

IAVI REPORT

A Newsletter on International AIDS Vaccine Research

Vol.4 No.4 September-October 1999

Conducting HIV Vaccine Trials Around the World: What We've Learned So Far

by Patricia Kahn

Over the past few months, three countries have made international headlines with launches of HIV vaccine trials: the U.S. and Thailand, which began the world's first large-scale (Phase III) trials of an experimental AIDS vaccine, and Uganda, the first African nation to join in testing candidate HIV vaccines. These steps may not sound like major news; it is unlikely that any other type of vaccine trial would generate so much press coverage just for getting started. But in practice, the decision

to launch an AIDS vaccine trial - and the issues that arise in running it - can be difficult and highly politicized, especially in poorer countries.

That is the picture which emerges from interviews presented in this issue of the *IAVI Report*, where four leading researchers conducting HIV trials on different continents describe the political, scientific and human issues they face. From Uganda - a country well-known for its early, proactive efforts against AIDS - Roy Mugerwa talks

about the recently-launched ALVAC HIV vaccine trial and the controversy it raised over being "guinea pigs" for the West. Nath Bhamarapravati describes how many Thais began with similar concerns, but the country went on to conduct five Phase I/II studies (completed or now underway) and to launch the recent Phase III gp120 study. As Dirceu Greco discusses, Brazil established an infrastructure for trials in the mid-1990s, but lost momentum after a single study. However, the researchers were able

continued on page 2

INSIDE THIS ISSUE

Focus: Conducting HIV Vaccine Trials Around the World	-1-
A long, rocky path: An interview with Uganda's Roy Mugerwa	-4-
From "guinea pig" fears to Phase III trials: An interview with Thailand's Nath Bhamarapravati	-6-
Studying the volunteers: An interview with the US's Susan Buchbinder	-8-
The ebbs and flows of AIDS vaccine trials: An interview with Brazil's Dirceu Greco	-10-
ALVAC Prime Boost Trial Results Announced	-1-
PMC's Canarypox Vectors	-13-
Vaccine Briefs	-2-
Viewpoint: Do HIV Clades Really Matter?	-3-
AIDS Vaccine Glossary	-14-

Preliminary Results of U.S. Phase II Prime Boost Combination Released

By Jim Thomas

Researchers released preliminary data from the first Phase II trial of a combination of two HIV vaccines given to individuals at high-risk for HIV infection. The study found that the combination was safe and capable of eliciting measurable cellular immune responses in approximately one-third of those immunized. The information was released on 13 July 1999 by Robert Belshe of Saint Louis University, a co-principal investigator on the study, at the International Society for Sexually Transmitted Diseases Research Meeting.

The study is being conducted by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) through its two HIV vaccine clinical networks: the AIDS Vaccine Evaluation Group (AVEG) and the HIV Prevention Trials Network (HIVNET). Fourteen U.S. sites are

involved in the protocol, known as AVEG 202/HIVNET 014.

The candidate vaccines used in the prime boost combination were the ALVAC vCP205 combined with a gp120 envelope protein. Produced by Pasteur-Mérieux-Connaught (PMC), vCP205 is a canarypox virus vector carrying several key HIV genes. It is designed to stimulate cellular immune responses, especially cytotoxic T-lymphocytes (CTLs). The gp120 product, manufactured by Chiron Vaccines, is designed to elicit antibodies to HIV.

Belshe reported that more than 50% of those who received only vCP205 developed antibodies, as did more than 90% of those who received the combination. In addition, one-third of those receiving either vCP205 alone or the combination

continued on page 13

VACCINE BRIEFS

U.S. Congress may boost Army AIDS program

The Walter Reed Army Institute for Research (WRAIR), which faced a cut of US\$15 million in the current fiscal year budget, may see some of those funds restored in fiscal year 2000. While U.S. President Bill Clinton's original budget failed to restore any of the cuts, the House of Representatives voted to allocate an additional US\$10 million to WRAIR for next year. However, since the Senate's budget failed to include the additional funds, the final allocation will be decided by a House-Senate conference committee. WRAIR has an extensive HIV vaccine research and development program and last year's reduction in funding drew strong criticism from vaccine advocates in the U.S.

Vical shares jump on Merck report; Douglas joins Vical board

Shares of Vical, a California-based biotechnology company, increased 35% on 30 July after *The Wall Street Journal* reported that pharmaceutical giant Merck was testing an HIV DNA vaccine using the company's technology. The article, which cited the *IAVI Report* as a source, said that Merck was planning to begin human tests of two candidate HIV vaccines as part of an extensive research effort.

That day, Vical's stock price jumped by US\$3.94 to US\$15. "When (Merck) is using your technology, it's obviously a big boon," said Hambrecht & Quist biotechnology analyst Richard Van Den Brook. Merck licenses the DNA vaccine technology from Vical. Albert Rauch of Everen Securities estimates that Vical's deal with Merck may be worth as much as US\$40 million in license fee payments, R&D revenue and milestone payments.

In related news, Vical announced that R. Gordon Douglas, Jr., would join the company's Board of Directors. The well-respected Douglas was president of Merck Vaccines from 1991 until his retirement earlier this year. He is also a member of IAVI's board of directors.

On the same day as the *Wall Street Journal* report, shares of VaxGen, the company developing gp120 vaccines (see *IAVI Report*, July-August 1999), dropped almost 10%. As of 17 August, VaxGen's stock was trading at US\$16, down from a high of US\$29.75. However, Prudential Securities, a leading brokerage firm, has put an "accumulate" recommendation on VaxGen's stock. In other VaxGen news, *The Seattle Times* reported on 18 July that Microsoft co-founder Paul Allen has been buying stock and now controls 8.1% of the company.

U.S. NIH panel calls for changes in peer review

A key committee at the U.S. National Institutes of Health (NIH) – the Panel on Scientific Boundaries for Review – has proposed changing the peer review system at the NIH to encourage risk-taking and to more closely link basic and applied research. NIH evaluates about 30,000 grant proposals per year, including a significant number related to HIV vaccine research.

The committee praised the peer review system as "outstandingly successful," but expressed concern that the present system tends to discourage risk-taking and undervalues new ideas. "Countering the conservatism of the peer review system is a critical issue that should become a long-term focus" of the NIH. The panel also called for "cultural changes" in the peer review process and cautioned that an "obsession [with] preliminary data can be the enemy of innovation."

In May 1999, David Baltimore, chair of the NIH's AIDS Vaccine Research Committee, called Innovation Grants Program reviewers "too conservative" and "not focused enough on the final goal."

Uganda and South Africa to cooperate on AIDS

Uganda and South Africa agreed to cooperate in fighting HIV/AIDS. Ugandan health minister Crispus Kiyonga and his South African counterpart, Manto Tshabalala-Msimang, announced the agreement on 5 August in Kampala. The two countries agreed to cooperate on the development of HIV vaccines, prevention of mother-to-child HIV transmission, drug research, procurement and distribution, and HIV surveillance. Tshabalala, who led a 23-person delegation to Uganda, said, "In the last few days, we have acquired additional experience and information." She hailed Uganda's political commitment and social mobilization against AIDS.

White House meeting on AIDS

As *IAVI Report* went to press, planning was underway for a White House meeting designed to spur global efforts to respond to AIDS. The meeting, to be convened on 7 September by U.S. First Lady Hillary Clinton, will reportedly include Vice President Gore, UNAIDS director Peter Piot, U.S. government cabinet members, and a small group of corporate and foundation leaders. It is intended to generate increased financial support and international cooperation in the fight against AIDS and to build support for the Clinton administration's US\$100 million global AIDS initiative. The meeting will reportedly focus on Africa.

VACCINE TRIALS AROUND THE WORLD continued from page 1

to maintain their valuable cohorts and hope to resume trials soon. Susan Buchbinder of the U.S. – where nearly four dozen HIV vaccine trials have been, or are being, conducted – discusses her research involving thousands of potential and actual volunteers, their motivations and concerns about participation, and her practical experience with informed consent and risk counseling in the

trial context.

We hope these portraits from countries at the forefront of AIDS vaccine clinical trials will bring to light the many ways that people around the world are dealing with, and resolving, the complex, critically important issues these trials raise. ♦

Viewpoint: Do HIV Clades Really Matter?

By Jaap Goudsmit

Editor's note: "Viewpoint" columns, an occasional feature of the IAVI Report, are a forum for researchers to present their opinions on key questions in AIDS vaccines. In this article, Jaap Goudsmit looks at the politically charged issue of HIV clades from a scientific perspective. He questions whether they have any real biological meaning, arguing that there is no evidence for clade-specific genetic differences translating into differences in how HIV replicates, is transmitted, or causes AIDS. Nor is it clear whether vaccines will have to be tailored to specific clades, or whether a "universal" vaccine is possible.

The extensive genetic diversity of HIV is often viewed as a serious barrier to development of an AIDS vaccine. Far from being a single virus, HIV is actually a family of related virus types, clades (also called subtypes) and strains, with the global AIDS epidemic caused by the eight subtypes of HIV type 1. These subtypes (designated A through H) differ from one another in about 30% of their total genetic sequence. Within subtypes, new strains are continuously being generated via HIV's very high rate of mutation, while genetic recombination – which shuffles the genomes of viruses from two different subtypes – also adds to the pool of new HIV variants.

Since the discovery of HIV-1 subtypes, there has been fierce debate about their significance: do their sequence differences translate into meaningful biological differences (for example, in pathogenicity or rate of transmission), or is subtype a mostly artificial distinction among viruses that are biologically much the same? For vaccine development, the key issue is whether viruses of different subtypes "look" different to the immune system, which in turn will affect whether a vaccine that works against one HIV subtype would recognize other subtypes equally well (or at all). Unfortunately there is too little data to answer these questions definitively.

The scientific debate on subtypes has also become highly politically charged. The reason is that the eight HIV-1 subtypes are not evenly distributed around the world but exist as distinct geographic clusters, with one or two subtypes dominating particular regions. On top of this, until very recently AIDS vaccine research has focused almost exclusively on subtype B, which predominates in Europe, the Americas, Japan and Australia (although infection rates with this subtype are declining worldwide), while HIV-1 subtypes A, C, D and the recombinant subtype E are spreading rapidly in Africa and Asia and cause far more cases of AIDS globally. This situation has raised concern that current efforts could yield a vaccine that is effective for industrialized countries but does not work against the HIV subtypes prevalent in the developing world. (It is for this reason that IAVI has argued strongly against concentrating solely on subtype B.) Such an outcome would reinforce the huge North-South gap that already exists with respect to the availability of triple drug therapy for HIV-infected people. It would also be particularly cruel, since lack of access to these effective but expensive drug treatments gives HIV vaccines an urgency in the developing world that they do not have in industrial nations. For the world's poor countries, a vaccine is the only realistic hope for stopping AIDS.

In asking whether HIV-1 subtypes are biologically distinct

entities, the first issue to consider is their uneven global distribution and unequal rates of spread. These patterns have sometimes been taken as evidence for intrinsic biological differences among subtypes. I believe there is little data to support this notion, and lean strongly towards an alternative explanation based on what is called a "founder effect." Once a subtype becomes established in a region (which means it must be well-adapted to the local host population), a new subtype can infiltrate the area only if it is transmitted more efficiently in the local risk population than the already-established subtype. Barring such differences, the geographic distribution pattern will simply reflect the HIV subtype(s) that happened to establish first in particular regions. It is important to realize that a higher transmission rate is not necessarily due to inherent properties of the virus; a new subtype can take over simply because it entered a population whose behavior favors rapid spread (e.g., due to more frequent sexual encounters or needle-sharing), or whose load of other (non-HIV) infections is higher, a condition which makes transmission more likely, as discussed below. So far, to my mind, no studies have firmly linked differences in transmission rate to intrinsic traits of HIV subtypes.

Similar considerations apply to the spread of inter-subtype recombinant viruses, several of which are causing new local epidemics in West Africa, Russia and China.

Recent data from the groups of Francine McCutchan at the Henry M. Jackson Foundation in Washington, D.C., Martine Peeters of the University of Montpellier and Marion Cornelissen in our own lab indicate that over 30% of all new infections in certain West African countries (e.g., Cameroon) come from recombinant viruses, while A/B recombinants are spreading rapidly in Russia. Recombinants presumably arise frequently in people infected with two subtypes, but they become established only if they are transmitted more rapidly than the already-present HIVs – again, either because they have an inherent ability to spread faster or because the right circumstances for efficient spread arise. More studies are needed to distinguish between these possibilities.

One factor that clearly does affect transmission efficiency (and therefore contributes to preferential spread of particular strains or subtypes) is viral load, a measure of how fast HIV replicates in a given host. It is generally accepted that the more HIV an infected person's cells produce, the likelier that this person will transmit virus. HIV-2 provides a good example: it grows poorly, so infected people have relatively low viral loads; it also spreads slowly and inefficiently, causing AIDS in only a few percent of infected individuals and only after an extremely long incubation time.

"I believe there is little evidence of intrinsic biological differences among subtypes."

continued on page 12

Uganda: A long, rocky path to Africa's first HIV vaccine trial

An interview with Roy Mugerwa

Uganda began preparing for HIV vaccine trials nearly ten years ago, and in February 1999 became the first African nation to start one when it launched a Phase I study of a vaccine made in France. Roy Mugerwa, M.D., is a principal investigator of the trial and the study site where it is being conducted, which is part of a U.S. NIH-sponsored network of HIV vaccine trial sites called HIVNET. Earlier, he was a principal investigator of Uganda's HIV vaccine trial preparedness program. He is a professor at Makerere University.

IAVI Report: How did Uganda's interest in AIDS vaccine development begin?

Roy Mugerwa: As early as 1986, there was an openness in Uganda about the seriousness of the HIV problem. I attribute this to the political leadership. President Museveni started consulting medical people when he came to power, and then spearheaded a campaign to educate the country about HIV. It was brave to talk about a problem which other leaders were quiet about because they feared discouraging tourism, among other reasons.

When the outside world saw this, research institutions and funding agencies became interested in collaborating with Ugandan researchers. In 1990, Uganda's President sent a group of scientists to meet the U.S. Secretary of Health and request assistance. There was something called PAVE – Preparation for AIDS Vaccine Evaluation. It provided U.S. government funds to institutions which collaborated with developing countries on HIV vaccine initiatives. Around this same time the WHO's Global Programme on AIDS named Uganda as a country where HIV vaccine trials might be conducted.

We then collaborated with U.S. researchers to set up cohorts of people attending STD clinics, in the military, and in the Rakai District. Our objectives were to study the prevalence of HIV, new infections and circulating subtypes. We also studied how much people knew about HIV.

How did people react when the ALVAC trial was first proposed?

Initially there was a lot of resistance. People had a lot of questions and misconceptions: They asked, "Why do we need a vaccine?" and "Why has Uganda been chosen, out of all African countries?"

Our answer to the first question was that, despite a lot of public education about how to avoid HIV infection, people were still getting infected and dying. So trying to change peoples' behavior was not enough – we needed other ways to combat HIV. Vaccines have historically been one of the most effective weapons against infectious diseases. While new drugs were becoming available, they were unaffordable for most Ugandans. We emphasized that the vaccine had been tested in France and the U.S. and found to be safe and somewhat immunogenic.

As for "why Uganda," we had several answers. Besides our political commitment, we had cohorts, laboratories and trained manpower, set up with outside funding.

There were also concerns that if a vaccine were eventually developed, it would not be available or affordable to Ugandans. People have not forgotten that Senegal participated in hepatitis B vaccine trials, but when the vaccine became available it was too expensive for the people of Senegal. Attempts to get the price down were unsuccessful. So Ugandans worried that they were being used only to benefit other populations.

How did you answer that?

We said we would negotiate with the vaccine manufacturer, Pasteur-

Mérieux-Connaught (PMC), which is a well-established company with a name to lose. We are doing that. Also, we said that IAVI and UNAIDS are working on how to make a vaccine available to poor countries.

We don't know exactly how this will work, but the issue is still far off. We're talking about a Phase I trial of a vaccine we are not even sure will work. That leaves plenty of time to address these concerns.

Testing a vaccine based on a clade B HIV strain also fueled concerns about Ugandans being used as "guinea pigs." What was your response?

At that time there were studies showing that people infected with clade B HIV had immune cells in their blood which recognized virus from other clades – what we call "cross-clade reactivity." Preliminary studies also showed that individuals infected with clades other than B had immune responses that recognized clade B virus. So there was evidence that cross-reactivity is possible – which could mean that we don't have to produce a vaccine matched to the virus circulating in every population.

But we don't know whether these findings can be reproduced in vaccinated individuals. This is exactly what we are trying to do – to see whether a clade B-based vaccine will cause our volunteers to produce cellular immune responses that recognize clades A and D, the HIV subtypes circulating here. We also need to find out how immunogenic the vaccine is in our population since we have a different genetic background, different nutritional status and different exposures to many infections compared to volunteers in the U.S. and French trials.

I think people came to realize that there is scientific justification for the study.

What were some of the common misconceptions?

Some people said that the vaccine to be tested contained HIV and that it was a plot to introduce more HIV into Uganda. Another was that we planned to inject HIV into people who got the test vaccine, to find out if it worked, or that we would deliberately expose vaccinated people to infected people.

Using the media, it was not hard to convince part of the population that there might be some truth to these claims. Initially, newspapers printed big headlines like "Vaccine to Kill Off Ugandans Will Be Tried." So we had to launch a campaign to disseminate accurate information, using workshops and seminars to explain to people what we were proposing.

Since then, has the media changed its attitude to the trial?

The media is now very supportive. Part of the negative reporting was because they did not have enough information, so they published whatever they got their hands on. Also, some newspapers and radio stations just wanted sensational stories that would get attention.

What formal approvals were needed to launch the trial?

This was not entirely clear at the beginning, since there is no legal



framework for biomedical research in Uganda. But we had to have political clearance at the parliamentary level. That meant not only the Minister of Health, but also the Cabinet. We talked with the Cabinet and organized meetings in Parliament, where the Minister of Health discussed why the trial was important. Then we needed scientific clearance. We presented our protocol to at least five committees, including an ethics committee. Once we had approvals at all these levels, people started to believe that there was probably nothing wrong with what we were doing.

It's striking that the whole process was so long and difficult, despite Uganda's early interest in AIDS vaccine development.

I think a big reason is that AIDS and AIDS research has been very politicized in many African countries. In fact there was some political maneuvering to take advantage of the initial negative media reports and try to damage the government. At one point the government wanted to pull out because of the possible political repercussions.

There were also questions that were difficult to address. People were saying, "Look, there are so many millions of people who are infected, why are you interested in those not yet infected? What are you doing about the infected people? Why are you not bringing in drugs for us?" Our best answer was that organizations like UNAIDS are trying to do this. But the situation is not very easy to swallow.

In retrospect, is there anything you might have done differently?

One mistake we made was with the media. Sometimes we did not give them information on time, so they wrote incorrect things. Since then, we have set up an information desk on HIV vaccine trials to give updates and correct misconceptions.

Some people say, "Why did you make so much noise about this trial? You should have gone ahead quietly and done this study like any other." But I think that would not have been wise. This has been a learning process. Our politicians are now comfortable with the idea of HIV vaccine trials, and see that they are being planned in countries outside and even within Africa, such as Kenya, Zambia and South Africa. The stigma of the words "HIV vaccine" is decreasing. And we are now establishing a committee to review future protocols so that researchers will not have to go through what we went through.

Tell us about your volunteers for this trial.

We are recruiting 40 low-risk people. Most are from the military - young men 18-40. We've been working with them for the last eight years, so they understand research, vaccines and how HIV is transmitted. To get more gender balance, we also approached women participating in other clinical studies.

How is enrollment going?

We started in February and now (August 1999) have 38 volunteers. We expect to enroll our last ones this week. Our difficulty was not the lack of volunteers - the response was very good - but the fact that many people had to be excluded. For some it was because of high-risk behavior, or because they were once infected with syphilis. Also, white cells and platelet counts in our population tended to be low compared to Caucasians, and other cells such as eosinophils were high. So we had to modify some exclusion criteria in the original protocol. A

lot of our subjects have intestinal worms and this can affect the results of the Western blot [antibody] test, which we were not aware before the trial started. So we had to examine people's stools and deworm some. Researchers need to know these things before the trials start.

How do you carry out informed consent?

The informed consent document was approved by review boards here and in the U.S. It is a five-page document with a lot of information in as simple language as possible. An individual reads the document or has it read to him. We explain the study, the possible risks and benefits, and that they can withdraw at any time. We assess whether people understand the information by asking them a series of questions.

Volunteers are free to take the document with them and consult their families. In fact, we encourage potential volunteers to inform their spouses. We are reluctant to enroll people whose spouses are unaware of their participation. If a spouse found out later on, it might cause problems and lead that volunteer to drop out of the study.

What about risk reduction counseling?

Before the trial started we trained our counselors and developed a document that clearly lays out what should be told to the participant. We emphasize that the vaccine may not work, so people must take the necessary precautions to protect themselves from getting infected, and we provide condoms.

Are there future trials planned or being considered?

Yes. We are already negotiating with PMC to do another study with a vaccine based on clades A and D envelope. They're already preparing these constructs. Other research groups are also making plans. The Walter Reed group in the U.S. is interested in testing envelope subunit and DNA vaccines, both based on subtypes circulating in Uganda.

Would Uganda be able to launch a Phase III trial?

Yes. In the military, we have enough young men who might participate in a Phase III study. But we are also looking at populations that include women. For example, in communities near Kampala, we are looking at seroprevalence and seroincidence in preparation for Phase III.

There is also the Rakai Project. For over ten years researchers have followed thousands of people in certain rural villages. It would be easy to do a Phase III study there, since they have access to a large population with more of a gender balance.

What advice would you offer other African nations considering hosting HIV vaccine trials?

The most important thing is that it takes political commitment to launch a successful program, since HIV vaccines are highly politicized in most developing countries. Obviously it also requires the proper infrastructure, including trained, indigenous personnel. We should not depend on foreigners to do studies here and then leave.

It's also important to have clear guidelines regulating biomedical research, so that you know exactly what you need to do to launch a study. In Uganda we are now working on this because of the lessons we've learned. There should also be an appropriate committee to review protocols. And researchers must build good working relationships with the media, scientists and communities. ♦

"This has been a learning process. Our politicians are now comfortable with HIV vaccine trials. The stigma of the words 'HIV vaccine' is decreasing."

Thailand: From “guinea pig” fears to Phase III trial

An interview with Natth Bhamarapravati

In March 1999, Thailand became only the second country in the world to launch a large-scale efficacy trial of an experimental AIDS vaccine. Natth Bhamarapravati, M.D., was closely involved with helping Thailand initiate this and other HIV vaccine trials. He is a professor at Mahidol University, and is a member of the National AIDS Commission of Thailand, IAVI's Scientific Advisory Committee and the UNAIDS Steering Committee for AIDS vaccines.

IAVI Report: Can you tell us about Thailand's decision to become involved in AIDS vaccine trials?

Natth Bhamarapravati: We began seven years ago, when the Thai National AIDS Commission added HIV vaccine development to its list of strategies against AIDS. Since Thailand was not in a position to do this itself, facilitating the testing of vaccines made by others was the next best solution. We were willing to test safe, immunogenic vaccines that had gone through Phase I testing in their country of origin, but Thais would be principal investigators and closely involved in planning the trials. A scientific subcommittee would review proposals, which then go to the National AIDS Commission for approval.

The policy evolved after a subcommittee was established. They decided that test vaccines should incorporate local HIV clades, and that Phase I studies of these vaccines could be conducted in Thailand instead of having to be done first in the country of origin. We got help building capacity for trials, for example, characterizing virus, data management, setting up facilities to store blood samples, and establishing good clinical and good laboratory practices.

The next stage in our evolution is for Thai scientists to participate in preclinical development of HIV vaccines. We are now collaborating with Japan on developing BCG-based vaccines.

Tell us about the launch of the VaxGen trial.

Thailand has conducted Phase I and II trials of gp120 vaccines since the dark day in 1994 when the U.S. NIH refused to support a trial of this vaccine.

The proposal for the VaxGen Phase III study was reviewed thoroughly, including the ethics. The scientific review subcommittee asked for assistance from UNAIDS, which set up a panel of experts for this purpose. In the end, the subcommittee approved the trial, knowing the objections to, and limitations of, the vaccine.

What were the objections?

Some scientists said that the vaccine is unlikely to be useful, so why pursue it? John Moore, a U.S. researcher, wrote a critical article about the breakthrough infections in Phase I and II trials. He used them as evidence that the gp120 vaccine is no good. But Phil Berman of VaxGen did a detailed analysis of these infections and found that a number of them happened soon after immunization, before the antibodies were well-established. And the number of breakthrough infections was relatively small. In Thailand, there were only one or two cases, and maybe five or six in the U.S.

So through UNAIDS, we consulted a wider group of international scientists. They concluded that we were doing a useful trial. About 80% of them recommended we move ahead.

How was this decision covered in the press and what was the general public's reaction?

Last year, UNAIDS gave a small grant to a Thai journalist to study newspaper coverage of AIDS vaccine trials over the past four years. She found that coverage went through three phases. The first one started before the VaxGen trial, when the U.S. Army tested a gp120 vaccine with the Thai Army. The media's immediate response was that Thais were being used as guinea pigs. This phase lasted for about a year, with claims and counterclaims from those who were for the vaccine and those against it. The next phase was to look at the issues more rationally. There was mention of our policy that vaccines are an important weapon against the AIDS epidemic. The third phase was resolving the issues and the negative claims.

Thais are familiar with large vaccine trials. There have already been three Phase III trials [for Japanese encephalitis vaccine, hepatitis A and malaria vaccines], and the public did not pay much attention to them.

So people were quite open about these trials, which is why the first phase passed rapidly. We are now in the third phase, and the public attitude to the VaxGen trial is, “we don't care.” The news media did not cover it much. Only news people from outside the country have showed a lot of interest.

Hasn't Thailand also strongly emphasized vaccines in its public health policy?

Yes. Infectious disease remains a big problem here, so we value vaccines highly. We were the first developing country to put hepatitis B vaccine on the Expanded Programme of Immunizations (EPI). The Japanese encephalitis vaccine is another EPI vaccine here, so our children are getting eight vaccines instead of the usual six. This was an important reason why the VaxGen trial moved rapidly and smoothly.

During the review process, were other concerns besides scientific ones raised?

There were two serious issues. One was counseling, and making sure that volunteers adopt safe behavior. The other was about medical treatment of trial participants. The Bangkok Metropolitan Authority agreed to provide treatment for any side effects from the vaccine. And if volunteers become infected with HIV during the trial, they will be given at least two drugs – but not a protease inhibitor because we can't afford it.

That issue went back and forth. One group said that people should get triple therapy, the best treatment. But triple therapy is not used in Thailand for most infected people since very few can afford it. Therefore, giving it within the trial could be an unethical

approach to buy the willingness of volunteers.

Was there discussion about making the vaccine widely available in Thailand, if it shows some efficacy?

Yes. For the first time in any vaccine trial in the world, the manufacturer gave us a letter of intent to work with Thailand in making the vaccine, if it proves to be effective. VaxGen will reach an agreement with the Thai Government Pharmaceutical Organization, which manufactures EPI vaccines, to have it produced in dosage form at reasonable cost. Further, there could be an agreement to produce the vaccine locally.

Of course, a letter of intent is not yet a real agreement – there's still a lot to be done. But the letter had a lot of visibility among the authorities and the public.

Can you tell us about your volunteers and their motivations for participating in the trial?

We are recruiting 2,500 former IDUs (injection drug users). Most say their reason is to help get a vaccine. Some are hoping for protection from the vaccine.

Why do people sometimes decline to participate?

A major reason is fear that the vaccine will cause HIV infection, so they do not differentiate between the virus and the vaccine. Others refuse because participation can be cumbersome, having to come for blood drawing, and so on. A few worry about problems with their families or employers. They are afraid that a positive HIV antibody response would label them as infected even though we can distinguish true infection from vaccine responses.

Peer approval is important for many Thai people. That might be a little different than in the West. Many consult their families and even their employers about participation – it's not as individual a decision-making process as you might expect.

How is recruitment going?

As of August 1999, they have immunized about four hundred subjects since starting in March. It was slow at first, but things are now accelerating. There shouldn't be any problem enrolling people. There are enough volunteers.

You mentioned discussions during the trial review about ensuring high standards for risk behavior counseling.

For these participants, counseling was not a problem because they had gone through the Center for Rehabilitation and knew the staff

very well. The drug rehabilitation center is an integral part of the trial. We use its personnel, and train them.

Is participation affecting peoples' risk behavior?

We had a meeting just last week and it was the consensus of the investigator and counselors that volunteers do not appear to change their sexual behavior. And so far there have been no HIV infections.

Are any other HIV vaccine trials planned in Thailand?

Phase I and II trials for canarypox plus gp120 were just approved. And we are organizing a workshop in September to discuss future Phase III trials. We have several groups of higher-risk people, for example commercial sex workers, who have a yearly infection rate of about 5%, and are candidates for efficacy trials.

We are also thinking about what is called a Phase IV trial. It could involve about 10,000 people who are not high-risk, but are more typical of the entire

country. The trial would tell us about side effects and reactions, compliance with getting several injections, and distributing a vaccine.

Thailand has recently had success in reducing HIV infection rates through stepped-up prevention efforts. Has that dampened enthusiasm for vaccines?

I am very uncomfortable that Thailand was cited by UNAIDS and other international agencies as a good model for this. There have been a lot of problems since this publicity. Some policy makers are becoming complacent about AIDS and infection rates in young men,

which had come down, are now picking up. So I don't want to say much about the "success" of Thailand.

We have managed to stabilize infection rates but there are still new infections. Early on, prevention efforts were very cost-effective, but at this point it is difficult and expensive to reduce the number of new infections more.

What have you learned from Thailand's experience that might be relevant to other developing countries?

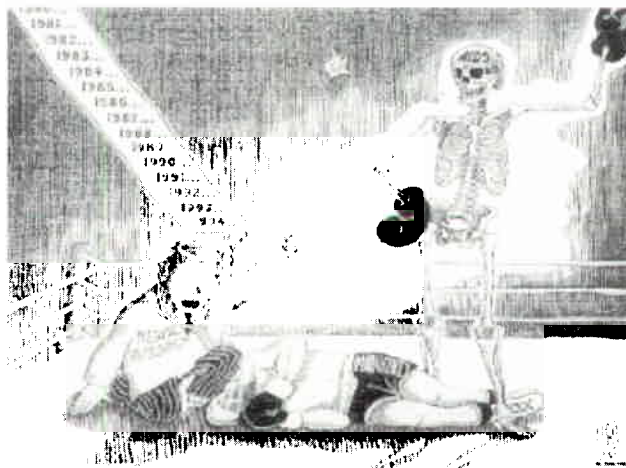
You first have to convince decision-makers that an HIV

vaccine is possible and desirable. This should include the medical and scientific communities, and the media.

Another important point concerns the international debate on HIV vaccine trials. Ethical guidelines like the Helsinki Declaration only consider an individual's rights or choice. We also must consider ethics in terms of communities and countries that benefit from vaccine trials. ♦



1991: The "guinea pig" phase (Bangkok Post) leads to . . .



. . . 1994: The next phase: fears that AIDS is defeating scientists' attempts to combat it (Bangkok).

U.S.: *Studying the volunteers who make HIV vaccine trials possible*

An interview with Susan Buchbinder

Susan Buchbinder is a leading figure in HIV vaccine trials in the U.S. and has followed the epidemic closely from her positions as Director of the HIV Research Section at the San Francisco Department of Public Health and at the University of California, San Francisco. She is also principal investigator of a site within HIVNET, the NIH-sponsored network that conducts HIV vaccine preparatory research and clinical trials. Buchbinder runs a trial site for the VaxGen Phase III study and serves on the Advisory Council of the Office of AIDS Research (OAR) within NIH and on OAR's Prevention Sciences Working Group.

IAVI Report: How did you become involved in AIDS vaccine trial research?

Susan Buchbinder: We started in 1993 with vaccine preparedness studies in San Francisco and other U.S. cities, initially as part of a CDC initiative and later within HIVNET. We needed to find out about high-risk, uninfected gay men - their interest in vaccine trials, baseline level of knowledge about such trials, and the rates of infection in the 1990s.

That work is still continuing. We are also participating in a Phase II vaccine trial that includes both lower- and higher-risk HIV-uninfected people, and are now part of the VaxGen Phase III study. In San Francisco, the predominantly affected population is men who have sex with men; it's the group I have the most direct experience studying. I have also looked at data collected through the HIVNET vaccine preparedness studies, which also involve injection drug users - both men and women - and women whose only risk is heterosexual contact.

What have you learned so far about the reasons why people volunteer for HIV vaccine trials?

Overwhelmingly, for all groups we've enrolled, the leading reason is that they want to help and the belief that their community will benefit from the research. But in Phase III trials there may be something else. The notion of being protected against HIV usually doesn't come up much in Phase I and II trials, but my sense is that more people may be entering Phase III trials because they hope to gain some degree of protection.

Why do people decline to participate?

The leading reasons are usually logistical - people can't make all the required study visits, or they have difficulty with transportation or the times the clinics are open. People lead very busy lives and sometimes don't have the time to participate in research. Fortunately some of these things can be changed so that trials are more accessible to more people.

Other concerns relate to safety. These are experimental products, and some people are not willing to take on the associated risks.

Some people are also concerned about the possibility of a false positive HIV test - or, more correctly, that they may develop antibodies to HIV which are then wrongly interpreted as meaning they're HIV-infected. That could lead to difficulties in obtaining insurance, jobs, housing, and so on.

Have problems with positive antibody tests actually materialized?

So far we've had very few instances where real issues came up.

When they did, the staff at the study site could usually help resolve them. What we don't know is whether the problems will grow when we move into large trials with thousands of participants. Also, as we get into more complex vaccine products, these may be more likely to trigger a positive test result.

We try to educate people up front about the potential problems and to prevent them from arising in the first place. We also offer people a letter stating that they're participating in a vaccine project, if they need to get tested for HIV. That's often helpful. But it's almost always better for them if we do the testing.

Has it been more difficult to get women involved in these studies, compared to men?

It has, and I think there are several reasons. The effort to include women started later, so we're a little further behind in terms of understanding their motivations and the barriers to participation. Women often have competing needs that get in the way of participation; such as childcare or economic issues.

There are also medical barriers. Most vaccine trials require women to not be pregnant or have plans to become pregnant during the course of a trial that could last several years. But women may not want to delay childbearing for so long. We're trying to identify other concerns women may have.

Were there any unexpected findings regarding peoples' willingness to participate?

One of the biggest surprises arose when we were trying to enroll young people - ages 18-25. We found that the parents often didn't want them to participate, and that this can make a big difference. We really hadn't thought about that before. Our educational efforts on HIV vaccine research tend to focus on affected communities, and the parents of these people may not be party to those efforts. We realized that we need a much broader educational program to incorporate families of potential participants.

What knowledge level about vaccines do you encounter in your cohorts?

Baseline knowledge about HIV vaccines is fairly low in general, which is not all that surprising - it's only recently getting more press. Most people have not participated in clinical trials, so don't know how they work. There are often misunderstandings about what a placebo is, what randomization is, what blinding is - all the basic trial concepts.

After putting people through an extensive informed consent process, we give them a quiz to see what they've understood. Usually they do remarkably well.

What are the hardest points to convey?

Many people don't understand that placebos can also cause side effects. That's important because participants need to know that no matter what they get injected with, it can cause some symptoms.

We also tell people that it's possible the vaccine could have harmful effects related to HIV infection or disease. For example, although we obviously hope it will make them less susceptible to infection, it could conceivably do the opposite. Or they could progress to HIV disease more rapidly. That's sometimes a hard concept for people to understand. The assumption is that a vaccine - even a test one - will be beneficial.

How well do people retain this information over time? Six months later do they still have the same understanding?

It's a very important issue and one we hope to assess in the VaxGen trial, through CDC funding. Our only data now is from the vaccine preparedness studies, where we gave people information and then tested to see how well they retained it over time. In general, people's knowledge increased over time because we reinforced concepts at each visit.

One concern about HIV vaccine trials is that participants might develop a false sense of security and increase their risk behavior. Do you have any data on that point?

We have mixed data. In the Phase II vaccine trial, we don't see an increase in risk behavior in the high-risk participants. Actually, most of them had already participated in an eighteen-month study [involving intensive risk counseling], where we'd seen significant declines in risk behavior. So it's not quite the same as recruiting a *de novo* population.

But an earlier hepatitis B vaccine trial involving gay and bisexual men gave some indirect evidence that men were increasing their risk. Although behavior wasn't measured, infection rates in the placebo group increased after people received all their injections. This suggests that people actually waited for this point and then increased their risk, thinking they were protected, even though they knew they were in a placebo-controlled trial. We don't know that for sure, but we can infer it from the data.

So we need to monitor this carefully. But we're also doing a much better job reminding people throughout the trial that they're in a placebo-controlled trial, that they don't know whether they're getting placebo or vaccine, and even if they get active product, we don't know whether or not it protects.

Some of your studies have used computers to collect information from participants. Can you tell us about that?

It's not part of these vaccine trials, but I hope it will be in the future. The main use is as a risk assessment tool. We and others have found that people will report higher levels of risk to a computer than they will in a face-to-face interview - depending on the behavior, by a factor of about 40 to 60%.

That's important for several reasons. One is that we want to find out what risks people are taking and whether this is changing over the course of the trial. Also, we'd like to know if people are getting

tested for HIV antibodies outside the trial, trying to figure out whether they got vaccine or placebo. Our vaccine preparedness study found that people were about 60% more likely to report this to a computer than to an interviewer.

There have been suggestions that counseling should be independent of trial investigators, to avoid possible conflicts of interest. Do you agree?

I understand this, but see it as a perception of a conflict of interest more than an actual one. At our site and many others that recruit high-risk individuals, the counseling staff come from the affected communities or work very closely with them, so their interest is to keep people's risks as low as possible. Actually, our staff feels that they need to have control over risk-reduction counseling because they want to be absolutely sure people are getting the best counseling and aren't increasing their risk because of participation in a vaccine trial.

But we make sure that staff who do the counseling are not involved with other parts of the trial. We don't want a situation where participants won't tell us what risks they're taking because the staff collecting this information are the same people telling them to reduce their risk behaviors.

What efforts are being made to fully engage communities in trials?

I think we need a lot more effort in this regard. Each HIVNET site has tried to institute an ongoing community education process not linked to specific trials. The idea is to educate people about the need for vaccines, what vaccine trial research involves, and keep them updated on progress. The sites also have community advisory boards that are a more formalized way of getting input into trial design and implementation issues, and on working with

community-based organizations. But there's a lot of variability as to how that's done, and I think it needs to be done in a more comprehensive way.

There are also other efforts. The AIDS Vaccine Advocacy Coalition has done a superb job in developing and disseminating educational materials and trying to generate community enthusiasm and involvement. They're trying to push the vaccine research agenda forward in the same way that HIV treatment agendas have been pushed by communities. So a lot is being done, but a lot more is still needed.

From your experience so far, including the new VaxGen trial, do you feel confident that other large-scale trials can be done in the U.S.?

I do. But we have to recognize that there are limitations to the number of trials we can do simultaneously, and perhaps even sequentially. Each trial requires a large number of participants, so we have to plan and choose wisely because there are limited resources - not just monetary but also community resources, in terms of willingness to participate and actual numbers of people who are vaccine-naive.

"If we underpower trials, if we don't power them to get an answer, then we're using up resources inappropriately and not moving the field forward."



Brazil: The ebbs and flows of AIDS vaccine trials

An interview with Dirceu Greco

In 1995, Brazil conducted its first – and only – HIV vaccine trial, a Phase I/II study of a peptide-based vaccine. Dirceu Greco, M.D., Ph.D., was principal investigator at that trial's Belo Horizonte site and is on the medical faculty at the University of Minas Gerais. Greco coordinates the Minas Gerais AIDS Vaccine Center and its Immunodeficiency Sector, the state's main center for evaluating and following HIV-infected people and those at risk.

IAVI Report: How did Brazil become involved in AIDS vaccine trials?

Dirceu Greco: In 1991, the WHO's Global Programme on AIDS (predecessor to UNAIDS) identified four countries in the so-called developing world – Brazil, Thailand, Uganda and Rwanda – that could start AIDS vaccine development programs. These countries had a high enough incidence of HIV infection, enough public and political awareness, and a sufficient infrastructure to conduct trials. After that, Brazil's Ministry of Health established a National AIDS Vaccine Committee, which developed a program.

In December 1992, an opportunity arose to test an HIV peptide vaccine produced by a U.S.-based company, United Biomedical, Inc. (UBI). That led to a search for suitable test sites, which was decided by competition among five institutes. An ad hoc committee chose two – our university and the Oswaldo Cruz Foundation in Rio de Janeiro.

At first, people were very afraid. They said, "It's a guinea pig thing. The vaccine is not really needed in Brazil." Many were confused about vaccines, and I think they still are.

This feeling about being used – it's not a feeling, it's a history. So it's very hard to say, "Look, from now on it will be different." Over the next 18 months, I spoke in many forums, answering a wide-range of questions. It was fantastic because it brought many issues to light, and we made some changes to the trial protocol.

All the hype made it clear that if we were going to do the trial, it would have to be very visible and ethical. People would be asking questions, and if researchers could not answer them, we would not go ahead. At the end of 1994, the trial was approved.

How did you ease concerns about the guinea pig issue?

First, we emphasized that this was only a Phase I trial involving small numbers of people with no known risk for HIV infection. We also said that we would only enroll people who fully understood the informed consent information. Before recruiting volunteers, we had several meetings talking through peoples' concerns and suggestions.

Of course, there were still some people against the trial. One group in Rio de Janeiro thought we should not test the vaccine because it was not going to work anyway. They had good contacts with the press. So from time to time someone would call us from one of the big newspapers and ask, "What are you doing there? We hear people saying that you are doing things you shouldn't."

Soon after the trial started, something interesting happened. One

of the volunteers in Rio decided to tell her story to the press so that people would understand the trial better. She ended up on the cover of one of our main weekly magazines, and across her picture was written, "guinea pig" (see photo). She didn't know it would turn out this way. The article itself was very positive, but the cover was meant to sell magazines.

But then things turned around. A month later one of our volunteers went to a newspaper, and this time they did not emphasize guinea pig issue but said that an HIV vaccine will help fight the epidemic.

What was the formal process for approving the trial?

Universities have local committees like the institutional review boards (IRBs) in the U.S. We went through a very thorough and rigorous approvals procedure over ethics. The proposal went to the IRB of my university and of the institute in Rio, then to the Minister of Health. At that time there was no national ethics commission, as there is now, but there was a national health commission. It wasn't an official body for saying yes or no but it has moral authority. If they said no, we would not have gone ahead.

"If the incidence of HIV declines in wealthy countries, AIDS might become just another tropical disease, and efforts to combat it could decrease. This makes me very afraid."

Since this trial, Brazil has not started any others. Why not?

We are now preparing for Phase II trials with canarypox-based vaccines, which could start by January 2000. But let me tell you about what happened in between.

AIDS vaccines have gone through something like an ebb and flow here. At first they were a big thing. But the UBI trial ended around the time that triple drug therapy was introduced, and optimism was high. People were saying, "Now we can eliminate 99% of the virus in infected people." So vaccines were very much put aside here. From 1996 until now, nothing happened with respect to vaccine trials.

But back in 1992, we started three high-risk cohorts in Brazil: in Rio; in Sao Paulo; and here in Belo Horizonte. These are cohorts of uninfected homosexual and bisexual men who receive risk-counseling and condoms. There were three objectives: to learn about the incidence of new infections, to work out the best ways to do counseling and to prepare for future vaccine trials.

Our site and Rio de Janeiro are each following about four hundred volunteers, and Sao Paulo has about six hundred. Rio now also has a fourth Brazilian cohort.

What have you learned from these cohorts?

Even with all the counseling and condoms, we have had 18 seroconversions in our cohort. Sao Paulo has about the same.

These cohorts are completely ready for trials. They understand a lot about clinical studies and can give autonomous informed consent. When we ask people whether they would participate in an HIV vaccine trial based on the information they have, about 70% say yes.

Do you think their risk behavior might change in a vaccine trial?

People express hope that participation would help them avoid infection, even when we emphasize that it would only be a trial. But if we keep our counseling good, it might go the other way. In a way we have to scare people and say, "We don't know if this vaccine will work, so you'd better behave yourselves." But 18 seroconversions is very little, considering the risks the participants took before. So risks are definitely decreasing.

What are the key issues you face with informed consent?

One is to help people understand exactly what is written. I chair the ethics committee at my university, so I've seen many informed consent forms. They can be very difficult to understand. We still don't know what the right balance is. Do we make it simple so that people understand everything? But then they could say we are not giving them complete information. On the other hand, if you include every possible issue, people may not understand because it's just too much information.

We're trying to implement a system involving not just one informed consent form, but a dynamic process. From time to time you go through the issues with volunteers to check that they still understand what's happening.

You and others in Brazil have taken a strong stand that volunteers who become HIV-infected during trials should receive triple drug therapy – the "best proven therapy" standard.

I'm sure a trial would not pass through our national IRB without this. Of course, this treatment is already well-established in Brazil. People receive triple therapy paid by the government – not as soon as they seroconvert, but when they reach a certain viral load, CD4 count or show early symptoms of AIDS. We provide drugs for at least 90% of

the people who need them.

How did this come about?

Brazil is a very unusual place in that the country is very rich but the people are very poor. We have the eighth largest economy in the world in terms of gross national product. But we have many diseases where people do not have access to medication as easily as they do for HIV.

There are many reasons for this. One is the very high public awareness about HIV. We also have a well-established National AIDS Commission. But more than that, we have public pressure, mainly from non-governmental organizations. Another factor is that prices for HIV drugs went down because the government does large-scale buying and because we produce many of them here.

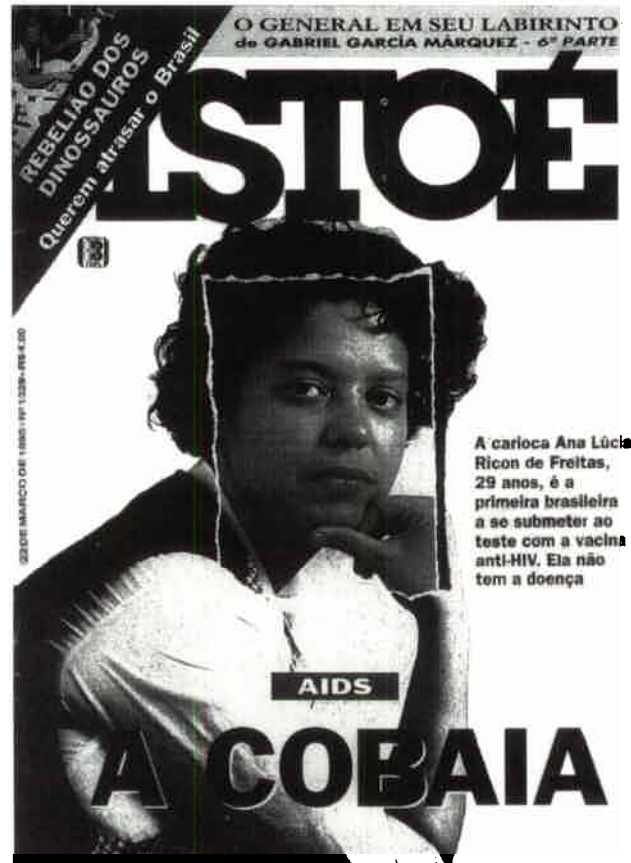
What about developing countries that want to participate in trials but don't have the resources or infrastructure to provide triple drug therapy?

I'd say it's premature to do trials in these countries. Of course these countries need a vaccine, but that doesn't mean they need to host vaccine trials just now. People with the burden of participating in a trial should get something back.

What do you consider the main challenges for future HIV vaccine trials?

There are many. One is deciding what products to bring into Phase III trials. Another is what to do if a vaccine gives low levels of protection, say 25%. Should we use it as a control for later trials? Should we use it in countries with a very high incidence of HIV? I think we will have big problems deciding such questions.

One of the biggest challenges will be keeping up the momentum of HIV vaccine development. As a physician, I see that many people are getting better. Patients are going back to work, and they're very happy. Of course, we don't know how long this will last, because drug resistance is coming and treatment is getting impossibly expensive. But in the so-called industrialized world, if prevention gets better and the incidence of HIV declines, AIDS might become just another tropical disease, like schistosomiasis, like leishmaniasis, and efforts to combat it could decrease. This makes me very afraid. ♦



1995: A leading weekly newsmagazine pictured this HIV vaccine trial participant on its cover, labeling her "a cobaia" ("the guinea pig").

For HIV-1, which replicates far better than HIV-2, multiple factors influence the rate of virus production – but once again, there is no clear proof that subtype-specific traits play a meaningful role. For instance, Berkhout in our lab has shown that reduced replication rates in a particular HIV strain (engineered in the lab to contain genetic deletions that weaken the virus) can be compensated by sequence changes in another region (the LTR) without repairing the original gene defects. This shows that HIV can walk many pathways towards optimizing virus production. We have noted several fixed but very different LTR sequence patterns in distinct lineages of the subtypes – a type of observation that is frequently misinterpreted as evidence for biological differences among subtypes. But instead, these variations in LTR sequences could simply reflect different routes to the common goal of all HIVs: to produce enough virus particles or infected cells for efficient transmission.

Other ways in which subtype could influence transmission rate include affecting the efficiency with which HIV enters host cells or via fundamental differences in co-receptor usage, but the accumulated data suggest that this is not the case.

In summary, there is little convincing evidence that inherent differences among subtypes underlie the observed differences in viral load, transmission rates or preferential spread. But then what explains these differences? I believe they reside in the host populations. HIV grows best in proliferating, rather than resting immune cells (immune cells replicate when they are mobilizing to fight an infection). So people with other active infections, such as malaria or TB (both widespread in many developing countries) provide more favorable conditions for HIV replication, which in turn means higher viral loads and therefore more efficient transmission. Similarly, HIV-negative people with other active infections, and hence with replicating immune cells, tend to be more susceptible to HIV infection upon exposure.

Data from another angle also fail to provide evidence for fundamental and *a priori* differences among subtypes. Recently Jan Albert in Sweden compared the rate of progression to AIDS in people living in Sweden and infected with different subtypes, and found no evidence for subtype-specific differences.

Other studies claiming to show such differences have not been done under well-controlled circumstances. For example, the progression rate of a subtype B-infected individual in the Netherlands is likely to be much slower than that of a subtype C-infected person in Ethiopia, even when the Dutch person is not on triple drug therapy and the two cases involve equal standards of clinical service and documentation. But there are other contributing factors that are usually not considered, such as the African's continuous exposure to virulent pathogens like the tuberculosis bacterium and the European's treatment with drugs that prevent PCP disease, both of which can lead to the erroneous conclusion that subtype C is more virulent than subtype B.

The last issue to address is the relevance of HIV subtypes in the vaccine context. Most HIV vaccine strategies aim to induce both antibody-mediated and cellular immunity, which are thought to protect against incoming viruses and virus-infected cells,

respectively. These two arms of the immune system do not recognize HIV's genetic (nucleotide) sequence directly, but rather, the protein (amino acid) sequence it encodes. The distinction is crucial because many of the nucleotides that differ among subtypes do not result in amino acid differences, while many stretches of nucleotides and of amino acids in HIV have strictly conserved sequences, so that the majority of amino acids are common to all subtypes. This is an important notion.

Let's do a thought-experiment. Cytotoxic T-cells (CTLs), the main actors in cellular immunity, recognize their prey via very short amino acid "target" sequences called epitopes. Many such epitopes have been identified for HIV and are common to many subtypes. Other epitopes vary among subtypes, but is this relevant? If the HIV epitopes relevant for a protective CTL response are common to different subtypes, who cares about subtypes in vaccine design? Unfortunately we do not yet know which epitopes on which HIV proteins are most important for vaccine protection, or whether they will turn out to be shared among subtypes. To me, resolving this issue should be a top priority for AIDS vaccine developers. (However, until we have clear answers, vaccine development efforts must be based on the "worst case scenario" that shared, protective epitopes may not exist, and therefore candidate vaccines should be matched to circulating subtype).

Antibodies are also considered crucial for effective protection against HIV. Yet not one of the many vaccine approaches tested so far in Phase I human trials has induced antibodies that can neutralize primary HIV isolates. On the other hand, Guido van der Groen at the University of Antwerp in Belgium showed that sera from about 10% of HIV-infected individuals neutralizes primary isolates from all HIV-1 clades and even the "outlier" group O strains, clearly demonstrating that broadly neutralizing antibodies can be elicited by virus of a single subtype. What is not known is how to mimic this property in a vaccine. Recently, however, Jack Nunberg's group at the University of Montana obtained promising results on this front when they immunized mice with the HIV envelope protein complexed to the surface of a host cell, in an attempt to capture the "transition state" molecular structures that exist fleetingly at the moment when HIV enters a cell. Another relevant point is that human monoclonal antibodies (against envelope) which neutralize primary isolates do so by recognizing the twisted, folded shapes of protein epitopes (i.e., their 2D and 3D structures), not simply their linear nucleotide sequences, and it is entirely possible that these shapes remain the same even if the underlying sequences do not; in other words, subtype-specific sequence variation may not alter these epitopes in any meaningful way. This idea is supported by the fact that these envelope epitopes are involved in essential functions of the virus (i.e., entry into host cells), increasing the likelihood that they are preserved across subtypes.

These data suggest that the key issue in vaccine design is how to generate and test a protective immune response against any subtype, and argue against the view that shifting from studying subtype B to subtype C will solve all the problems. However, as stated above, this is not to suggest that subtype should be ignored. On the contrary, it

*"Differences in transmission rates
of HIV subtypes could reflect
differences in the populations
they infect."*

remains crucial to include non-B subtypes in all HIV vaccine development efforts; it would be a tragic mistake if we finally generated an AIDS vaccine and found that it protects against subtype B but not other subtypes or recombinants. Therefore, a priority should be to produce the viruses and other reagents needed for more research across clades. These include stocks of pathogenic and nonpathogenic SHIVs with envelope sequences from subtypes A, C and D and perhaps from intra-envelope recombinants and stocks of nonpathogenic subtypes (A, C and D for chimpanzee experiments, to evaluate immune responses that cannot be tested in the monkey/SHIV model). In addition, as many parallel human Phase I trials as possible should be initiated to test for ways of inducing cross-clade immune responses, and the appropriate non-B laboratory reagents produced (such as tetramers and peptides).

In conclusion, I caution against overemphasizing the importance of HIV subtypes for vaccine design and getting distracted from the most crucial challenges: optimizing the immunogenicity of different vaccine approaches in a series of human Phase I trials and then making the hard choices as to which candidates are most promising and should be moved forward into Phase II and Phase III trials in areas of the world most in need of a vaccine. It may be more important to focus on what all HIV subtypes have in common rather than on how they differ. ♦

Jaap Goudsmit is head of the Department of Human Retrovirology at the University of Amsterdam and chair of IAVI's Scientific Advisory Committee. He is the author of Viral Sex (1997: Oxford University Press) and the upcoming Viral Fitness.

ALVAC TRIAL
continued from page 1

developed anti-HIV CTL responses.

The study began in May 1997 and enrolled 435 HIV-negative individuals at high risk for infection. One-third received vCP205 and a placebo, another third received the combination and the remaining third received only placebo. The numbers are not statistically significant for determining efficacy of the vaccine combination, but plans are being made for a larger trial to begin to assess this.

Of the 435 participants, so far 11 individuals have become infected with HIV through high-risk behavior. Six were from the placebo group, three in the vCP205 alone group and two from those receiving the combination.

The trial is part of NIAID's overall efforts to test a prime-boost combination approach. NIAID's plans, according to Peggy Johnston, who heads the Institute's AIDS vaccine program, is to "identify the best canarypox vector and the best boost, determine the optimum dosing schedule and consider moving into efficacy trials."

The strategy has not been without bumps in the road, however. It had been expected that this combination would move into a larger trial years ago. But PMC developed two new canarypox vectors that it hopes will induce CTLs in more vaccinees. The newer constructs have had to go through Phase I safety and immunogenicity studies to determine which works best or, indeed, if they are improved products.

For instance, a Phase I study currently underway is comparing three canarypox products - vCP205, vCP1433 and vCP1452 (see box). The boost is a gp160 envelope protein, also manufactured by PMC.

In the AVEG 202 study, the boost was a gp120 construct with a MF59 adjuvant emulsion. However, the manufacturer, Chiron, has backed out of the "test of concept" trial, so NIAID will probably use a newer gp120 construct, VaxGen's bivalent gp120 (AIDSVAX) that is currently in Phase III testing in the U.S. (see *IAVI Report*, July-September 1998). Chiron also has a newer clade B gp120 in development. Reports suggest that negotiations among the various companies involved haven't been easy.

Preparations for the test of concept trial come as NIAID is preparing to reorganize its clinical networks. AVEG currently handles Phase I and II vaccine trials. HIVNET was created to handle Phase III trials, but with no such trials on the horizon, it also has participated in non-vaccine prevention research, such as microbicides and drugs that prevent mother-to-infant transmission in developing countries. By July 2000, non-vaccine research should be centered in the new Prevention Trials Network, while everything from Phase I to Phase III vaccine trials will be handled by the new Vaccine Trials Network.

The larger ALVAC trial could begin by September 2000. It will likely include sites in the U.S., as well as the Caribbean (Haiti, Trinidad) and Brazil, and will be designed to detect efficacy. Preliminary plans are for a trial with four arms: one receiving the combination, one receiving only the canarypox vaccine, one only the subunit and the other, placebo.

Recruitment will focus on men who have sex with men and men and women at high risk via heterosexual transmission. The trial is likely to include more than 8,000 participants.

Yet concerns remain about the canarypox vectors. Studies to date, including AVEG 202, show that a significant number of those immunized do not generate measurable CTL responses at any point during the trial. "There's always something that's going to look better," says Johnston, "especially before it enters human trials. But if we can show that vaccine-generated CTLs have at least some protective effect, it would be a major step forward." ♦

Jim Thomas is a founding member and chair of the community advisory board (CAB) for the AIDS Vaccine Evaluation Unit at Saint Louis University and a member of AVEG's national CAB. He also serves on the board of directors of the AIDS Vaccine Advocacy Coalition.

Pasteur-Mérieux's Canarypox Vectors

ALVAC vCP205, the most widely studied canarypox vector, contains genes coding for the envelope, gag and protease proteins (clade B). In a recent Phase II study (see main article), vCP205 was given as a "prime" in combination with gp120 as a "boost". Phase I studies in the U.S. are examining vCP205 administered via mucosal surfaces and given with GM-CSF, a cytokine commonly used to improve blood cell production. A Phase I study of vCP205 is also underway in Uganda (see page 4).

vCP1433 includes all the HIV genes in vCP205, plus pieces of the *pol* and *nef* genes. A Phase I study in the U.S. is now comparing vCP1433, vCP1452 and vCP205, all given with PMC's gp160 construct.

vCP1452 is PMC's most advanced canarypox vector. It contains the same genes as vCP1433, but was designed for increased antigen expression. ♦

AIDS Vaccine Glossary

The following is a modified version of a glossary compiled by the U.S. National Institute of Allergy and Infectious Diseases. Bold-faced words within definitions are those defined elsewhere in the glossary.

adjuvant: a substance sometimes included in a vaccine formulation to enhance or modify its immune-stimulating properties.

adverse reaction (also called **side effect**): in a clinical trial, an unwanted effect detected in participants and attributed to the study vaccine.

antibody (also called **immunoglobulin**): an infection-fighting protein in blood or secretory fluids that recognizes, neutralizes, and helps destroy pathogenic microorganisms (e.g., bacteria, viruses) or toxins. Antibodies are made and secreted by **B-lymphocytes** in response to stimulation by **antigens**. Generally, each antibody binds only to the specific antigen that stimulated its production.

antigen: any substance that is recognized by a component of the immune system (ie. **antibodies**, cells). Antigens are often agents such as invading bacteria or viruses. (See **immunogen**.)

arm: a group of participants in a clinical trial who receive the same treatment, intervention or **placebo**. Other arms receive different treatments.

attenuated: weakened. Attenuated viruses are often used as vaccines because they can no longer produce disease but may still stimulate a strong **immune response**. Examples include vaccines against polio (Sabin oral vaccine), measles, mumps, and rubella.

B-lymphocyte (B-cell): white blood cells of 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: a clinical trial in which participants are unaware whether they are in the experimental or control **arm**. (See **double-blind study**.)

booster: a second or subsequent vaccine dose given after the primary dose, to increase **immune responses**. A booster vaccine may or may not be the same as the primary one. (See **prime-boost**.)

breakthrough infection: an infection which the vaccine is intended to prevent, but that nevertheless occurs in a volunteer during a vaccine trial.

canarypox: a virus that infects birds and is being used to carry HIV genes into human cells in several HIV vaccines now in clinical trials. Canarypox virus cannot grow in human cells, an important safety feature. (See **vector**.)

CD: abbreviation for "cluster of differentiation," referring to molecules on the surface of immune cells. CD markers are used to identify stages of maturation of immune cells, for example, CD4⁺ T-cells.

CD4⁺ T-lymphocyte (also called **helper T-cell**): **immune cell that carries a CD4 marker on its surface**. CD4⁺ cells are the primary targets of HIV. They help orchestrate both antibody and killer T-cell responses. (See **T-cell**.)

CD8⁺ T-lymphocyte: immune cell that carries the "cluster of differentiation 8" (CD8) marker. CD8 T-

cells may be cytotoxic (killer) T-cells or suppressor T-cells. (See **CTL**; **T-cell**.)

cell-mediated immunity (also called **cellular immunity**): the branch of the immune system that targets host cells infected with microorganisms such as viruses, fungi and certain bacteria. It is coordinated by **helper T-cells** and **CTLs**.

challenge: in vaccine experiments, the deliberate exposure of an immunized animal to the infectious agent. Challenge experiments are *never* done in human HIV vaccine research.

clade (also called **subtype**): a group of related HIV isolates classified by their degree of genetic similarity. There are two major groups of HIV-1 isolates, called M and O. Group M consists of at least eight clades, A through H. (See **isolate**.)

cohort: groups of individuals who share one or more characteristics in a research study and who are followed over time. For example, a vaccine trial might include two cohorts, a group at low risk for HIV and a group at higher risk.

control: an inactive substance (also known as a **placebo**) sometimes given to trial participants. In a vaccine trial, the control group is compared with one or more groups of volunteers given experimental vaccines.

core: the protein capsule surrounding a virus' **DNA** or **RNA**. In HIV, the precursor for the core protein (called p55) is broken down into the smaller molecules p24, p17, p7 and p6. HIV's core is primarily composed of p24.

correlates of immunity (also called **correlates of protection**): the specific **immune responses** that correlate with protection from a certain infection. The precise correlates of immunity for HIV are unknown.

CTL (cytotoxic T-lymphocyte; also called killer T-cells): immune cells that destroy host cells infected with viruses, fungi or certain bacteria, in contrast to **B-lymphocytes**, which generally target free-floating viruses in the blood. CTLs carry the CD8⁺ surface marker and are thought to play an important role in immunity to HIV, but this is still unproven. (See **CD8⁺ T-lymphocyte**.)

cytokine: a group of soluble, hormone-like proteins produced by white blood cells and that act as messengers between cells. Cytokines can stimulate or inhibit the activity of immune cells and may prove useful as immunologic **adjuvants**.

deletion: elimination of a gene, in nature or in the laboratory.

dendritic cell: an immune cell with thread-like tentacles called dendrites that "capture" **antigen** and present it to **T-cells**. Examples of dendritic cell types include Langerhans cells, found in the skin, and follicular dendritic cells, found in lymphoid tissues.

DNA (deoxyribonucleic acid): the genetic material of all living things (except for **RNA**-carrying viruses, such as HIV). DNA is a double-stranded, helical molecular chain found within each cell. It contains the information needed for cells to produce proteins, molecules that enable cells to

reproduce and carry out their functions.

DNA vaccine: an experimental vaccine technology in which one or more genes coding for specific **antigen(s)** are directly injected into the body, where they hopefully produce antigen(s) in the recipient and trigger **immune responses**. The technology is highly promising for producing simple, inexpensive and heat-stable vaccines.

double-blind study: a clinical trial in which neither the study staff nor the participants know which participants are receiving the experimental vaccine and which are receiving **placebo**. Double-blind trials are thought to produce the most objective results.

DSMB (Data and Safety Monitoring Board): a committee of independent clinical research experts who review data while a clinical efficacy trial is in progress to ensure that participants are not exposed to undue risk. Also monitors the trial for differences in infection rates between those receiving the vaccine and those receiving **placebos**.

efficacy: in vaccine research, the ability of a vaccine to protect vaccinated people against a specific infection or disease. A vaccine may be tested for efficacy in **Phase III** trials if (smaller) **Phase I** and **Phase II** trials show it to be safe and promising.

ELISA (enzyme-linked immunosorbent assay): a blood test that detects antibodies and is often used to test whether a person is infected with HIV.

endpoint: the final results of an intervention such as vaccination, compared among different groups in a clinical trial. In early vaccine trials, common endpoints are safety and specific types and levels of **immune responses** (e.g., **neutralizing antibodies**, **CTLs**).

enhancing antibody: a type of **antibody** that may increase the ability of a pathogen to infect cells and produce disease. It is currently unknown whether enhancing antibodies have any effect on the course of HIV infection. Enhancing antibodies can be thought of as the opposite of neutralizing antibodies.

enzyme: proteins that accelerate the rate of a specific chemical reaction without themselves being altered. Enzymes are generally named by adding the suffix "ase" to the name of the substance on which the enzyme acts (for example, protease is an enzyme that acts on proteins).

env: a gene of HIV that codes for gp160, the precursor molecule that gets split into the envelope proteins **gp120** and **gp41**. (See **glycoprotein**.)

envelope: outer surface of a virus, also called the coat. Not all viruses have an envelope. (See **virus**; **env**.)

epitope: a specific site on an **immunogen** that stimulates specific **immune responses**, such as the production of **antibodies** or activation of immune cells.

expression system: in **genetic engineering**, the cells into which a gene has been inserted, with the aim of producing its encoded protein. Chinese hamster ovary (CHO) cells and baculovirus/insect

cells are two expression systems often used to make recombinant HIV vaccines.

gag: an HIV gene that codes for p55. p55 is the precursor of HIV proteins p17, p24, p7 and p6 that form HIV's core, the inner protein shell surrounding the viral RNA.

genetic engineering: the laboratory technique of splicing together genes to produce specific proteins, for example, to use as medications (such as insulin) or vaccines.

genome: the complete DNA present in an individual cell or virus.

gp (glycoprotein): a protein molecule with one or 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.

gp41 (glycoprotein 41): a protein embedded in the outer envelope of HIV that anchors gp120. gp41 plays a key role in HIV's entry into CD4⁺ T-cells by facilitating the fusion of the viral and cell membranes.

gp120 (glycoprotein 120): the glycoprotein on the outer surface of the HIV envelope. gp120 binds to the CD4⁺ molecule on helper T-cells during infection. It has been studied as an experimental HIV vaccine because the outer envelope is the first part of the virus "seen" by neutralizing antibodies.

helper T-cell: T-lymphocyte bearing the CD4⁺ cell surface marker. Helper T-cells are the chief regulatory cells of the immune system, controlling activities such as turning antibody production on and off. They are the main targets of HIV infection. (See CD4⁺ T-lymphocyte.)

HLA (human leukocyte antigen): a diverse group of human cell surface molecules that play important roles in cellular immunity.

immune complex: the result of binding between an antigen and its specific antibody. Such antigen-bound antibody may or may not cause adverse reactions in people.

immune deficiency: a breakdown or inability of certain parts of the immune system to function, thus making people susceptible to diseases that they would not ordinarily develop.

immune response: the body's reaction to foreign 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 by administering a vaccine, thereby "teaching" the immune system to recognize certain antigen(s) and thus prevent infection or illness when it subsequently encounters the infectious agent.

immunogen: a substance capable of provoking an immune response.

immunogenicity: the extent to which an immunogen or vaccine stimulates immune responses.

immunoglobulin: a general term for antibodies, which recognize invading organisms, leading to their destruction. There are five classes of immunoglobulins: IgA, IgG, IgM, IgD and IgE.

inclusion/exclusion criteria: the medical or social reasons detailing the grounds by which a person qualifies for participation in a clinical trial. For example, some trials may exclude people with chronic liver disease or certain drug allergies.

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. (See protocol.)

in vitro: a laboratory environment outside living organisms (e.g., a test tube or culture plate) used to study diseases and biological processes.

in vivo: testing within a living organism, e.g., human or animal studies.

IRB (Institutional Review Board): a committee of physicians, statisticians, community representatives and others that review clinical trial protocols before they can be initiated at a specific institution. IRBs ensure that a trial is ethical and that the rights of participants are adequately protected.

isolate: a particular strain of HIV-1 from a person (primary isolate) or cultured cell line (laboratory isolate).

live-vector vaccine: a vaccine using a non-disease-causing organism (virus or bacteria) to transport HIV or other foreign genes (encoding antigens) into the body. This type of vaccine often generates CTL responses. (See canarypox; vaccinia.)

continued on page 16

I AVI REPORT

David Gold
Editor

Patricia Kahn
Associate Editor

Wayne Koff, Peggy Johnston
Scientific Advisors

Victor Zonana
Editorial Advisor

Ephen Colter
I AVI Report Online

Nick Marinacci
Web Advisor

Kay Marshall
Design Advisor

Paul Beyersdorf
Production Manager

Nicholas Gouede, Betty Dodet
French Edition

Penelope Anderson
Office Manager

Brandon Burkhart
Circulation Manager

Jean Rothstein
*Type Impressions
Art Design*

Denise Gray-Felder
Founding Managing Editor

The *I AVI Report* is published bi-monthly by the International AIDS Vaccine Initiative. To obtain a subscription to *I AVI Report*, send name and address, by e-mail to: iavireport@iavi.org; by fax to: 1-212-843-0480; by mail: IAVI, 810 Seventh Avenue, 31st floor, New York, NY 10019, USA. Copyright © 1999. All rights reserved.

IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Lean in structure and catalytic in nature, IAVI focuses on three key areas: accelerating scientific progress; education and advocacy and creating a more supportive environment for industrial involvement in HIV vaccine development.

IAVI is a UNAIDS Collaborating Centre. Its supporters include the Rockefeller, Alfred P. Sloan, Starr, William H. Gates, Until There's A Cure and Vincent P. Belotstky, Jr. Foundations, as well as the World Bank, UNAIDS, the National AIDS Trust and Fondation Marcel Merieux. IAVI also receives support from the UK Government, Crusaid, the Elton John AIDS Foundation, Levi Strauss International, Angel Music, Ltd., Glaxo Wellcome and generous individuals around the world.

INTERVIEW WITH SUSAN BUCHBINDER
continued from page 9

What are some of the key challenges for future trials?

It's essential that we get more at-risk women involved in prevention research in general and vaccine research in particular, because they are quite vulnerable to becoming HIV-infected. We need to develop and design products that specifically address their needs.

We also need more work on understanding the barriers to participation in trials, so we can address those that can be fixed. Besides the logistical issues I mentioned earlier, we need to deal with concerns about discrimination and potential harm. Whether or not those ultimately become real problems, they're perceived problems, and they should be addressed proactively.

One of the most critical things is to design trials that will get us clear answers to our questions. If we underpower trials or don't store adequate specimens, if we don't design them to get an answer - whether it's a positive or negative answer - then we're using up resources inappropriately and not moving the field forward. ♦

AIDS VACCINE GLOSSARY

continued from page 15

lymphocyte: the diverse set of white blood cells (each with different functions) that are responsible for **immune responses**. There are two main types: **B-cells** (responsible for producing antibodies) and **T-cells** (which orchestrate all aspects of the immune response and carry out specialized functions such as destroying cells infected with pathogens.) The cells are produced in the bone marrow and thymus, respectively.

macrophage: a type of large immune cell that devours invading pathogens and other intruders. Macrophages stimulate other immune cells by "presenting" them with small pieces of the invaders. Macrophages also can harbor large quantities of HIV without being killed, and may therefore act as viral reservoirs.

memory cell: memory cells are 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**) even if infection occurs many years later.

MHC (major histocompatibility complex, also called **HLA** in humans): the gene cluster that controls certain aspects of the **immune response**.

MN: an HIV-1 **strain** belonging to **clade B**, the most prevalent clade in North America and Europe. MN has been widely used in vaccine development.

monoclonal antibodies: a collection of identical antibodies that recognizes the same single **epitope**.

mucosal immunity: resistance to infection across the body's mucous membranes. Mucosal immunity depends on immune cells and antibodies present in the linings of the reproductive and gastrointestinal tracts and other moist body surfaces exposed to the outside world (the most frequent routes of HIV infection).

nef: a gene present in SIV and HIV that is not required for but regulates viral reproduction. Vaccines made of live SIV lacking *nef* (*nef*-deleted) have been studied in monkeys.

neutralizing antibody: antibody that prevents virus from infecting a cell, usually by blocking viral entry points (**receptors**) on the virus.

p24: a protein in HIV's inner core. The p24 antigen blood test is often used to detect HIV infection.

parenteral: administered intravenously or by injection. Vaccines may be administered by injection into the fatty layer immediately below the skin (subcutaneous), or into the muscle (intramuscular). Medications, but **not** vaccines, can also be administered into a vein (intravenous).

PCR (polymerase chain reaction): a sensitive laboratory method used to detect and measure amounts of **RNA** or **DNA**. Used to determine viral load in people infected with HIV.

peptide: a molecule made of two or more linked amino acids. Proteins are made of peptides.

Phase I vaccine trial: a clinical trial with a small number (usually 60 or less) of healthy volunteers, typically at low-risk for HIV infection. Phase I trials test a vaccine's safety in humans, including its metabolic and pharmacologic actions and any **side effects** seen with increasing doses.

Phase II vaccine trial: controlled clinical study to identify common short-term side effects and risks

associated with the test vaccine and to collect expanded information on its **immunogenicity**. Phase II trials enroll some volunteers with characteristics similar to potential participants of an **efficacy (Phase III)** trial. They enroll up to several hundred participants and generally have two or more **arms**.

Phase III vaccine trial: large controlled study to determine the ability of a vaccine to produce a desired clinical effect on the risk of a given infection, disease, or other clinical condition at an optimally selected dose and schedule. These trials also gather additional information about safety needed to evaluate the overall benefit-risk relationship of the vaccine. Phase III trials usually include several hundred to several thousand volunteers.

placebo: an inactive substance given to some study participants, while others receive the test substance (e.g., a vaccine). Placebos provide a basis for comparison. (See **control**.)

polyvalent vaccine: in HIV vaccine development, a vaccine produced from multiple viral **strains**.

prevalence: the proportion of people with a particular disease or condition in a specific population and at a given time.

priming (also called prime-boost): giving one vaccine dose to induce certain **immune responses**, to be followed by or together with a second type of vaccine (**booster**). A prime-boost combination may induce different types of immune responses and/or enhance overall responses beyond those seen with only one type of vaccine.

protocol: the detailed plan for a clinical trial, outlining its rationale, purpose, methodologies (such as vaccine dosages, routes of administration, length of study, eligibility criteria) and other aspects of trial design.

pseudovirion: a particle resembling a virus but lacking its genetic information, and therefore unable to replicate. In some viral diseases, pseudovirions interfere with infection by the real infectious virus.

randomized trial: a study in which participants are assigned by chance to one of two or more **arms** of the trial. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms.

receptor: a molecule on the cell surface that serves as a recognition or binding site for a specific **antigen, antibody, enzyme** or other molecule.

regulatory genes: HIV genes (*nef, rev, tat, vpr*) whose protein products are not required for but help regulate viral replication in infected cells.

retrovirus: HIV and other viruses that carry their genetic material in the form of **RNA** rather than **DNA**. These viruses also contain the **enzyme, reverse transcriptase**, which transcribes RNA into DNA. That process is the opposite of what normally occurs in animals and plants, where DNA is made into RNA; hence the prefix "retro."

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. When people develop antibodies to HIV or an experimental HIV vaccine, they "seroconvert" from antibody-negative to antibody-positive. Vaccine-induced seroconversion is not an infection.

SHIV: a **genetically engineered** "hybrid" virus with an HIV **envelope** and SIV core. SHIV is widely used for testing vaccines in monkeys.

side effects: see **adverse reaction**.

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 collected data.

sterilizing immunity: an **immune response** that completely prevents the establishment of any detectable infection.

strain: one type of HIV. HIV is very heterogeneous, with no two **isolates** exactly the same. When HIV is isolated from an individual and studied in the lab, it is given its own unique identifier, or strain name (i.e., MN, LAD).

subtype (also called clade): for HIV, a classification scheme based on genetic differences among **isolates**.

subunit vaccine: a vaccine consisting of only one protein from the virus or other pathogen. HIV subunit vaccines produced by genetic engineering are called recombinant subunit vaccines.

T-cell: one of two main types of white blood cells critical to the immune system. They include **CD4⁺** and **CD8⁺** T-cells. The "T" stands for the thymus, where T-lymphocytes mature. (See **lymphocyte**.)

T-lymphocyte proliferation assay: a test used to measure the memory of **T-cells** to **antigens** such as HIV, specifically their ability to replicate which happens only if they have "seen" the antigen before.

V3 loop: a part of the HIV **gp120** surface protein that appears to be important in stimulating **neutralizing antibodies**.

vaccinia: a cowpox virus, formerly used in human smallpox vaccines and now as a **vector** in some experimental HIV vaccines.

vector: a bacterium or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport **antigen-encoding genes** into the body to induce an **immune response**. Examples include **vaccinia** and **canarypox**.

viremia: the presence of virus in the bloodstream.

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.

Western blot: a blood test to detect antibodies to specific components of a virus such as HIV. This test is most often used to confirm a positive **ELISA**.