

IAVI Report

THE NEWSLETTER ON INTERNATIONAL AIDS VACCINE RESEARCH

VOL 6 / NUM 1 JAN/FEB 2002

NIH Drops Plans for Phase III Trial

BY PATRICIA KAHN

In a major decision for the AIDS vaccine field, the US National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), announced on 25 February that it will not proceed with a Phase III trial which was tentatively planned for early next year.

The Phase III study would have tested an HIV vaccine (called ALVAC 1452) based on a canarypox viral vector, both as a stand-alone vaccine and in a prime-boost combination with VaxGen's gp120 product, AIDSVAX. Several different ALVAC vaccines, each with different HIV genes, have been developed by the French-German pharmaceutical company Aventis Pasteur and tested in over 40 Phase I and II trials since the late 1980s; AIDSVAX is now in efficacy trials as a single-component vaccine. The new Phase III study was to be carried out by the NIAID-sponsored HIV Vaccine Trials Network (HVTN) at its clinical research sites in the US and Latin America, and to enroll about 11,000 high-risk heterosexuals and gay men.

The decision revolved around a specific goal of

the trial other than testing efficacy: to determine if a particular cellular immune response to HIV (measured from blood cells by the Elispot assay) correlates with protection against HIV. Identifying such a correlate would greatly ease the testing of future vaccines, even if ALVAC/gp120 proved to be only weakly effective. But results emerging from an ongoing Phase II study of the two vaccines (HVTN 203) indicated that the proportion of volunteers showing this response was too low to answer the question definitively, leading NIH to shelve the trial.

In announcing the decision, NIH reaffirmed its support for a planned efficacy trial of a different ALVAC vaccine (ALVAC 1521) with a gp120 boost. That study will be done through a long-standing collaboration between the US Army's AIDS vaccine program and the Thai government. It is designed solely to determine whether the two vaccines protect 50% or more of the volunteers from HIV, and is not powered to establish a correlate of protection. Pending approvals by the requisite Thai committees and the US FDA, the trial is expected to begin in mid-2002.

continued on 2 ▶

RETROVIRUS 2002: MERCK DEBUTS PHASE I DATA

BY RICHARD JEFFERYS AND EMILY BASS

Last year, organizers of the annual Retrovirus conference—the largest US HIV research meeting—inaugurated a separate AIDS vaccine conference, leading many to expect that vaccines would not be featured at Retrovirus 2002. But the massive event, held February 24-28 in Seattle, found room for several vaccine talks, including the much-anticipated debut of data from human trials of Merck's new adenovirus-based vaccine candidate.

Merck's Early Trial Data

In a packed plenary session

Emilio Emini, Merck's head of vaccine research, presented early immunogenicity results (up to 42 weeks post-vaccination) from HIV-negative volunteers. Merck is also testing these vaccines as potential therapeutics in HIV-positive people.

The ongoing trials, which will enroll about 600 people, include one study of a *gag*-expressing DNA vaccine (1mg or 5mg) given either in saline or with one of two adjuvants (aluminum phosphate or CRL-1005, an experimental polymer). A second trial is testing different doses of a *gag*-

containing vaccine made from an adenovirus vector (Ad5).

Emini reviewed partial data on T-cell responses so far (see table, page 9). Starting with the DNA vaccine in saline, Emini called the responses "moderate," while stressing that, with adjuvant, they could be sufficient to prime HIV-specific T-cells prior to an Ad5 boost. Immunogenicity of Ad5 was stronger than with DNA alone.

Emini then addressed a key question relating to the Ad5-based vaccine: the effect of pre-existing neutralizing antibody (NAb) to

continued on 9 ▶

Inside:

VACCINE HEROES

Brazilian AIDS Activist Jorge Belouqui	3
South African Health Worker Winnie Serobe	4

African Vaccine Initiatives: An Interview with Malegapuru William Makgoba	7
---	---

US Army AIDS Vaccine Program Transferred to NIH	10
---	----

New Head for South Africa's Vaccine Program	11
---	----

Barcelona Vaccine Events	12
--------------------------	----

Mumbai Meeting Surveys AIDS in India	13
--------------------------------------	----

Vaccine Briefs	16
----------------	----

NIH will be a major funder of the trial, since oversight of the Army's program will soon move from the Department of Defense to NIH.

(See article, page 10.)

NIAID officials also emphasize that the decision is not a vote of no-confidence in the vaccine strategy, but is based solely on the correlates-of-protection issue. "NIAID and the HVTN are eager to see the Thai trial go forward," says Peggy Johnston, NIAID's associate director of vaccines and prevention research. Ed Tramont, who heads NIH's Division of AIDS, went further, saying that "if for any reason the Thai trial would not go ahead, we would probably redesign our trial as an efficacy study and move it forward."

Behind the Decision

To all but those who follow the AIDS vaccine field closely, it may seem surprising that, after so many years of clinical testing, the level of immune responses induced by the ALVAC vaccines was not already well-known.

The explanation lies in the methods used to measure cellular immunity, an arm of the immune system thought to be key for protection against HIV. Until recently, vaccine developers relied on an old assay that detects the presence of "killer" cells (cytotoxic T-lymphocytes, or CTLs) by measuring whether CD8+ T-cells in blood samples from vaccinated people can specifically kill HIV-infected target cells. In the ALVAC trials to date, 20-40% of vaccinees show CTL responses; the decision to proceed with the Thai trial was based on finding CTLs in about 30% of the Phase II volunteers.

But vaccine developers have long known that the CTL assay's many disadvantages—it is highly labor-intensive, non-quantitative and difficult to do with frozen cells—make it unusable in large-scale trials. So they turned to a new generation of simpler, more reproducible assays, including Elispot—which measures the presence of HIV-specific, "activated" T-cells based on their production of an immune-stimulating molecule such as gamma-interferon.

"Elispot can be transferred to every country where vaccines are tested," says Tramont. "We gambled on Elispot and made it the cornerstone of our Phase III trial." For the trial to resolve whether it correlates with protection, at least 36% of vaccinees would have to show Elispot responses on day 182, or alternatively, 47% on either day 98 or 182, according to protocol co-chair Susan Buchbinder (San Francisco Department of Public Health)—a higher response rate than that seen with CTLs but attainable, the researchers hoped, through Elispot's presumed greater sensitivity.

But HVTN 203, the first ALVAC trial to gather Elispot data on a larger number of volunteers (330), found otherwise. By early 2002, with about 80% of the data analyzed, it became clear that they were

below the threshold, said Johnston—so the no-go decision was made.

What About Efficacy?

This leaves the more important question of efficacy riding on the trial in Thailand, where preparations are in full swing: Community and media activities are underway, a high-throughput HIV diagnostic lab is being readied, the vaccines are made and procedures to freeze plasma and blood cells from all volunteers at selected timepoints are in place. (See *IAVI Report*, Oct/Dec 2001, pages 4 and 7.)

But the current trial plan potentially leaves a key gap in assessing efficacy, since it tests ALVAC only in combination with gp120, but not alone. So if the combination shows some efficacy, it will be unclear whether ALVAC protects by itself or if the gp120 boost is needed. This was left out because the low incidence of new HIV infections in the Thai study population makes even a two-arm trial (ALVAC/gp120 and placebo) very large (16,000 people); the HVTN study, with an ALVAC-only arm, would have filled the gap, albeit with a different vaccine and different populations. As things now stand, if the prime-boost shows any protection it could mean licensing this more expensive, complex regimen and then taking several more years for another trial to resolve the issue. Although NIH and HVTN scientists are talking with the Thai team about possible enhancements to the trial, says Tramont, especially to boost its statistical power, an ALVAC-only group is not on the table.

Another issue that will arise if the trial shows any efficacy is whether regulatory authorities would license these subtype E-based vaccines for use in countries where other subtypes predominate.

So far, there's been no official reaction to the NIH decision from Thailand. Privately, however, some investigators are worried—less about getting approval from the requisite Thai committees than about the possible impact on public perceptions and willingness to volunteer. "It's very hard to convey the distinction between an efficacy trial and a correlates-of-protection study to the press and public," says one. "Even trying to do this generates some suspicion."

Moving On

Despite the decision not to conduct the large-scale trial, HVTN will continue studies on ALVAC vaccines, says the network's director, Judith Wasserheit. Besides HVTN 203, an ongoing study in Brazil, Haiti and Trinidad and Tobago (HVTN 026) will provide comparative data on safety and immune responses to ALVAC 1452 in populations with different ethnicity and nutritional and immune status. Plans for further ALVAC trials include a study of higher vaccine doses and another to evaluate immunogenicity with a different boost: a mixture of lipopeptides, developed and tested in France, and which (like ALVAC 1452)

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continued on 10 ▶

VACCINE HEROES

For the third year, the IAVI Report profiles two individuals who have made important contributions to the AIDS vaccine field. This time, in recognition of the crucial role of community education and mobilization for vac-

cine trials, we feature two community advisory board (CAB) members. Both these individuals entered the AIDS vaccine arena in step with their respective countries—ten years ago for Brazilian AIDS activist Jorge Beloqui, and two for Winnie Serobe, a South African women's health activist and granny. Here, they share their perspectives on public health, community needs, and the responsibilities and rewards of lifelong activism.

"Motivated by the Context"

Jorge Beloqui's lifetime of activism blends AIDS treatment, vaccines and human rights

BY ALEXANDRE DO VALLE MENEZES

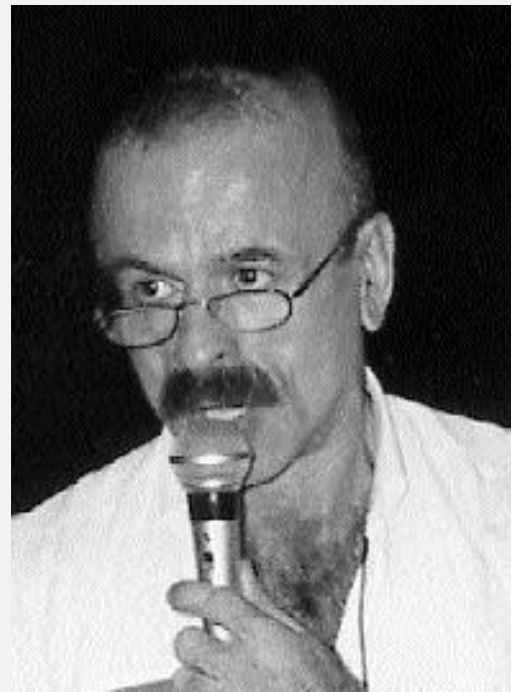
As a student in the late 1960s it was impossible not to be aware of the political turmoil in many parts of the world. In Argentina, where a new dictatorship was rising after years of unstable governments, young men and women organized themselves in groups to debate their country's situation. "It was something common for my generation to be politically active, to think of issues collectively and try to change things," says Jorge Beloqui, recalling his early political involvement. "We were motivated by the context." Some twenty years later, the AIDS crisis created a new political context. As an activist and a person living with HIV himself, it was a natural path for Beloqui to take a leading role in the fight against HIV/AIDS.

These days, Beloqui is a respected mathematician and professor at Sao Paulo University, where he has worked for over 15 years. At the same time, he has developed a singular role as a leading AIDS advocate, both within Brazil and internationally, who embraces treatment and vaccine issues with equal passion. "Jorge is a unique person in many regards," says José Esparza, head of the WHO-UNAIDS HIV Vaccine Initiative, who has regarded Beloqui as a constant partner since they met in the early 1990s. "As a community advocate, he fiercely defends the rights of people living with HIV/AIDS, and at the same time he is fully committed to vaccine development. He usually plays 'hardball,' yet still has the capacity to dialogue with everyone. His approach is not to close doors, but to open avenues for negotiation—without compromising his ideals."

Beloqui arrived in Brazil in 1975, as the suffocating political situation in his home country wors-

ened. Not wanting to leave Latin America, he began a mathematics Ph.D. program in neighboring Brazil—and quickly became involved with the larger issues around him. "You become part of where you are. You are touched by the good things, the bad things," he says. In his case, being "touched by the bad things" meant doing something about them. At that time, the Brazilian military dictatorship was starting its transition towards a democratic regime, and the resulting sense of openness allowed new groups to organize. Jorge became involved in the sprouting gay movement, where he met some of the people who, years later, would become his companions in the AIDS struggle.

Beloqui says that a strong sense of community with friends, loved ones and colleagues has always been the fuel for his efforts as an advocate. In the 1980s, he was one of the founders of the Grupo Pela Vidda branch in Sao Paulo, an NGO that brought together people living with HIV, their families, friends and others driven to transform the reality they were facing. During those early years, Beloqui focused on AIDS treatment issues, and in 1991, helped found a newsletter covering the field (*Cadernos Pela Vidda*), which gave him a chance to closely follow developments in AIDS research and make them accessible to a



continued on 4 ►

broader public.

During this same period, Brazil began to take steps that would affect the lives of HIV-positive Brazilians and dramatically alter the debate over HIV treatment and care in the developing world. The Brazilian government began distributing anti-retroviral drugs (ARVs) in the early 90s, although somewhat irregularly, adding new drugs to the national formulary under pressure from AIDS activist groups. Cost was recognized as a major barrier to widespread availability.

Activist and community groups kept up the pressure and called on the government and the National AIDS Program to translate its political commitments—the right to health care is enshrined in the Brazilian constitution—into action. They used a combination of media and legal strategies, building on a heritage of prioritizing public health and human rights. The result: the inclusion of ARVs—many of which are produced as generics in Brazil—in the National Health Plan, starting in 1998.

Beloqui was one of the people who spoke out publicly for universal access in Brazil. And he tells the story from a very personal perspective: He doubts that he would have been able to maintain his own ARV treatment regimen if not for the mass mobilization that took place in the country. “I consider it a kind of personal benefit for being actively involved in this community,” he recalls. “Many things that were accomplished would not have been possible if this were an isolated effort.”

Building Brazil's Vaccine Experience

Even in the early days of the drug access campaign, AIDS vaccines were also part of the national discussion. “[In 1992] a group from the World Health

Organization visited Brazil as part of an effort to develop plans for future AIDS vaccine trials,” Beloqui says. “We wanted to make sure that everything was being done properly. So we got involved.” This early participation was key to developing the feeling of ownership that has empowered activists to take on vaccine issues ever since.

In 1992, Beloqui joined the Brazilian AIDS Vaccine Committee, a group that advises the National AIDS Program. Three years later, Brazil launched its first AIDS vaccine trial, a Phase I study involving 30 volunteers. When the trial was first discussed publicly, there were loud cries of “guinea pig” in some national media, but it proceeded smoothly.

Even so, nearly ten years went by before the next Brazilian AIDS vaccine trials, due largely to the dearth of products ready for testing. As Beloqui points out, in a context of other immediate needs, vaccine advocacy continued—but without some of the urgency it might have had if trials were in the cards.

The waiting ended in 2001, when the country began a Phase II study (of a canarypox/gp120 prime-boost strategy) in Rio de Janeiro, followed by a similar trial in Sao Paulo, both under the auspices of the US HIV Vaccine Trials Network. Beloqui, who serves on the community advisory board (CAB) for the Sao Paulo trial, uses this role to advocate for widespread availability of vaccine materials in local languages. “There are very few AIDS vaccine materials in Portuguese and Spanish, which makes it impossible to get real involvement from the local population,” he says.

He himself is responsible for one of the few exceptions: the Portuguese language national AIDS

“With Our Own Hands”

A South African activist brings 50 years of experience to an AIDS vaccine CAB

BY EMILY BASS

As a sixty-eight year old nurse, vaccine community advisory board (CAB) member, abortion rights activist and grandmother of 12, Winnie Serobe knows that a healthy community is built from the ground up—literally, if need be. In 1978, Serobe and her women comrades from Soweto, South Africa built a health clinic using bricks salvaged from the ruins of government buildings that were destroyed during the anti-apartheid riots of 1976 in Johannesburg.

They built the clinic on the grounds of a township worker's hostel that also housed thousands of families who had lost their homes during flooding. “We went to them and we asked them what their most dire need was. We thought they were going to say houses but they said a clinic. So we had to build a clinic

with our own hands. Even now, the residents of the area respect us very much,” she says, breaking into a broad smile.

And today there is a big, new clinic building inside the hostel area, this one funded by the government. “We are proud that we were the people who led the local authority to this community,” Serobe says.

It was an aunt's shiny white nursing uniform that inspired Serobe in 1951 to leave her rural home province of Free State and travel to Soweto for nursing school at Baragwanath Hospital, then a blacks-only teaching hospital. She earned her certification in nursing and midwifery and spent the next twenty-five years working at the Baragwanath family planning clinic—always with the belief that communities must mobilize themselves to get results.

vaccine newsletter (*Boletim Vacinas Anti-HIV/AIDS*) he founded 8 years ago, now distributed throughout Brazil, and abroad. "I recently had an evaluation done with a few focus groups and was very surprised to learn that people really rely on the vaccine newsletter, using it as a source of information and a fuel for their vaccine activities," he says. "It is very rewarding."

Beloqui hopes that increased Brazilian involvement in trials, combined with more widely-disseminated information, will boost the country's vaccine advocacy. Still, he is realistic, suggesting that activists who are new to the field start by incorporating vaccine issues into existing prevention and care programs: "It is more likely to work this way."

As usual, he's doing everything possible to see that it does. As a board member of Grupo de Incentivo à Vida (GIV), another NGO based in Sao Paulo—the city with the highest number of AIDS cases in the country—he is involved in skills-building workshops and meetings that encourage others to take an active role in vaccine advocacy.

Last October, Beloqui broadened involvement even more, when he led a community vaccine meeting attended by over 100 participants (see *IAVI Report*, Oct/Dec 2001, page 12). Originally planned as a national gathering for Brazilian activists, it responded to strong regional interest and expanded to include participants from seven other Latin American countries. Building vaccine advocacy into broader AIDS campaigns was a key recommendation to emerge from the group.

Pairing Treatment and Prevention

Beloqui's work as a vaccine advocate has not detracted from his commitment to treatment and

care for HIV-positive people worldwide. Recently he helped author a report for UNAIDS on the status of access to treatment in Latin America, and has participated in international meetings that addressed the treatment access gap in the developing world.

Beloqui sees no real dichotomy between advocacy for treatment and for vaccines. "The culture of public health that combines prevention and care is very well-disseminated in Brazil," he says. "They are part of the same goal." Paulo Teixeira, who has known Beloqui for many years and now leads the Brazilian AIDS Program, calls him indispensable for both aspects of the national AIDS effort. "Jorge's advocacy has contributed to Brazil's inclusion in the international network committed to the development of an AIDS vaccine," he says. "His contribution is remarkable, as he is able to combine community activism with academic excellence."

Crossing such boundaries has been a constant in Beloqui's life: from Argentina to Brazil, from the university to community groups, from treatment to prevention. Now, with more products entering the testing pipeline and vaccines taking on a greater immediacy, there is a need for broader Latin American advocacy. Within this new context, Beloqui is playing a major role linking activists from different countries and ensuring that Latin America is on the "international vaccine map," demonstrating that, with the right leadership, the vaccine community can truly transcend national borders.

Alexandre do Valle Menezes has been an AIDS advocate with Brazil's Grupo Pela Vida Rio de Janeiro since 1993. He currently consults for IAVI on policy issues and is a graduate student at NYU's Tisch School of the Arts.

RETURNING TO THE FRONTLINES

Last year, Serobe returned to Baragwanath—re-named Chris Hani Baragwanath Hospital in honor of slain apartheid freedom fighter Chris Hani—as a member of the vaccine CAB at the Perinatal HIV Research Unit (PHRU), where a Phase I trial of a vaccine developed by South Africa, IAVI and the AlphaVax Corporation is due to start in late 2002, through the US HIV Vaccine Trials Network (HVTN). (See interview, page 7.)

Led by James McIntyre and Glenda Gray, the PHRU has spent nearly two decades investigating strategies for treating and preventing HIV in Soweto. Their efforts include pioneering work on prevention of mother-to-child transmission, along with research on social risk factors such as endemic violence against women. Vaccine research is a logical extension of the work, and McIntyre and Gray see the Phase I trial as a first step in preparing the foundation for future large-scale trials—preparations that include community outreach, cohort development and the

creation of a CAB.

That's where Serobe comes in. "It is important that I be on the CAB because I am a community worker," Serobe explains. "I am involved with youth, with churches, with women. I can educate other communities, even outside Soweto, about AIDS and vaccines. And it is very, very important, because AIDS is a killer. In my area, if we say we haven't had many deaths, it means we only buried four young people that week."

GRASSROOTS POWER & CUTTING-EDGE RESEARCH

The PHRU is housed in the Baragwanath building that once served as a segregated residence for black nurses. Today it holds the unit's newly-refurbished suite of offices. At a December 2001 CAB meeting, participants settled into a conference room decked out in geometric patterns and bright, sherbet tones—colors echoed in the fleets of red, green and blue minibus taxis, or *kombis*, in constant motion on the streets below.

continued on 6 ►

Bringing the real world of the Soweto community into the research setting is a long-standing priority for the PHRU team. In addition to Serobe, the current CAB includes traditional healers, representatives of women's groups, youth groups, church leaders, nurses and counselors. It's a mix that works, says Serobe. "I am very happy that we have the traditional healers in the CAB—they can educate their clients about whether to come and enroll in the trial."

At the meeting, the CAB—researchers included—gives resounding approval to the traditional healers' request for a goat to sacrifice in a ceremony enlisting ancestors' support for vaccine work. "Right," exclaims Gray, another Sowetan example of perpetual motion. "We'll put a budget line for a goat into our proposal to the HVTN."

Other issues are more difficult to resolve. Serobe, who, as an elder sits next to the CAB chairwoman, is concerned about how CAB members will field questions from the media. This is a serious matter, Gray agrees. "We have to be very careful. One wrong word and the trial could be destroyed."

In South Africa, the media provides a daily mirror of the ravages of the disease: photo essays of the country's nearly 400,000 AIDS orphans, anguished editorials about the mind-numbing rape statistics, and updates on the campaign to secure widespread access to nevirapine for pregnant women with HIV—who make up nearly 30% of antenatal clinic attendees in many parts of the country. The reality of the epidemic—and the need for many interventions, including vaccines—is as present in the daily papers as it is in the CAB members' daily lives.

Sipewe, a slender woman who works with a local youth group, says that she has already had friends tell her that they think a vaccine is the cure for HIV, and that it will allow people to have more sexual partners. It's an example of the misconceptions that CAB members must be prepared to debunk,

and of the education task that lies ahead. Another issue raised frequently is why only 40 people will be enrolled in the Phase I trial. Is this fair? And are trials a government ruse to get people tested, and identify those who are positive?

INSPIRED OUTREACH

Serobe, who has sat on other CABs in the past, thinks the key is education. "At the last CAB we didn't meet often enough and that made me unhappy," she tells the group. "I expect us to be honest and well-informed about how to go about spreading the gospel of AIDS vaccines."

Serobe might add "creative" to those qualities as well. As a family planning nurse, she followed up irregular Pap smears at a time when "cancer was not a known disease in the black nation." To preserve women's confidentiality, she often had to resort to fast thinking and fancy footwork. On one home visit, she knocked at the door of a woman who had begged Serobe not to disclose her clinic visits to her husband, a hulking policeman. When the husband answered the door, Serobe was stuck—until she scooped up a cat that was standing at his feet. "I said, 'Ooh, how I love cats. I have been following this one. Please give it to me,'" she recalls. "I took the kitten and went out, miserable. I had not talked to anyone, and I already had three cats."

But Serobe built on the feline bonding, stopping by for friendly visits and warming up the husband. Eventually, she was able to bring her patient to Baragwanath for an exam, and to convince the husband that a hysterectomy—required to prevent the spread of cancer—was necessary. "And we're friends to this day," she says.

She may not return to animal rescue, but Serobe is again ready to do whatever it takes to reach the young women and girls who are disproportionately becoming infected with HIV. "The education really must start in the schools," she says.

And she's ready for the tough discussions that are likely to take place as the CAB dives into rocky waters, like dealing with confidentiality, particularly for women and young people who might volunteer to be screened for the trial. What will happen if someone is not chosen to participate and the family finds out? Will they assume it's because he or she is HIV-positive?

Serobe hopes to use the youth group she runs as a channel for HIV education. She tells the CAB about her plans to provide the group with information, so that the young people—many of whom will confide their HIV status to her before they tell anyone else—become advocates for vaccines themselves. "It should come from them," she says. "I want them to come back to me and say they are interested in vaccines."

When the CAB meeting is over, Serobe sits back and laughingly notes that she can't volunteer for the trial (which will enroll 18 to 55-year-olds) herself—"I am a *go-go*, a granny now"—and then grows thoughtful. "Now I am old, I am looking forward to one day getting young people going in my shoes whilst I am still alive, so that I can train them, educate them, and lead them. I shouldn't die with this knowledge."



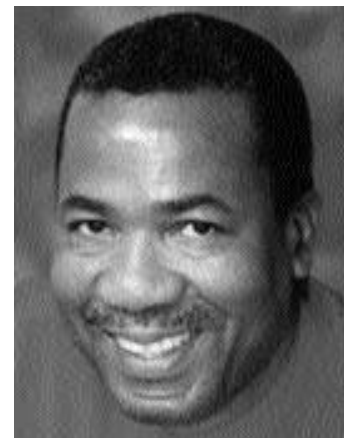
The Next Steps for African Vaccine Initiatives

AN INTERVIEW WITH

Malegapuru William Makgoba is president of South Africa's Medical Research Council (MRC) and is involved in AIDS vaccine development on a national, continental and global level. He began his scientific career as a child, tending his family's sheep and goats in Sekhukhueland, South Africa and paying close attention to the details of their life cycles, experiences he describes in his 1997 memoir "Mokoko." From

there he went on to receive M.B. and Ch.B. degrees from the University of Natal in 1976 and a Ph.D. in human immunogenetics from Oxford University in 1983, followed by further research at the National Cancer Institute in Bethesda. In addition to his MRC role, Makgoba chairs the steering committee of the African AIDS Vaccine Programme and is a member of IAVI's Board of Directors.

Malegapuru William Makgoba



What do you see as SAAVI's primary role?

SAAVI has roles at three different levels. One has to do with national buy-in on development and testing of vaccines in South Africa. Then, because South Africa is one of the few countries in the region with a research infrastructure and a history of doing basic science research, particularly in vaccine development, SAAVI plays a role in galvanizing the little expertise that exists and becoming its focal point. SAAVI's third role is to assist in connecting the nation and the region to global efforts on finding a vaccine, accelerating access, and providing any other assistance needed. A fourth issue is that, particularly in the MRC, we have a long history in the culture of ethics and regulatory processes. SAAVI can link whoever wants to be involved in trials in South Africa and SADC [the Southern African Development Community] with reasonable ethical committees, reasonable regulatory processes and institutions like the Medicines Control Council [MCC].

In your plenary talk at last year's AIDS Vaccine Conference in Philadelphia, you said that all South African vaccine trials will take place under the auspices of SAAVI.

That is "law" in South Africa. SAAVI was established precisely for this purpose: to develop and test vaccines in a coherent coordinated manner that is standardized throughout the country.

So all vaccine trials coming in from the outside will go through SAAVI to the sites.

Yes. We don't want to find people doing research in our backyard and not being held accountable. That has happened throughout the history of research in various clinical trials. We are trying to protect our own citizens and have a process that is really coordinated, coherent and accountable--from the scientists to the highest political accountability.

Does the decision to approve vaccine trials still lie with Medicines Control Council?

Yes. But SAAVI works very closely with the MCC.

How will SAAVI coordinate these activities?

SAAVI has created an infrastructure so that all the trial sites in South Africa talk to each other and do things together. They are managed almost centrally. Let me

add this proviso: SAAVI reports every quarter to the board of the MRC and the Department of Health, which connects us to the political structure of our country. That will continue when we start clinical trials.

Where does the African AIDS Vaccine Program fit into all of this?

The AAVP is actually based on the concept of SAAVI, but is a continental process to bring out all the countries in Africa where there is a bit of infrastructure in basic science, ethics, regulatory processes, population studies and so forth. It will bring African leadership into the process of vaccine trials.

And it is based on the same principle as SAAVI, which is to protect our societies against the fly-by-night researchers who want to come into Africa and simply set up shop. We come from a history of abuse and exploitation that happened because there was no infrastructure in one country, no capacity in another. So people come and do what they like.

But it will also provide African scientists and leaders with a forum around which they can share common problems. For example, the AAVP is going to be linked to the African Union, which is an important political power.

What mechanisms can help collaborating countries reach consensus on some of the thorny issues raised by vaccine trials?

There is nothing that helps people understand each other except dialogue. Part of the reason why SAAVI was started was to begin a dialogue within South Africa and within the region. That dialogue is now being extended to the African continent with the AAVP. We could never do that in the old era of colonial powers when people were just interested in dividing Africa and carving it up for their own uses.

A few years ago, people worried that too little attention went to vaccines based on subtypes prevalent in developing countries. Have we now gone too far in the other direction, in terms of countries wanting to test only vaccines made from local strains?

Let me play Devil's advocate. There is a real reason to tribalize clades. First, we don't understand this phenomenon of cross-clade immune responses in detail.

continued on 8 ▶

Second, we don't understand in detail how cross-reactivity translates into cross-protection. We know how HLA diversity [diversity of a certain set of genes] influences the type of immune responses you get, depending on the particular antigen used. If you have a clade C vaccine that induces immune responses which cross-react with HIV clade A, and a clade A vaccine that cross-reacts with C, we don't know which one of those will provide the best cross-protection. You cannot answer that question by streamlining scientific thinking. You can only answer that question if you know what a clade A does, and you know what a clade C does.

South African scientists have made a clade C consensus sequence. Botswana also has one. Is this level of national specificity necessary?

We don't understand what each one of them will do. The idea is not to be competing. But in South Africa, we need to test a clade C because that is the prevalent strain here. We need to test a clade C that is closer to our own strains. That doesn't mean we shouldn't take a clade C from China or from another place, but for heaven's sake, we do need to test our own clade C before we can understand what the closer relatives can do.

If a non-clade C vaccine shows efficacy—for example, in the ongoing VaxGen trials, how will that affect trial design in South Africa?

We would have to rethink how we would do our efficacy trials.

Would it be fair to say that you might build it in as a placebo?

It will have to be done. It would seem to be unethical not to do that.

You said that one of SAAVI's aims is to shift from the traditional MRC approach to more of a business model. What does that mean?

Business models are based on deliverables. Traditional scientific models are not based on deliverables. That is the difference. We are trying to maintain the excitement and creativity of science and also raise social consciousness among scientists that there are deliverables.

Speaking of deliverables, next year South Africa will be producing DNA and MVA vaccines to be tested here. Do you anticipate scaling up production if these vaccines move into Phase III?

I don't think they will be produced in South Africa [for Phase III]. But we are discussing this with various arms of government to try and develop venture capitals to support entities that can actually manufacture vaccines. I think that is a long way away, but it is part of the long term strategy for SAAVI.

Right now there is an ongoing lawsuit about the use of nevirapine, and the government is publicly

expressing skepticism about the safety of anti-HIV medicines. Does this present challenges for vaccine trials? [Editors note: The South African courts recently ruled in favor of national access to nevirapine.]

Life is not only full of surprises but also of contradictions. It is important to say this on record: South Africa has always supported the development of an AIDS vaccine as one of its major strategies, and this support came long before AIDS vaccines were fashionable. AIDS vaccines are something that has been etched in the minds of South Africans. They have always seen vaccines as the hope for eliminating HIV/AIDS, and they have seen a program to develop a vaccine as something they support.

SAAVI is supported by the government and ESKOM. There is no way—with this commitment and the time that has been invested in planning these trials—that the government will buy out of a process it has nurtured from the beginning.

So the fact that there has been controversy over nevirapine availability and toxicity [for prevention of mother to child transmission]—

That has nothing to do with vaccines. It will have virtually no impact. Government is updated quarterly about what is happening with vaccines. If they wanted this work to stop, or change direction, they have had the opportunity. But they have always given full support and encouragement.

Is the difference that the project has originated here, and the product is explicitly South African?

Partly. South Africans are not only patriotic but they are a little bit arrogant. We take our national pride very seriously. We like things that are South African. We are not isolationist, but we do like things that we have put our effort and participation into.

Is South Africa in a position to offer anti-retrovirals to people who become HIV-positive during vaccine trials?

Yes. I think that is standard. I mean, South Africa offers antiretrovirals to prevent mother-to-child transmission.

Only in pilot programs.

That is a semantic issue. In principle, antiretrovirals are being used in South Africa all the time.

But researchers at nevirapine pilot sites have been told by the Ministry of Health to stop distributing nevirapine to other clinics that request the drug. In principle a clinical trial will not be out of phase with what is happening at the so-called pilot sites because it is a trial, a research project. It won't be out of that kind of jurisdiction. A clinical trial, by definition, is equivalent to a pilot site. So there is no question about it.

What are your goals for SAAVI for next year?

There is only one goal at the moment. It is to try to start the Phase I clinical trial [of a vaccine based on the Venezuelan equine encephalitis virus vector] early next year and to make sure it runs smoothly. After that, other consequences will follow, and we will see whether we can begin to test other

clades that are coming up.

We need to make sure that we take the lessons from this trial before making the next step. We don't start walking without crawling, and we need to crawl early next year—to get the capacity and infrastructure we need. ♦

◀ **RETROVIRUS 2002** *continued from 1*

adenovirus on immunogenicity. Since many people are naturally exposed to adenoviruses (which cause severe colds), they already have NAb to Ad5, which could dampen the vaccine's effect. The prevalence of these antibodies is estimated at about 40% in North America, but is unknown for many other populations.

Because the Elispot data showed that some participants did not respond at all to Ad5, Emini drew a plot to assess whether this non-response was related to a pre-existing anti-adenovirus NAb titer above 1:200 (30% of North Americans exposed to adenovirus have titers above this level). All responders in the 10⁸ and 10⁹ group had titers below 1:200. Of the non-responders, 1/3 from the 10⁸ group had NAb below the cut-off; for the 10⁹ group, the number rose to 4/5, hinting that NAb do indeed have a dampening effect. This uneven distribution of pre-existing NAb titers may also help account for the fact that there was no obvious dose response seen in Ad5 vaccinees.

Merck then tested whether the effect could be overcome with a higher dose of Ad5 vaccine. Data from the highest dose (10¹⁰) group suggested that this might be the case: Non-responders had NAb titers above 200, but so did 4 of the 5 responders.

Cross Clade Responses

Emini also presented data on cross-clade reactivity of HIV-specific T-cells, a key question for the HIV vaccine field. The study tested whether T-cells from the blood of HIV-infected individuals from Brazil, Thailand, Malawi and the US—which he said represented infection with clades A, B and C—respond to a panel of clade B con-

sensus peptides (covering the viral proteins Gag, Pol, Nef, Rev and Tat) in an Elispot assay. The results showed that the frequency and magnitude of responses to Gag, Pol and Nef was indistinguishable by region. Rev and Tat induced a lower response in all samples, except those from Malawi, where no responses were seen. The researchers then looked at responses to clades A and C Gag peptides in people who responded to B and found them nearly indistinguishable in magnitude, although there were a few individuals who showed poor cross-clade reactivity.

Complementing the cross-clade studies done in HIV-positive individuals, Merck also looked at cross-reactivity in HIV-negative volunteers from the Ad5 trials, using consensus Gag peptides from clade A or C. Encouragingly, the results showed that T-cells from 10 of 13 (77%) responding individuals cross-reacted.

In closing, Emini looked to the future: Immunogenicity data from the highest (10¹¹) Ad5 dose group and the DNA/Ad5 prime-boost vaccinees, as well as safety and immunogenicity data from ongoing trials in HIV-infected individuals, should be available sometime in mid-2002.

A Novel Adenovirus Vector From Chimpanzees

While Merck's vaccine data underscored the challenge posed by pre-existing immunity to adenoviruses, a late-breaker presentation from Hildegund Ertl and colleagues at the Wistar Institute in Philadelphia suggested a potential solution: a chimpanzee adenovirus virus called AdC68 that is not neutralized by antibodies to human adenoviruses.

The Wistar team is in the early stages of testing whether AdC68 can be developed as a vector for vaccines, and presented results obtained so far in mice. They began by deleting an essential region (called E1) of AdC68 to create a replication-defective vector expressing a truncated form of HIV-*gag* and found that it induced strong CD8 T-cell responses in mice, as measured by Elispot. They plan to study AdC68 in non-human primates and, eventually, to conduct clinical trials.

DNA Prime/NYVAC Boost

In Rhesus Macaques

Genoveffa Franchini presented results on macaques challenged with the highly pathogenic

MERCK'S PHASE I AIDS VACCINE TRIALS		
Vaccine	Time of sampling	
	week 8	week 42*
DNA vaccine (saline) 1mg	(N/A)	7/34 [#] (20.6%) [105] [†]
	(N/A)	16/38 (42.1%)
Ad5 vector 10 ⁸ vp (viral particles)	6/9 (67%) [149]	6/9 (67%) [239]
	4/9 (44%) [149]	4/7 (incomplete data) [337]
	5/9 (56%) [257]	No data

* 4 weeks after final immunization
[#] number of people showing immune responses.
[†] number of spots in Elispot assay (geometric mean)
 See Conference website for webcast presentation: www.retroconference.org

SIVmac251, after immunization with DNA and NYVAC (attenuated vaccinia virus) vaccines. Pre-challenge immunogenicity data from this study was published last year (*J. Immunol.*, 2001; 167:7180-7191). SIVmac251 is considered

continued on 10 ▶

contain epitopes from *nef* and *pol*—and might therefore broaden the vaccine-induced responses.

In a broader sense, it still remains to be seen if and how the no-go decision will influence the larger discussion of how to decide which vaccines should move into large-scale efficacy studies—a debate that was largely bypassed this time, given the focus on the correlates of protection aspect of the trial.

Some researchers in the field

see the ALVAC vaccines as relatively unpromising, since they fail to protect rhesus monkeys against high-dose intravenous challenges with pathogenic SIV, and because of the low (20-40%) CTL response rate in vaccinees.

Others are less confident of our ability to predict which vaccines are likely to work. “People sometimes decide these things based on what they think, not what they know,” says NIH’s Tramont. For example, data from

Marta Marthas’ group (University of California at Davis) showed good protection of infant macaques immunized with an SIV-canarypox vaccine and then challenged orally with a low dose of the highly pathogenic SIVmac251 (see *IAVI Report*, Oct/Dec 2001, page 11).

Interestingly, these animals show no detectable Elispot responses in their blood, says Marthas. ♦

US Army AIDS Vaccine Program Transferred to NIH

The US Army program on AIDS vaccines will be transferred from the Department of Defense (DOD) to the National Institutes of Health (NIH) on 1 October 2002. The move was ordered by the Bush administration’s Office of Management and Budget in a directive issued on 4 January.

Details of the new arrangement are being negotiated and will be formalized in a Memo of Understanding between DOD and NIH.

While the Army program is tiny relative to that of the National Institute for Allergy and Infectious Diseases (NIAID), the government’s lead agency for AIDS research,—its budget for the 2002 fiscal year is US\$ 22 million, compared with over US\$ 400 million for NIAID—it has

nonetheless been an important player in the AIDS vaccine field. Focused on pre-clinical product development and clinical trials (rather than basic research), it has established robust programs at home and in a number of developing countries, through the Bethesda-based Walter Reed Army Institute of Research (WRAIR) and its civilian sister institute, the Henry M. Jackson Foundation. A Bangkok-based team, working with the Royal Thai Army and other Thai collaborators, has conducted several Phase I and II trials of prime-boost combinations and is expected to launch a Phase III trial later this year. Clinical sites have also been established in Kenya, Uganda, and Tanzania, with plans to move other candi-

dates—based on locally predominant strains—into trials there. The Jackson Foundation is a global leader in monitoring the HIV subtypes and recombinants circulating in many parts of the world.

The Army has a long tradition of vaccine development work in developing countries, and played a major role in finding vaccines against hepatitis A and meningococcal meningitis, and in field-testing several others.

The NIH-DOD agreement under negotiation, which covers the next seven years, would keep the program intact rather than parceling out its individual activities to other NIH groups working in related areas, according to Peggy

Johnston, associate director of vaccine and prevention Research at NIAID. At the same time, budgeting and oversight will move to NIAID, which will bring some changes. “The [Army staff] should continue to feel ownership of the program,” says Ed Tramont, head of NIH’s Division of AIDS. “It can be the linchpin for our international efforts. But it will have to respond to a different level of scientific oversight.”

Just how that will work is a major part of the ongoing discussions, which must be concluded before the deal kicks in on 1 October—although the parties seem hopeful that a deal will be sealed within the next few months.

—PK

◀ RETROVIRUS 2002 *continued from 9*

one of the most stringent challenge strains, and there have been only a few studies showing good vaccine-induced protection against it.

Franchini found that 5 out of 8 animals immunized with NYVAC alone showed some reduction in viral replication, to a set point below 100,000 copies after a typical acute phase. In contrast, 5/8 animals given a DNA/NYVAC prime-boost combination had significantly lower viral load peaks and controlled SIVMac251 replication to

undetectable levels at set point. These five animals have preserved their CD4 cell counts and maintained control of SIV replication out to a year. Looking at correlates of protection, Franchini found that pre-challenge T-helper responses to p27^{gag} and CD8 T-cell responses to the CM9 Gag epitope correlated with post-challenge virus control.

One caveat concerns the genotype of the animals used: 5 out of 8 monkeys in the prime-

boost group were Mamu *A01 positive (an MHC class I type associated with a natural ability to control SIVmac251); these animals accounted for 4/5 of those that contained viral load. But 4/8 animals receiving NYVAC alone (and which controlled viral load only partially) were also Mamu *A01 positive, and the less robust control of viremia in this group indicates that the prime-boost regimen had a significant effect, independent of Mamu *A01. ♦

NEW HEAD FOR SOUTH AFRICA'S VACCINE PROGRAM

BY EMILY BASS

In June 2001, Tim Tucker—a medical doctor and clinical virologist—took over as director of the South African AIDS Vaccine Initiative (SAVI), the umbrella organization that coordinates South Africa's robust AIDS vaccine development program. He inherited an ambitious, comprehensive project—since its launch in 1998, SAVI has established a unit overseeing clinical trials; another, based at the University of Natal, working on ethics and law; a third supporting community mobilization and education; and a fourth focusing on HIV immunology. Tucker's job is to integrate these elements of a new, overarching structure with the existing clinical trials approval process, which already includes input and oversight from institutional review committees and community advisory boards (CABs) in host and donor countries.

Watching Tucker at his job evokes an architect charged with blending the blueprints for several different structures already under construction—without calling anyone away from their jobs. At a meeting last November in Botswana, Tucker and Glenda Gray (Chris Hani Baragwanath Hospital, Soweto), a principal investigator on the upcoming Phase I trial of an HIV vaccine based on the Venezuelan equine encephalitis (VEE) virus vector, put their heads together to decide when and how SAVI's ethical review committee should step in to review the informed consent procedures in the protocol, which was devised months before the SAVI ethics group came into existence. How should SAVI's newly-formed community education group work with Soweto's active CAB? And what would happen if the ethics and law group raised questions about an informed consent procedure that had already received approval from the institutional

review boards at the site where the trial will be carried out?

There are no clear answers. "This is what I do every day," says Tucker, with a rueful smile.

But Tucker is optimistic about SAVI's partnership with other vaccine stakeholders. "The only way they can work together is in a cooperative framework," he says. "Overlap is often very healthy. I think it becomes unhealthy when, for example, there are two units with a brief to do community education and CAB development and they start to compete for the same site, or have different messages going out. That's why it was important to incorporate the HVTN (the US HIV Vaccine Trials Network), which will co-sponsor the VEE trial into SAVI,—so that if something is in the brief of both groups, there is an agreement on how best to go forward. Duplication is not always bad—it can allow one to double the work. The challenge is to ensure that the two groups do twice as much work rather than twice as much fighting."

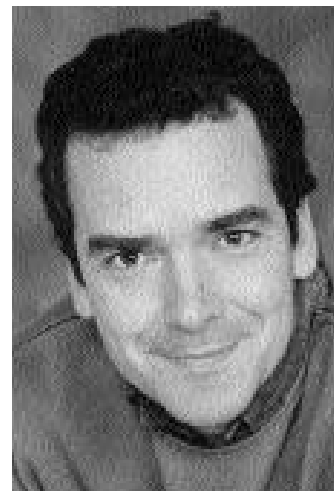
In addition to working with the different groups within South Africa, Tucker also works with regional partners. "SAVI was specifically set up to have a regional brief. We inform the regional ministers of health and the regional regulatory authorities about what we are doing, so we can streamline the Medicines Control Council with equivalent bodies in the Southern African Development Community (SADC) region. When we put a [candidate vaccine] before one of the regulatory control bodies, it is appropriate for other countries' regulatory bodies as well," he explains. "Not that they need to rubber stamp it—but so that the process is organized in a similar way."

To the north, South Africa's richest neighbor, Botswana is likely to be one of the next

entrants into the vaccine trials arena in the region. The country recently unveiled a gleaming reference laboratory funded by the Botswana government and the Botswana-Harvard AIDS Partnership (BHP). As the leader of SAVI, Tucker has had discussions with the BHP about their hopes to conduct an HIV-VEE trial within the year. Here, too, he's conscious of coordinating without losing speed. "I think that if we are not cooperating with Botswana then there is something wrong with how we operate," he says. "We have already set up a meeting to standardize some of the lab parameters, so we are off to a very good start."

Tucker is matter-of-fact about the potential for competition between two state-of-the-art labs in the same region. "I think, though, that we are going to have to look very carefully at how we deal with the laboratory immunologic testing. Both sites are HVTN sites, and the HVTN has been vociferous in the US about centralizing the lab assessments—so irrespective of where you're doing trials, [blood samples from trial volunteers] all go to a central lab [in the US] for immunologic testing. The South African National Institute for Communicable Diseases is the only HVTN-accredited lab outside of the USA, and I think that the same principle should apply."

Reaching for his own metaphors, Tucker compares his job to that of a coach who must keep one eye on winning the race and the other on the health of the team. "I am always concerned, living in a country with such high incidence rates, that scientists put themselves under unrealistic pressure. It is my role to ensure that we succeed by putting ourselves under appropriate amounts of pressure and ensuring that we don't try to run a marathon at the same pace that you would run a 1,500 meter race." ♦



Tim Tucker, the new director of the South African AIDS Vaccine Initiative, talks about planning and pacing the search for an AIDS vaccine

AIDS Vaccines for the World

Working Together to Accelerate Development & Delivery

A one-day satellite meeting prior to the XIV International AIDS Conference

SATURDAY, 6 JULY 2002 • BARCELONA, SPAIN

The first ever one-day satellite meeting to focus exclusively on AIDS vaccines around the International AIDS Conference is being held in Barcelona, Spain on 6 July 2002. Community/NGO representatives, researchers, policy makers, health care providers, industry representatives, journalists, and individuals interested in AIDS vaccines are all invited to attend. Expert speakers from Africa, Asia, Latin America, North America and Europe will present and lead discussions on the following themes:

- Fundamentals of Vaccine Development and Delivery
- Products in Development
- Clinical Trials, Vaccine Preparedness, and Community Involvement
- Access and Delivery Issues

Registration is free, beginning 1 March 2002. There is space for up to 200 participants. A balance in the number of participants from each sector will be ensured.

Este evento se desarrollará en inglés con traducción simultánea al español.

Participants must pre-register for this event. Registration forms and procedures are available on the IAVI website at <http://www.iavi.org/barcelona/satellite>.

This full-day event is being hosted by the International AIDS Vaccine Initiative (IAVI), the Brazilian National AIDS Program/ Ministry of Health, South African AIDS Vaccine Initiative (SAAVI), WHO-UNAIDS HIV Vaccine Initiative, AIDS Vaccine Advocacy Coalition (AVAC), HIV Vaccine Trials Network (HVTN), Global Business Council on HIV/AIDS, Grupo de Trabajo sobre Tratamientos del VIH/SIDA (GTT) and International Council of AIDS Service Organizations (ICASO), and others.

OTHER VACCINE AND COMMUNITY-RELATED EVENTS AT BARCELONA

The International Council of AIDS Service Organizations (ICASO) will host a skills-building session during the conference to increase knowledge about vaccine research and promote meaningful involvement of community in development and testing of vaccines. Contact Sophia Mukasa Monico (sophiamm@icaso.org) for more information.

The AIDS Vaccine Advocacy Coalition (AVAC) will host a meeting for vaccine advocates during the conference. For more information, contact Chris Collins (ChrisCSF@aol.com).

The Canadian HIV/AIDS Legal Network, South Africa Law Project, HIV/AIDS Unit of the Lawyers Collective (India) and UNAIDS will host a one-day satellite meeting on vaccines, access to treatment and the law on 5 July 2002. For more information contact David Patterson (gbugg@aidslaw.ca).

The African American AIDS Policy and Training Institute, European AIDS Treatment Group and Red 2002 will host the International community Treatment and Science Workshop for community based treatment educators/advocates and Black Journalists on 5-6 July 2002. For more information contact Antonne Moore at +1 (213) 353-3610 or e-mail at Info@www.BlackAIDS.org.

Mumbai Meeting Surveys AIDS in India

BY SAMEERA KHAN

For three days last December, over 500 Indian and international scientists, health professionals, government planners and non-governmental agencies gathered in Mumbai for the International Conference on HIV/AIDS.* The broad mix of people was mirrored in the meeting's agenda, which ranged from the biomedical front, including treatments and vaccines, to the battle to reduce gender inequality, poverty and other barriers that limit the use of existing and potential technologies.

In a keynote address, Geeta Rao Gupta, President of the International Center for Research on Women, borrowed from Charles Dickens to describe the HIV/AIDS situation today as "the best of times and the worst of times." On one hand, "we have therapies and treatments today to substantially improve the quality of life of those living with HIV and AIDS," she said. "We have political will in some quarters. We have prevention strategies that work. We have a greater number of supporters and more resources." On the other hand, "the rates of infection in some cities in sub-Saharan Africa and in some populations such as sex workers in India, range from 20-30%, exceeding our worst nightmares." Today the promise of biomedical innovations is being eroded by scant resources, social inequality and stigma, and "it is this that makes these the worst of times."

India and HIV/AIDS

P.L. Joshi, Additional Director at India's National AIDS Control Organisation (NACO), the country's lead agency for HIV/AIDS, gave an epidemiological overview of India. Although overall prevalence is still low, India has the second largest population of HIV-positive people in the world (after South Africa), estimated at 3.9 million at the end of 2000. The vast majority is due to sexual transmission, but there are also significant numbers of infections through injecting drug use (5%), contaminated blood (4%) and, increasingly, perinatal transmission (2%). Though about 75% of HIV-positive people are male, an increasing number of Indian women are now being infected—as seen in the growing prevalence rates among pregnant women at antenatal clinics, which exceed 1% in several states (see the NACO website: www.naco.nic.in)—portending a much wider general epidemic.

Interventions and the National Response

Joshi went on to outline NACO's priorities in mobilizing a national response through establishment of a basic prevention and care infrastructure. These

include enhancement of India's voluntary testing and counseling (VTC) centers and programs for preventing mother-to-child transmission, much of which should be in place by the end of 2002. Other goals include expanded provision of low-cost care (such as for opportunistic infections), home and community-based services, research on prevention of mother-to-child transmission (PMTCT), and vaccines and indigenous medicines. NACO is not prioritizing anti-retroviral (ARV) delivery for now, although doctors at a handful of clinics around the country are looking at strategies to provide them beyond a small group of affluent private patients.

Finding ways to deliver effective PMTCT programs is another high priority, said Joshi. After completing an 11-center study of an AZT regimen, clinicians are now assessing the feasibility and acceptability of a single-dose nevirapine treatment. Deployment beyond pilot programs will be phased in over the coming year, starting with medical colleges in high-prevalence states, followed by state district hospitals, and moving to states with lower prevalence rates.

But scaling up a comprehensive package of MTCT interventions will be challenging, said R.R. Gangakhedkar of the National AIDS Research Institute (NARI) in Pune. "About 27 million pregnancies annually taking place in India, with 40% of women choosing home delivery and another third delivering in private hospitals," he said. So the first challenge is bringing pregnant women into contact with the health care system. Another is preventing breast milk transmission: as in many African countries (see *IAVI Report*, July/Sept 2001, page 3), there is ongoing discussion about the feasibility of bottle-versus breastfeeding in settings where lack of clean water, cultural pressures to breastfeed and other issues complicate feeding decisions.

Women, AIDS and Vaccines

In a rousing plenary presentation, Geeta Rao Gupta turned the spotlight onto the interplay of poverty, vulnerability, gender and stigma, and on how this could apply to vaccines. "Most of the world's poor are women, and most of the world's women are poor," she began. An AIDS vaccine would offer the ultimate female-controlled prevention, since getting vaccinated without a male partner's consent is far easier than using condoms or even, potentially, microbicides, with an uncooperative partner.

But several barriers could limit women's use of vaccines. Chief among them is the possibility that vaccination (or trial participation) could be seen as an admission of risky behavior—a significant barrier to adolescent girls and married women. Gupta emphasized the need for community-based research grounded in local realities, customs and culture. This

“An AIDS vaccine would offer the ultimate female-controlled prevention.”

*The International Conference on HIV/AIDS, Mumbai, 16-19 December 2001, organized by the Mumbai-based Institute for Research in Reproduction (a wing of the Indian Council of Medical Research), the Indian Society for the Study of Reproduction and Fertility, and the University of California, Irvine.

continued on 14 ▶

means engaging and supporting women's groups, educating community health providers, and planning to offer vaccines within a broad healthcare context rather than in stand-alone settings.

HIV SEROPREVALENCE IN INDIA*		
Group	Place	Prevalence (%)
HIGH RISK CSWs	Tamil Nadu	58
	Mumbai	71
IDUs	New Delhi	45
	Imphal (Manipur)	48.8
	Churachandpur (Manipur)	68.4
Truck drivers	Tamil Nadu	9 (1997)
STD patients	New Delhi	<1
	Tamil Nadu	16
	Mumbai	14-16
	Bangalore	16.8
LOW RISK Pregnant women	New Delhi	0.3
	Mumbai	2.6
	Tuensang (Nagaland)	4.9
	Churachandpur (Manipur)	5.3
	Tamil Nadu	6.5

*Data are current through 1999
Sources:
 •UNAIDS, Epidemiological Fact Sheets on HIV/AIDS: India, 2000 Update (Revised).
 •US Census Bureau, HIV/AIDS Surveillance Data Base, HIV/AIDS Profile: India, June 2000.
 •World Bank, India HIV/AIDS Update 2001.

Vaccines for India

Bonnie Mathieson of the US Office of AIDS Research began the scientific session on vaccine development by reviewing candidates just entering, or poised to enter clinical trials, such as GlaxoSmithKline's protein-based vaccine (see page 16) and the DNA/MVA approach being developed by Harriet Robinson's group (see *IAVI Report*, Oct/Dec. 2001, page 13). Looking to the future, Mathieson underscored the need to start planning now for Phase III trials in high-risk, hard to reach, populations.

Two speakers presented approaches involving Indian collaborations. Vijay Mehra, lead scientist for IAVI's India program described the three-way partnership with IAVI, India's Ministry of Health and Family Welfare (through the Indian Council of Medical Research) and Therion Biologics (Massachusetts). The joint project is developing an MVA vaccine incorporating six HIV genes (*env*, *pol*, *gag*, *rev*, *nef* and *tat*) from an Indian

subtype C consensus sequence, and should enter clinical testing in India starting in 2003. Mehra also outlined other aspects of the partnership, including capacity-building for clinical trials, transfer of manufacturing technology to India, and HIV/AIDS education and advocacy projects.

Rama Amara of Emory University, who works with Harriet Robinson on DNA/MVA vaccines, presented a summary of data on monkey challenge studies of this strategy, which should soon enter clinical trials in the US. He also reported that clade C versions of the vaccines will be made through a collaboration with the Indian government's Department of Biotechnology.

Vaccine Trials, Ethics and Communities

In a panel session later that day, discussants examined the social, ethical, and logistical aspects of conducting AIDS vaccine trials. It's a topic that touches

on many sensitivities in India, which has an uneasy history of clinical trials—particularly contraceptive studies—conducted on poor, illiterate communities without proper informed consent.

Quarraisha Abdool Karim of the University of Natal reported on activities in Hlabisa, South Africa, a remote, rural community where almost 1 in every 3 adults is HIV-positive. Hlabisa began preparing for vaccine trials back in the mid-1990s, picking up momentum in 1997 when it became part of the US-sponsored HIV vaccine trial network (then called HIVNET, now the HVTN).

Initially, this meant producing a detailed map and census of households in the area, which has no formal system of addresses. With that infrastructure, community workers began a house-by-house survey of consenting people, collecting information such as basic demographic data, risk behaviors for HIV, and HIV infection rates (which involved providing HIV testing, pre- and post-test counseling). The researchers also strived to understand the community decision-making process through extensive consultation with community leaders, and have helped form and nurture a community advisory board. "It is about good science being backed by good ethics and community participation," Karim said.

Punnee Pitisuttithum of the Bangkok Vaccine Evaluation Group (BVEG) also stressed the importance of starting preparedness early. BVEG is conducting the Phase III trial of VaxGen's gp120 vaccine in a cohort of 2545 intravenous drug users (IDUs)—one of two ongoing AIDS vaccine efficacy trials worldwide. Preparations for the trial took years, starting with the establishment of HIV-negative IDU cohorts at 16 methadone clinics. Cohort members were followed and given HIV/AIDS prevention counseling for four years, allowing investigators to gather data on the rate and subtype of new HIV infections, key risk factors and willingness to participate in vaccine trials.

Moving from the preparedness phase to the actual Phase III cohort proved fairly smooth, Punnee said. "Our concern was whether volunteers really understood the implications of participating in a clinical trial before enrolling in it. They had to pass two comprehension tests so we could precisely judge this before we enrolled them."

The questions and discussions that followed the presentations suggested that it was heartening for Indian NGOs to hear about ethical clinical trials being devised in South Africa and Thailand. "If NGO concerns on transparency, full information, and accountability are addressed, we might be able to proceed towards vaccine trials more smoothly," said Ashok Row Kavi of the Humsafar Trust, which works primarily on MSM-related issues and who is a well-known AIDS activist in India.

Vaccine Testing in India: Hopes and Fears

Turning to perceptions in India, Hema Viswanathan

of Probe Qualitative Research (PQR), an Indian market research agency, reported on a small survey she carried out through the IAVI-India partnership. In the study, 24 people, most of them leaders of key HIV/AIDS development agencies and NGOs in Mumbai, Delhi or and Chennai, were questioned in depth about their attitudes towards AIDS vaccine trials. None of the respondents had prior experience with vaccine trials.

On the whole, the respondents' attitude was one of cautious acceptance. Acceptance was predicated on a number of caveats, such as:

- that the trials be carried out with, and through, the Indian government and other Indian partners;
- that there is extensive expert review at each stage of the trials, including ethical review;
- that trials are run in an open and transparent manner, and stakeholders, communities and the public are kept well-informed;
- that trials test vaccines which would be relevant and available to India.

Respondents' key concerns arose from scenarios in which these conditions are not met, for example, that Indians could be used as guinea pigs in studies that would help only prosperous people in prosperous countries. (On the contrary, India plans to test vaccines based on local strains and targeted for Indian use.) There were also fears that people from already-marginalized high-risk groups could be exploited, and that India was being "chosen" for vaccine trials because they could be run less expensively there than elsewhere.

Viswanathan also remarked on the dynamics of the interviews, noting that most respondents moved from an initial acceptance of the idea of trials to a realization, as the detailed questioning progressed, of the complexities involved. As understanding increased, so did the sense of unease and rejection. Finally, participants came to a stage of cautious acceptance, with the caveats noted above. She also said that, if this type of dynamic is seen on a broader public scale once a trial is officially announced, "there might be an easy-going acceptance at the outset, but this could be misleading. It would be important to not take that at face value or expect a smooth passage," she said.

In the next phase of the work, Viswanathan and other IAVI-India partners are conducting a series of focus groups among affected communities and meeting with other stakeholders to probe their attitudes and concerns.

The HIV-TB Association

Tuberculosis (TB) is the most common opportunistic infection associated with HIV infection in India, and several speakers presented data showing that the two diseases are now inextricably linked. Among patients attending a chest clinic at the Sassoon General Hospital in Pune in the year 2000, 33% of the men and 20% of the women were infected with

HIV, according to Srikant Tripathy of Pune's National AIDS Research Institute (NARI).

Infection with HIV also greatly increases the lifetime risk of developing active TB—by about 6-fold (60% versus 10%) in the patient population at the Tuberculosis Research Centre in Chennai, reported Soumya Swaminathan, the Centre's Deputy Director. Studies are underway there to evaluate prophylaxis for reducing active TB in HIV-positive populations. Speakers at this session emphasized that current TB control strategies may not be enough to avoid the worsening of an already bad situation. One encouraging note is the trend towards integrating HIV and TB services, starting with the introduction of TB detection at India's HIV VCT centers.

Future Pathways: Improving Treatment

The growing threat of TB underscored the need to expand treatment services for the growing numbers of Indians with HIV/AIDS. Despite enormous financial and logistical obstacles, a few clinicians are researching strategies for providing ARVs in these resource-poor settings. One of them is Subhash Hira of ARCON (a Mumbai-based HIV/AIDS collaboration between the Maharashtra state government and the University of Texas at Houston) and advisor to NACO on national AIDS policy, who stressed the link between offering care and greater uptake of testing and prevention services.

Current estimates are that only 9,000—10,000 HIV-positive people receive antiretroviral therapy, despite substantial recent price reductions and India's production of generic HIV/AIDS drugs. Hira said that, while budget constraints should not stop India from providing ARVs, which are cost effective in the long run, he called for targeting treatment initially to the sickest people who can still benefit. To assess just who that is, ARCON is following 125 HIV-positive people who started ARVs in 1996-1997, looking for correlations between initial CD4 level and clinical benefit. Hira estimates that about 1 million people in India have CD4 cell counts below 350, a possible threshold for starting treatment.

For these and almost any other initiatives, community buy-in is key. Throughout the meeting, many speakers emphasized that investment in community education and mobilization is the only way to ensure implementation of the many interventions—MTCT programs, testing and counseling services, vaccines, and care—needed to stem the rising tide of HIV/AIDS in India. ♦

Sameera Khan is a freelance writer specializing in health care issues, especially HIV/AIDS, TB, and tobacco. She was previously an assistant editor with The Times of India in Mumbai. A graduate of Columbia University's School of Journalism, Ms. Khan teaches at the Saboo Siddik Polytechnic in Mumbai and also writes about travel, gender and urban issues.

EDITOR

Patricia Kahn

FOUNDING EDITOR

David Gold

SENIOR WRITER

Emily Bass

CONTRIBUTING WRITERS

Mike Isbell, Richard Jefferys,
Sameera Khan,
Alexandre do Valle Menezes

DESIGN AND LAYOUT

Stephen de Francesco

ASSISTANT MANAGING EDITOR

Michael Hariton

EDITORIAL ASSISTANT

Rozsa Szappanos

PRINTER

West End Graphics

FOUNDING MANAGING EDITOR

Denise Gray-Felder

The IAVI Report is published bi-monthly by the International AIDS Vaccine Initiative. To obtain a subscription to the IAVI Report, send name and address, by e-mail to: iavireport@iavi.org; by fax to: 1-212-847-1112; by mail: IAVI, 110 William Street, 27th floor, New York, NY 10038, USA. Copyright © 2001 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. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access 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, Bill & Melinda Gates, Until There's A Cure and John & Marcia Goldman Foundations; the governments of the United Kingdom, The Netherlands, Canada, Ireland, Denmark, Norway and the United States; and the Mercury Phoenix Trust, World Bank, UNAIDS, National AIDS Trust, New York Community Trust and Fondation Marcel Mérieux. IAVI has also received support from Crusaïd, the Elton John AIDS Foundation, the Vincent P. Belotsky, Jr. Foundation, Levi Strauss International, and other generous corporate and individual donors around the world.

White House Proposes Funding Increase for AIDS Vaccines

Although President Bush's proposed budget for the 2003 fiscal year keeps most health-related spending flat, it includes sharp increases for HIV vaccines and for prevention and care programs in developing countries.

Released in early February, the Bush budget hikes spending on AIDS research at the National Institutes of Health (NIH) by 10%, bringing the total to almost US\$ 2.8 billion. Under the Bush plan, the NIH vaccine research program would grow by 24% over current funding, to \$422 million. An estimated \$22 million of the proposed increase stems from the transfer to NIH of the Department of Defense's vaccine research program (see article, page 10). Even discounting this amount, vaccine-related funding will jump by approximately \$80 million if the Bush budget is approved by Congress.

While holding the line on spending for domestic HIV care and prevention programs, the White House also calls for a 30% increase in HIV/AIDS funds by the US Agency for International Development. The budget also includes a \$200 million contribution to the Global Fund to Fight AIDS, TB and Malaria, and Health Secretary Tommy Thompson told a Senate hearing in late February that the administration is open to further investment in the fund.

With a growing budget deficit and bipartisan demands for additional military spending, money is expected to be tight for most US government programs. However, Congressional support for medical research retains broad and deep support, so the proposed increases for NIH are likely to be sustained—or even increased—by Congress.

Recruitment Opens for First GlaxoSmithKline Vaccine Trial

On 31 January 2001, the UK-based pharmaceutical giant GlaxoSmithKline announced that recruitment has begun for a Phase I trial of its first preventive HIV vaccine candidate. The vaccine contains a mixture of a recombinant Nef/Tat fusion protein and gp120, all from HIV subtype B, with a new proprietary adjuvant (AS02).

The trial (designated HVTN 041) will be conducted through the HIV Vaccine Trials Network (HVTN) and sponsored by the National Institute of Allergy and Infectious Diseases. Scheduled to run for 12 months at 11 sites nationwide, the study will test the safety and immunogenicity of the vaccine in a randomized, double-blind trial involving 84 HIV-negative, low-risk adult volunteers (70 given vaccine and 14 placebo).

The vaccine has shown some ability to protect monkeys against challenge with SHIV89.6P, which is partially heterologous (i.e., genetically different) to the HIV strains used in making the vaccine. (See *IAVI Report*, April/June 2001, page 2.)

AVAC Appoints Chris Collins as New Executive Director

In January, the AIDS Vaccine Advocacy Coalition announced the appointment of Chris Collins as its new executive director. Collins is an AVAC co-founder and previously worked on the Congressional staff of US Representative Nancy Pelosi, specializing in health policy and appropriations. Most recently, he has been a Principal with Progressive Health Partners, a health policy consulting group.

A West Coast native, Collins recently moved to New York City along with AVAC, which relocated there from Washington, D.C. In the coming months he will focus on preparing AVAC's community forum for vaccine advocates at Barcelona's International AIDS Conference in July and on finalizing "Five Years and Counting," AVAC's annual review of where the AIDS vaccine field is—and where it should be. This year's report will spotlight what needs to happen in some key areas, he says, such as educating people about vaccine trials. In the longer term, he plans "a closer look the vaccine access agenda" and to build AVAC's international activities through stronger links to related fields, including microbicides and malaria research.

Gallo and Montagnier Announce Global Partnership

At a news conference on 14 February, the two AIDS pioneers also known for their disputed claims to first isolating HIV, surprised the research world by announcing plans to create a new AIDS vaccine development partnership: The Gallo/Montagnier Program for International Viral Collaboration.

The mission of the Program, created under the World Foundation for AIDS Research and Prevention within UNESCO, is to provide leadership, raise money, develop research program areas, and conduct cohort studies and trials globally. Montagnier, who is president of the Foundation, and Gallo, head of the University of Maryland's Institute of Human Virology (IHV), will co-direct the program at laboratories in Rome and Baltimore (Maryland). Montagnier will also serve as adjunct professor at the IHV.

The immediate task for the partnership will be to find the US\$ 3-4 million in funding needed to get started, according to IHV's co-director, William Blattner. Looking forward, the program expects to test five vaccine candidates in high-incidence areas. Support for Phase I testing of a Salmonella-based oral vaccine in Baltimore and Uganda is already in place from IAVI, through a multi-million dollar vaccine development partnership begun with IHV in May 2000. (See *IAVI Report* April/June 2000, pages 1 and 12.)

On the same day, Gallo publicly conceded that it was indeed Montagnier's lab which made the breakthrough discovery of the AIDS virus in 1983, effectively ending an 18-year dispute.