HIV protein for a vaccine.

genome

The complete genetic material in an individual cell or virus. The HIV genome contains 9 genes; the human genome contains between 20,000 and 25,000 genes.

glycoprotein**gp**

A protein molecule with one or more branches of sugar molecules attached to it. Many cellular and viral proteins are glycoproteins, including the outer coat proteins of HIV. A number after the gp (e.g., gp160, gp120, gp41) is the molecular weight of the glycoprotein.

glycoprotein 41**gp41**

A glycoprotein embedded in the outer envelope of HIV, and which functions to anchor gp120. gp41 plays a key role in helping HIV enter CD4+ T-cells during infection by facilitating the fusion of the viral and cell membranes.

glycoprotein 120**gp120**

The glycoprotein on the outer surface of the HIV envelope. It is widely used in experimental AIDS vaccines because the outer envelope is the first part of the virus “seen” by the immune system. When HIV in the blood infects a cell, gp120 binds to the host cell membrane, which initiates its entry into the cell.

Good Clinical Practice**GCP**

An internationally accepted set of principles and procedures for conducting research involving humans in a manner that is ethical, scientifically sound and properly documented. It covers elements such as the responsibilities of trial investigators, sponsors and Institutional Review Boards (IRBs) and the information that must be included in the trial protocol and informed consent documents.

Good Manufacturing Practice**GMP**

An internationally accepted set of procedures and standards for how experimental products (i.e., those being evaluated in clinical trials) should be manufactured, handled and stored.

h **helper T-cell**
see **CD4+ T-cell**

herpes simplex virus

HSV

A group of viruses that cause blisters. HSV type 1 usually causes blisters on the lips or mouth (called cold sores or fever sores); HSV type 2 is sexually transmitted and causes lesions in the genital and anal areas. A vaccine against HSV type 2 is in development.

human papilloma virus

HPV

A group of sexually transmitted viruses that cause cervical cancer in women. Candidate vaccines against HPV are now in clinical testing.

humoral immunity

Branch of the immune system consisting mainly of B-cells. Its role is to make proteins called antibodies, which recognize and help destroy pathogens in the blood. Certain antibodies can block (or neutralize) pathogens in the blood, thereby preventing infection of the body's cells.

immune deficiency

The inability of certain parts of the immune system to function as they should, thus making people susceptible to diseases they would not ordinarily develop.

immune escape

Process in which a microorganism undergoes changes (usually mutation) that alter it enough so it becomes unrecognizable to the immune system, which in turn allows it to evade the immune response.

immune response

The body's reaction to foreign molecules (antigens). This response may neutralize or eliminate the antigens and provide immunity.

immunity

Natural or vaccine-induced resistance to a specific disease. Immunity may be partial or complete, specific or nonspecific, long-lasting or temporary.

immunization

The process of inducing immunity to a specific pathogen by giving someone a vaccine, which "teaches" the immune system to recognize the pathogen and thus prevents illness upon exposure to the same pathogen at a later time.

immunogen

Any substance capable of provoking an immune response.

immunogenicity

The strength and breadth of an immune response induced by a given antigen. The more immunogenic an antigen is, the better an immune response it induces.

immunological memory

The ability of the immune system to “recall” specific antigens it encountered during an earlier infection and then to quickly mobilize an immune response. Long-term memory is the basis of protection against re-occurrence of a disease.

incidence

The rate of new infections in a specific population over a certain period of time, usually one year.

inclusion/exclusion criteria

The medical and social characteristics which qualify or disqualify a person for participation in a clinical trial. For example, some trials may include people between 18 and 49 years of age and exclude those with chronic liver disease or certain drug allergies, or who are pregnant.

informed consent

An agreement signed by all volunteers participating in a clinical research study, indicating their understanding of: 1) why the research is being done; 2) what researchers hope to learn; 3) what will be done during the trial, and for how long; 4) what risks are involved; 5) what, if any, benefits can be expected from the trial; 6) what other interventions are available; and 7) the participant's right to leave the trial at any time.

Institutional Review Board

IRB

Committee of physicians, statisticians, community representatives and others. Its role is to review all proposed clinical trial protocols at a specific institution before a study can begin. IRBs are responsible for ensuring that a trial is done in a sound, ethical manner and that the rights of participants are adequately protected.

isolate

A particular strain of HIV-1 from an infected person (primary isolate) or a cultured cell line (laboratory isolate), defined by its genetic sequence. Isolates of HIV from different people are almost never identical.

k **killer T-cell**
see **CD8+ T-cell**

l **lipopeptide**
Segment of a protein, linked to a fatty molecule called a lipid. Lipopeptides derived from HIV are being used to make candidate AIDS vaccines. The presence of the lipid seems to enhance immunogenicity.

live vector vaccine

A vaccine made by using a virus or bacteria that cannot cause disease to transport genes from HIV (or some other pathogen) into the body. Once inside cells, the genes produce proteins, which in turn induce immune responses. This type of vaccine often generates cellular immunity. Examples include vaccines based on adenovirus vectors or the bacteria *Salmonella*.

long-term non-progressor

LTNP

An HIV-infected person who remains free of AIDS symptoms (such as immune system decline or opportunistic diseases) for an unusually long period of time. LTNP typically have strong CD8+ T-cell responses, minimal lymph node damage and a relatively low viral load. About 10% of HIV-positive people seem to be LTNP.

lymphocyte

The diverse set of white blood cells that carry out many of the functions of the immune system. There are two main types: B-cells (responsible for producing antibodies) and T-cells (which orchestrate the overall immune response and destroy cells infected with pathogen, among their many roles).

m **macrophage**

A type of large immune cell that devours invading pathogens and other intruders. Macrophages then stimulate other immune cells to respond by “presenting” them with small pieces of the invaders. They can also harbor large quantities of HIV without being killed, and may therefore act as viral reservoirs. (see **antigen-presenting cell**)

membrane

see **cell membrane**

memory cell

Long-lived subsets of T-cells and B-cells that have been exposed to specific antigens and can “recall” them (and then quickly mobilize an immune response) if that antigen is encountered again during a later infection, even many years later.

microbicide

Product (such as a gel or cream) that could be applied topically to genital surfaces to prevent or reduce the transmission of HIV and other disease-causing organisms during sexual intercourse.

Microbicides might also take other forms, including films, suppositories, and slow-releasing sponges or vaginal rings. The development of safe and effective microbicides could help many women substantially lower their risk of HIV infection.

MTCT

mother-to-child transmission

Transmission of HIV from a mother to her unborn child in the womb or during birth, or to infants via breast milk.

mucosal immunity

Immune responses localized in the body's mucous membranes. Mucosal immunity depends on immune cells and antibodies in the linings of the reproductive and gastrointestinal tracts and other moist body surfaces exposed to the outside world, which are entry points for many types of infection (including HIV).

mucosal tissues

Moist layer of tissue lining the body's openings, including the genital/urinary and anal tracts, the gut and the respiratory tract.

mutation

A genetic change that is inherited in all progeny of the mutated cell or virus.

MVA

modified vaccinia Ankara

A harmless relative of the smallpox (vaccinia) virus, and which has been engineered for use as a live vector vaccine. MVA is used in several AIDS vaccine candidates now in development.

n *nef* (gene)

Nef (protein)

HIV gene encoding Nef, a regulatory protein. Nef is not essential for the virus but helps regulate viral replication.

neutralizing antibody

NAb

An antibody that docks onto a pathogen and prevents it from infecting cells. Inducing strong, broad neutralizing antibodies is thought to be key for the development of AIDS vaccines that block infection, but has so far not been achieved.

NYVAC

A member of the poxvirus family (like MVA and canarypox) and also used as a live viral vector for AIDS vaccines.

Oligomer

A protein with two or more separate subunits that associate with one another. In HIV virions, the envelope protein is an oligomer with three gp120 subunits.

Pathogen

Disease-causing microorganism.

peptide

Segment of a protein molecule. In AIDS vaccine development, peptides are used both in testing immune responses to HIV and as components of vaccines.

Phase I trial

Controlled clinical study done in the first stage of evaluating experimental products (such as medicines or vaccines) in humans. Phase I vaccine trials test a product's safety in humans, including any side effects seen with increasing doses, and usually also monitor whether it induces immune responses. They typically involve a small number of healthy volunteers (usually 60 or less); for AIDS vaccine studies, the volunteers are generally selected to be at low-risk for HIV infection.

Phase II trial

Controlled clinical study done in the second stage of testing new products in humans. Phase II vaccine trials extend the safety data gathered during Phase I, collect more information on the product's ability to induce immune responses and determine the best dose and immunization schedule. They enroll up to several hundred volunteers, sometimes including people with characteristics similar to potential participants of a future efficacy (Phase III) trial. For example, Phase II studies of candidate AIDS vaccines may enroll some volunteers at higher risk for HIV infection.

Phase IIb (proof of concept) trial

Controlled clinical study designed to look for preliminary evidence of a product's efficacy. Phase IIb studies are smaller, shorter and less expensive than a full-fledged Phase III study.

Phase III (efficacy) trial

Large, controlled clinical study done in the third stage of human testing, to determine if and how well a vaccine or medicine works. For AIDS vaccines, efficacy is measured by looking for prevention of HIV infection, reduction in the severity of disease and/or delay of disease onset. A Phase III study should gather sufficient data so that the product can be approved for licensure if it is found to work. This usually includes further safety data for evaluating the overall benefit-risk relationship of the vaccine. Phase III trials of AIDS vaccines will typically need to enroll at least several thousand volunteers.

Phase IV trial

Study conducted after a vaccine or medicine has been licensed, to determine its true effectiveness under “real world” conditions of use rather than under the controlled conditions of a clinical trial. For vaccines, they measure properties such as how long protection lasts and look for any late-emerging or very rare side effects. A Phase IV study can involve up to many thousands of people.

placebo

Inactive substance given to some study participants, while others receive the test substance (e.g., a vaccine). Placebos provide a basis for comparison.

placebo-controlled clinical trial

Clinical trial in which one group of volunteers is given the experimental vaccine or medicine, and the other is given a placebo. The results of the two groups are then compared to see if the experimental product was effective relative to the placebo.

plasmid

Small, independently-replicating piece of bacterial DNA. Researchers often use harmless plasmids to transfer foreign genes into cells, for example, in making DNA vaccines.

pol

The HIV gene that encodes a group of enzymes needed for viral replication (called protease, integrase and reverse transcriptase).

prevalence

The proportion of people with a particular disease or infection in a given population.

prime-boost

An approach to inducing immunity, which uses a first vaccine dose (prime) to induce an initial set of immune responses, followed by a second type of vaccine (booster) to amplify the desired responses. A prime-boost combination may induce different types of immune responses and/or better overall responses than those seen with only one type of vaccine.

pro (gene)

protease (protein)

HIV gene encoding an enzyme called a protease, which cleaves proteins. HIV protease cuts the large precursor proteins produced from viral RNA into their component parts, which are then assembled into new viral particles.

protein

A large, varied class of molecules that are the main constituents of cells and carry out the different functions that cells (or viruses) perform. For example, they can be structural proteins (like the HIV envelope protein), regulatory proteins (like cytokines) that control the activity of other proteins, antibody molecules or enzymes (like HIV reverse transcriptase). Proteins are long chains made from twenty different building blocks called amino acids. Each protein has a unique, genetically defined amino acid sequence which determines its three-dimensional shape and its function.

protein subunit vaccine

A vaccine containing a protein from the virus or other pathogen. Subunit vaccines produced by genetic engineering are called recombinant subunit vaccines.

protocol

The detailed plan for a clinical trial, outlining its purpose, methodologies (such as vaccine dosages, routes of administration, length of study, eligibility criteria) and other aspects of trial design.

pseudovirion

Non-infectious particle resembling a complete virus but lacking its genetic material and one or more viral proteins, so it is unable to replicate. AIDS vaccines based on pseudovirions are in pre-clinical development.

randomized trial

A clinical study in which participants are assigned by chance to one of the arms of the trial, such as the vaccine and the placebo arms. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms.

recombinant protein subunit vaccine

Vaccine produced by genetic engineering and consisting of a particular protein from the virus or other pathogen.

recombination

A process that increases genetic diversity by exchanging pieces of the genomes from two viral strains, or two individual organisms. All types of living things undergo recombination.

regulatory proteins

Proteins that help regulate viral replication in infected cells, in contrast to the structural proteins that make up the virus particle itself. The HIV regulatory proteins are encoded by the *nef*, *rev*, *tat* and *vpr* genes.

replication

For HIV, the process of multiplying, or producing progeny particles. Replication involves many steps: copying the genetic material, producing all the different proteins that go into a virus particle, and then assembling the particles. Like all viruses, HIV cannot replicate on its own but must be inside a host cell so it can co-opt some of the host's cellular machinery.

retrovirus

A group of viruses (including HIV) that carries its genetic material in the form of RNA rather than DNA, unlike all other living things. These viruses contain an enzyme called reverse transcriptase which transcribes RNA into DNA—a process opposite that which normally occurs in animals and plants (where DNA is made into RNA), and which accounts for the prefix “retro.”

reverse transcriptase

RT

An enzyme found only in retroviruses, which copies RNA into DNA. It is encoded by the HIV RT gene.

RNA

ribonucleic acid

A single-stranded molecule composed of chemical building blocks similar to those DNA. RNA is the sole genetic material of retroviruses and an intermediary in making proteins in all living things.

Seroconversion

The development of antibodies to a particular antigen, due either to an infection or a vaccine that exposes the immune system to the antigen. When people develop antibodies to HIV, they “seroconvert” from antibody-negative (**seronegative**) to antibody-positive (**seropositive**).

SHIV

simian/human immunodeficiency virus

A genetically engineered hybrid virus with an HIV envelope and SIV core. SHIV is widely used for testing vaccines in monkeys.

SIV

simian immunodeficiency virus

An HIV-like virus that infects monkeys and causes an AIDS-like disease in some species.

statistical significance

The probability that an observed difference (for example, between two arms of a vaccine trial) is due to the vaccine rather than to chance alone. This probability is determined by using statistical tests to evaluate the trial data. In general, results of a clinical trial are considered statistically significant if there is a less than a 5% probability that the observed difference would occur by chance alone.

sterilizing immunity

An immune response that prevents the establishment of any detectable infection.

strain

A genetically distinct isolate of HIV. HIV is very heterogeneous, and two isolates are rarely ever the same. When HIV is isolated from an individual and studied in the lab, it is given its own unique identifier, or strain name.

structural proteins

In HIV, the proteins that make up the virus particle. These include Env and Gag proteins.

subunit vaccine

see **protein subunit vaccine**

subtype

also **clade**

A classification scheme based on genetic differences among isolates.

T-cell

One of two main types of lymphocytes critical to the immune system. It includes CD4+ and CD8+ T-cells. The “T” stands for the thymus, where T-cells mature.

Variation

see **genetic variation**

vector

Bacteria or virus that does not cause disease in humans and can be used in making vaccines, by virtue of its ability to transfer foreign genes into cells. Different vectors have different properties, which in turn determine how suitable they are for particular vaccine strategies or designs. (see **live vector vaccine**)

VEE virus

Venezuelan Equine Encephalitis

A virus causing disease in horses, and which has been engineered to make a non-pathogenic live vector vaccine against AIDS. VEE targets mainly a class of antigen-presenting cells called dendritic cells.

viral core

The internal portion of the HIV particle, containing proteins encoded by the *gag* gene.

viral load

The amount of HIV in the blood. Viral load is used as an indicator of the state of an HIV infection.

viral replication

see **replication**

viral vector vaccine

A type of live vector vaccine, made by using a virus that cannot cause disease to transport HIV or other foreign genes into the body. This type of vaccine often generates cellular immunity and is widely used in AIDS vaccine development.

viremia

The presence of virus in the bloodstream.

virion

A complete virus particle outside a host cell.

virus

A microorganism composed of a piece of genetic material (RNA or DNA) surrounded by a protein coat. To replicate, a virus must infect a cell and direct its cellular machinery to produce new viruses.

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aids vaccine handbook

edited by PATRICIA KAHN

THE NUMBER OF PEOPLE LIVING WITH HIV/AIDS now approaches 40 million worldwide, and over 3 million people died of AIDS in 2004 alone. Each day 14,000 more men, women and children get infected—95% of them in developing countries. Beyond the health emergency this represents, AIDS is also a global development crisis that devastates families, villages, cities and countries.

We need to do much more with today's prevention methods, and we must expand access to treatment. But no viral disease has ever been controlled without a vaccine.

A safe, effective AIDS vaccine remains the world's best chance to curb the relentless epidemic.

As the global effort to develop an AIDS vaccine scales up and expands internationally, the need for information geared to lay readers is growing quickly. This is especially true for the clinical testing of candidate vaccines, which cannot be achieved without tens (and ultimately hundreds) of thousands of volunteers from at-risk communities around the world. It also applies to the advocates, policy makers, community health workers and others interested in AIDS vaccine development.

The *AIDS Vaccine Handbook* aims to meet these needs. Through a collection of easy-to-read, lively essays, it gives an overview of clinical trials and the questions they raise for communities, of the key scientific, advocacy and policy issues and challenges, and of the experiences gained and lessons learned so far. The essays are written by people involved in this work in many different ways in many parts of the world.

In the time it took to read this, 15 more people became infected with HIV/AIDS.

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