

# IAVI REPORT

The Newsletter on International AIDS Vaccine Research

Vol.5 No.5 Dec. 2000 - Jan. 2001

## A New Generation of T-cell Assays Comes to Vaccine Trials

*After years of cumbersome, non-quantitative assays, T-cell responses can be assessed with precision. Now state-of-the-art methods are moving into real AIDS settings.*

by Patricia Kahn

Over the past few years, the mounting evidence that protection against HIV will require cellular immune responses (as well as antibodies) has fueled the development of vaccine candidates aimed at stimulating this arm of the immune system.

As these candidates now move into the early rounds of clinical trials, vaccine researchers face the task of figuring out how well they induce T-cell responses and what kind(s) of responses they induce. They will also need to compare

responses among different candidates, to address issues such as which HIV antigens or vaccine platforms are the most immunogenic.

As straightforward as these questions seem, however, they represent new

*continued on page 2*

### INSIDE THIS ISSUE

Gates Foundation Pledges "Challenge Grant" to IAVI	1
A New Generation of T-cell Assays	1
Phase I DNA Vaccine Trial Begins in Nairobi	3
Letter from the Editor	4
Nigeria Workshop Builds Consensus on HIV Vaccine Action Plan	5
Perspectives on AIDS Vaccines: An Interview with Jaap Goudsmit	7
<b>SPECIAL FEATURE</b>	
Cohorts, Communities and HIV Vaccines: On the Ground in Africa	10
● Soweto: A Seasoned Clinical Trials Site Looks to Vaccines	11
● Rakai: Twelve Years of Work, Hopes and Uncertainties	13
● Carletonville: Research in the Eye of the Storm	17
Vaccine Briefs	20

## Bill & Melinda Gates Foundation Pledges \$100 Million to IAVI

*Yahoo! gives \$5 million for global awareness campaign*

DAVOS – In a challenge to the world to move faster in developing an AIDS vaccine, the Bill & Melinda Gates Foundation has announced an unprecedented US\$ 100 million in support of IAVI's \$550 million funding target, bringing the amount of secured commitments to \$230 million – over 40% of the total. The pledge is intended to spur mobilization of additional global support towards reaching this funding goal.

Speaking from the World Economic Forum in Davos, Gates said that the gift is intended to correct "an unbelievable market failure" in developing an AIDS vaccine. "With most infected people living in the world's poor nations," he said, "there's no way commercial companies are going to see this as a priority." Seth Berkley, IAVI president and CEO, added that the funds will help IAVI "create a broad-based global movement in which the public and private sectors come together to overcome the scientific, political and economic challenges to developing an AIDS vaccine. That's why we welcome the Foundation's challenge to encourage others, large and small, to join this campaign."

Berkley also announced that Yahoo! Inc., the Internet commerce, communications and media company, pledged \$5 million to IAVI, becoming IAVI's first corporate sponsor. The gift will go towards developing an integrated campaign to raise awareness and funds across the Yahoo! global network. "AIDS is a devastating global problem and we look forward to lending

*continued on page 19*

scientific terrain: no preventive vaccine trials have ever used careful quantitation of T-cell responses as an endpoint. The methods to do so simply didn't exist – the available assays were difficult to carry out and only semi-quantitative.

But that has changed, thanks to several new, far more precise T-cell assays taking root in immunology labs. Although all of them need further development, including clarification of just what functions the T-cells they measure have, these new techniques represent a huge boon for clinical studies of HIV vaccines – assuming they work as well in detecting vaccine-induced responses as they do in virus-infected people, who usually show much stronger immune responses than vaccinees.

Over the past year, much effort has gone into vetting these assays for use in HIV vaccine trials. That has involved analyzing and optimizing a myriad of parameters, from specificity, sensitivity and reproducibility, to ease of use in the developing countries where trials will take place. Here we present a rundown of the assays and an update of which ones are on the list for upcoming trials. This issue featured prominently in the recent meeting of NIH's AIDS Vaccine Research Committee (22-23 January 2001) and was the topic of two consultative IAVI meetings (18 April 2000 and 17 January 2001).

**CTL killing assay:** The workhorse of the older methods, this assay measures the ability of cells removed from whole blood (peripheral blood monocyctic cells, or PBMC) to kill target cells expressing a specific antigen. The assay is carried out after culturing PBMCs for roughly two weeks, together with cells expressing the specific antigen. Killing is then measured as the amount of radioactivity released when the cultured PBMCs are mixed with radioactively-labelled target cells.

The assay's big advantages are that it measures a clear, important T-cell function, and it has been used in all HIV vaccine trials so far that looked at T-cell responses. For both these reasons, it remains on the list for NIH's HIV Vaccine Trial Network (HVTN). But besides being cumbersome to carry out, CTL assays are not very quantitative and are relatively insensitive. Also, they work poorly on previously frozen cells – a huge drawback for vaccine trials. Yet another disadvantage is in determining whether the responding cells belong to the CD4+ or CD8+ subset, which can only be done by the laborious procedure of depleting one or the other cell population with antibodies.

**Limiting Dilution Analysis (LDA):** This method quantitates the bulk lytic assay described above by culturing dilutions of PBMCs. For example, if a 1:100 dilution of PBMCs still shows lytic activity when tested after the two-week culture but a 1:1000 dilution does not, it means that the numbers of cells able to kill targets

is between 0.1% and 1% of the fresh PBMC. While this method does yield quantitative data, it is even more cumbersome than the CTL assay and therefore ill-suited for scale-up.

**ELISpot:** The most widely used of the new generation of assays, ELISpot measures the number of T-cells secreting a specific cytokine, such as interferon-gamma or tumor necrosis factor-alpha, that serves as a marker of T-cell effectors. The starting PBMCs are first stimulated with antigen (whole protein or peptide) for 6-24 hours and then mixed with enzymatically-tagged cytokine antibodies. The mixture is then chemically treated so that bound antibody–cell complexes (i.e., cytokine-secreting cells) are stained blue.

Its advantages are many. ELISpot is highly sensitive, quantitative and easy to perform, even in low-tech settings, and it can be scaled up for large numbers of samples. A big breakthrough was the finding that, although the assay initially performed poorly on thawed cells, the problem was solved by using peptides rather than whole proteins as the stimulating antigen. Scoring the assay (counting stained cells) is increasingly being done with automated image analyzers, reducing some of the subjectivity that arose with manual counts and therefore enhancing the assay's reproducibility – a key to using it in multi-site trials. The

remaining disadvantages include a high background in many peoples' hands, which makes it harder to distinguish low responders from background with confidence, and its inability to distinguish CD4+ from CD8+ responders without the cumbersome cell separation procedure mentioned above.

Yet overall the ELISpot assay is a major step forward for the field. It will be a key T-cell assay in HVTN trials, and Kent Weinhold of Duke University in Durham, principal investigator (PI) of the HVTN's Central Immunology Laboratory, says that he and Julie McElrath (PI of the University of Washington, Seattle laboratory site) are well on their way towards validating it. Merck is also using ELISpot (and has validated it extensively) in its HIV vaccine program, including the ongoing DNA vaccine Phase I study, and IAVI will use it as well.

The ELISpot assay is also working well in labs in Entebbe, Durban and Nairobi, among other developing country settings, so transferring the technology should not prove to be an obstacle for vaccine trials. At IAVI's recent consultative meeting, Philip Goulder (Oxford University) described its use in a collaborative project based in Durban (with Hoosen Coovardia of the University of Natal and Bruce Walker of Massachusetts General Hospital) to map HIV epitopes recognized by people infected with HIV subtype C. By optimizing the procedure step by step, Goulder said

---

*Differences in infection load of study  
volunteers in developing countries  
can affect immune responses  
and assay performance*

---

# Phase I DNA Vaccine Trial Begins in Nairobi

by Bonnie Levings

NAIROBI – On 25 January 2001 the Kenyan Government endorsed plans for a Phase I trial of an HIV-DNA vaccine based on subtype A, the predominant strain in East Africa. Their action cleared the way for the trial to begin. Last month the study was approved by Kenya's National Council on Science and Technology and the Kenyatta National Hospital's Ethics and Research Committee.

The trial is the first one to test a vaccine made from an HIV strain common in Africa, and only the second HIV vaccine clinical study to take place on the African continent. The vaccine was developed through an IAVI-sponsored Vaccine Development Partnership (VDP) between Oxford University in the UK and the University of Nairobi in Kenya. The University of Nairobi's new HIV Vaccine Evaluation Unit, housed in the Department of Medical Microbiology, will carry out laboratory work for the trial, including T-cell measurements by ELISpot.

The vaccine has already entered Phase I testing in Oxford, UK. Since 31 August 2000, 17 of the 18 planned volunteers have been immunized, and so far no adverse effects observed.

## Strategy for the Prime-Boost Studies

The Oxford and Nairobi trials mark the first steps in testing a combination (prime-boost) vaccine with two components: the HIV-DNA and the same construct in a viral vector (the Modified Vaccinia Virus Ankara strain, or MVA). Full clinical testing will involve three separate studies – the HIV-DNA vaccine alone, HIV-MVA alone and then both, given to volunteers a few weeks apart. Each step will begin with a trial in the UK, followed by a Kenyan trial several months later. The lag makes it possible for preliminary safety data to inform the Kenyan approval process.

The second component of the combination vaccine, the HIV-MVA, received UK regulatory approval in September 2000. That Phase I trial is expected to begin in late February, once further data on volunteers given HIV-DNA are evaluated by the trial's Data Safety and Monitoring Board. Each of the components is designed to stimulate broad cytotoxic T cell (CTL) responses to multiple HIV epitopes. Both include most of the *gag* gene (from a clade A consensus sequence) fused to a string of 25 partially overlapping CTL epitopes from *gag*, *pol*, *nef* and *env*. The epitopes were identified in people infected with subtype A HIV strains circulating in Kenya, but many of them are relatively conserved among other HIV subtypes. (For a complete description of the vaccines, see *Nature Med.* 6: 952, 2000).

The scientific rationale for a CTL-based AIDS vaccine initially grew out of studies with sex workers in Nairobi and elsewhere in Africa. A small minority of these women remain seronegative despite continual exposure to HIV, and were found to have significant levels of HIV-specific T-cells in their bloodstream. The Nairobi study has been ongoing for over ten years and involves a collaboration among the groups of Andrew McMichael, Sarah Rowland-Jones and Rupert Kaul from Oxford and J.J. Bwayo, Omu Anzala and Frank Plummer in Nairobi.

## Intellectual Property Issues

The trial preparations also involved negotiations over intellectual property (IP) issues, catalyzed by a series of articles in the Kenyan press starting in October 2000. The articles criticized a patent filed in December 1999 by the UK's Medical Research Council (MRC) covering the HIV sequences used in the vaccine. The patent lists Oxford researchers Andrew McMichael and Tomas Hanke, but no Kenyan investigators, as co-inventors. The articles expressed concern over the issue of ownership, which affects Kenyan rights to the vaccine, and over inventorship and credit for the work.

In response, the three partners in the project (the MRC, the University of Nairobi and IAVI) issued a joint statement reiterating their commitment to developing an AIDS vaccine together and stating that the original patent was "filed in good faith to protect the candidate DNA vaccine from unauthorized third-party exploitation." But they also acknowledged that the formal basis of the partnership – bilateral memoranda between MRC and Nairobi and between IAVI and MRC – was insufficient, since there were no written agreements among all three parties.

That acknowledgement led to the formation of an Intellectual Property Task Force, which met on 12-14 November 2000. The Task Force agreed that the partners should be equal owners of the vaccines and share any future revenues they generated. Under patent law, "ownership" is determined contractually and can be shared however the partners choose. In contrast, "inventorship" is strictly defined under patent law, and subsequent legal consultation led to the conclusion that the patent's inventors should not be changed. The Task Force is currently working on a "Memorandum of Understanding" which will encompass these agreements and provide a framework for IP decisions in the future. ♦

*Bonnie Levings is working for a Masters degree at Columbia University's School of Public Health and is a former member of IAVI's development staff. Before joining IAVI she was a volunteer with the US Peace Corps in West and Central Africa.*

# A Note to Our Readers

We would like to update you about a number of new developments at the *IAVI Report*.

Four and half years ago, IAVI published the first issue of the *IAVI Report*. Released at the 11th International Conference on AIDS in Vancouver, the publication set out to report on the emerging field of AIDS vaccine research throughout the world. Today, the *IAVI Report* reaches approximately 9,000 subscribers in more than 138 countries. Published six times a year, it is the world's only publication devoted solely to AIDS vaccine research and development.

IAVI created this publication to provide researchers, public health officials, policymakers and advocates with useful information on AIDS vaccine research and to focus critical attention on gaps in research and policy-making. The growing demand for the *IAVI Report* has demonstrated the keen interest in this field. We are proud to be cited as a source of information by a growing number of scientific journals, newspapers and magazines.

Beginning with the last issue, careful readers may have noticed that Patricia Kahn has become editor of the publication. This change follows my move to a newly created position at IAVI—Vice-President of Policy and Public Sector Support. In this post, I am overseeing IAVI's growing work on vaccine access, encouraging industrial investment in AIDS

vaccine development and increasing political and governmental support for AIDS vaccines in North America, Europe, Japan and Australia.

Having joined IAVI in 1999 as associate editor of the *IAVI Report*, Patricia brings a wealth of experience to the job. She is a researcher by training, and has worked in immunology, retrovirology and genomics, much of it at the European Molecular Biology Laboratory in Germany. Patricia began writing for *Science* in 1992 and later became a European correspondent for the magazine. Under her direction, the *IAVI Report* is expanding and instituting some important changes, which she will describe in the next issue.

Over these last four years, we have witnessed significant changes in AIDS vaccine research. The field is clearly advancing. But real advancements still take far too long. Each month we delay in developing and distributing an AIDS vaccine means 500,000 new HIV infections.

On a personal level, covering the field of AIDS vaccine research has been a very special opportunity for me. I have seen extraordinary individuals conducting, participating in and advocating for vitally important research. Most important, I now see signs that an AIDS vaccine is at least in sight.

David M. Gold  
Founding Editor

## T-CELL ASSAYS

*continued from page 2*

they have reduced background by 10-100 fold, allowing them to score low responses far more reliably.

He also described their use of a peptide "matrix" – a defined set of pools containing 6-7 peptides each, where each peptide is present in several different pools. The method is an effective internal control for avoiding false positives, Goulder said, since each peptide recognized by a given individual should give a positive reaction in every pool containing it. The matrix method is also a quick way to identify the specific epitope(s) being recognized – a use that Goulder says is the real strength of ELISpot.

**Intracellular cytokine staining (ICC):** Like ELISpot, this assay also measures cytokine-producing cells following antigen stimulation, in this case detecting the intracellular (rather than secreted) form. Detection is based on fluorescent labelling of cells, which are then counted using a fluorescence-activated cell sorter (FACS). Sensitivity is similar to ELISpot, although this still varies from lab to lab, and it works well with thawed cells.

ICC offers several advantages over ELISpot. One is the simplicity of sample preparation: it works with whole blood (i.e.,

without separating PBMCs first); alternatively, samples can be processed through a few simple steps, then fixed, and frozen for later workup. Another plus is that cells can be stained for several markers simultaneously, so that a single assay can detect not only cytokine-positive cells but other characteristics of the responding cells, for example, whether they are CD4+ or CD8+. Its biggest disadvantage is that it requires an expensive FACS machine and personnel trained to use it, making it far from trivial to introduce in developing country settings. Yet that has also proven solvable: the method is well-established at several African sites, for example the Ugandan Virus Research Institute (UVR) in Entebbe.

Another perceived weakness of the assay – wide variability among labs – was addressed by Holden Maecker of Becton Dickinson (BD; San Jose), the company developing this methodology, at IAVI's January meeting. He described a study in which the same samples were assayed at four different sites and found to show about 25% variation. But variation was reduced by half when BD collected the computer data sets from the four sites and re-set the fluorescence parameters, suggesting that the actual biological variation is smaller than it first appears. He also reported that BD

*continued on page 6*

# Nigeria Workshop Builds Consensus on HIV Vaccine Action Plan

by Akin Jimoh

ABUJA – From 15-17 January 2001, over 100 scientists, policy makers and representatives from multilateral organizations gathered in Nigeria's capital city for a "Consensus Building Workshop Towards the Development of a Nigerian National HIV Vaccine Strategy." It was an unprecedented event for the country, marking its first meeting on HIV vaccine development and attracting a level of interest far exceeding even that anticipated by the organizers, the National Action Committee on AIDS (NACA).

An overwhelming consensus was clear from the start: Nigeria, the most populous nation in Africa, must place high priority on participating in HIV vaccine development. That agenda dominated the rest of the meeting, and by the time the workshop was over, participants had mapped out the major elements of an interim plan, including specific goals and timelines. The finished plan will be adopted by NACA, the country's coordinating committee on HIV/AIDS, and will guide Nigeria's activities over the next 12-18 months. In the meantime, a long-range vaccine strategy is being developed and will be incorporated into the overall National Strategic Plan for HIV/AIDS that is also in the works.

Outside the conference hall, the workshop was also followed closely by the media and general public. That was because of the melodrama introduced by the presence of Jeremiah Abalaka, a surgeon who stepped into the national limelight in late 1999 when he announced his discovery of a "curative vaccine" for HIV/AIDS. His claims continue to attract enormous attention, fueled by the government's order last year that he stop dispensing his unproven treatment, for which he has never presented even the barest scientific description. Abalaka has openly refused to comply, setting off an escalating battle with the government that now includes mutual threats of court action. Accompanied at the workshop by a vocal entourage of supporters and insisting that Nigeria already has a vaccine, he created something of a circus atmosphere at several sessions, but the workshop managed to avoid being derailed from its goals.

Ibironke Akinsete, head of NACA, opened the meeting with an affirmation of the new government's commitment to combat HIV/AIDS – a drastic departure from the past military regime.

Since taking office just over a year ago, the democratic government has established NACA as well as a Presidential Action Committee (PAC) on HIV/AIDS, chaired by Nigeria's President Olusegun Obasanjo, to ensure political coordination and top-level attention to the AIDS agenda.

They face a daunting task in this highly diverse country. Nigeria is home to one in five Africans, and its population of 108.2 million is spread over 250 ethnic groups and growing at an annual rate of 2.8%. It is divided into six geopolitical zones, 36 states and 774 local government areas, which complicates efforts to take concerted action. Since the first case of AIDS was reported in 1986, there has been a steady, although relatively slow increase in seroprevalence, from 1.8% in 1983 to 5.4% in 1999, according to the 1999 Sentinel Survey by Nigeria's National AIDS and STD Control Programme. The highest prevalence rate is in the 19-24 year age group, and 2.6 million Nigerians are now estimated to be living with HIV.

Nigeria's health minister, Tim Menakaya, emphasized another key goal of the work-

shop: to bring together the disparate players in AIDS work and establish cohesion to their efforts. Already several domestic institutes are active, including the Nigerian Institute of Medical Research (NIMR), the National Institute of Pharmaceutical Research and Development (NIPRD), the Universities of Ibadan, Jos and Maiduguri, and the Obafemi Awolowo University, all of which in the past have faced a severe lack of resources.

Several Nigerian researchers working overseas are also playing key roles. Alash'le Abimiku, an assistant professor at the Institute for Human Virology (IHV) in Baltimore, has established a base of activity there, in addition to her presence at the University of Jos and the International Center for Scientific Culture World Laboratory (ICSC-World Lab), also based in Jos, a middle belt city in Nigeria. The World Lab has played a key role in her work to identify the most prevalent strains of HIV throughout Nigeria, data which she presented at the meeting. She is also analyzing the immune responses typical of local populations and laying the groundwork for establishing a clinical trials infrastructure in the country, in collaboration with many in-country researchers.

---

*In a drastic departure from the past military regime, Nigeria's new democratic government seems committed to combatting AIDS. The top-level national committee is chaired by the President.*

---

Simon Agwale, also at the IHV, described the HIV vaccine candidate he is developing, based on the envelope genes of three different HIV strains (subtypes A/G and G, and a common variant of subtype C). The DNA is carried via Salmonella or Shigella bacterial vectors, which have the advantages of being inexpensive to produce and usable as oral vaccines, and which may also elicit both mucosal and systemic immune responses.

Participants identified a number of specific areas for action. These include:

- Building regional laboratory capacity for HIV surveillance, virus isolation and characterization, and data management. This could be accomplished by expanding existing centers now focused on other diseases (such as Lassa fever), which have good human resources but poor equipment and funding;
- Establishing a national ethics committee and other regulatory and scientific review committees;
- Preparing for large-scale efficacy trials by establishing cohorts and infrastructure;
- Establishing mechanisms for community input into planning, implementation, monitoring and evaluation of vaccine research;
- Investing in community infrastructure, access to health care resources;

#### T-CELL ASSAYS

*continued from page 4*

is working on automating much of the assay. IAVI plans to use this method alongside ELISpot in its upcoming trials, while the HVTN is looking at it in the just-launched HVTN 203 trial (see below).

**Tetramer staining:** This assay uses flow cytometry to measure CD8+ T-cells that recognize (and bind) a specific HIV epitope. It works by mixing the cell sample with four molecules of a single epitope (as peptide) joined to a class I HLA molecule (a molecule on the surface of CD8+ cells that helps display the epitope to the immune system). Key advantages are that it directly measures cells with receptors for a specific epitope without prior antigen stimulation, it is highly quantitative and sensitive and it can be used on thawed cells. But tetramer assays require knowing the HLA type of each person being sampled and having a specific epitope known to be recognized by that HLA type – effectively eliminating it for broad screening of diverse populations. Yet it is very useful for in-depth analysis of responses in specific populations where this information is available.

#### Remaining Questions

Topping the list for the near future is the need to better understand the cells detected by each of these assays – what their functions are and how they overlap. One effort was described by the HVTN's Kent Weinhold at the recent AVRC meeting. Using stored samples from previous HIV vaccine trials, Weinhold

- Coordinating the efforts of the many organizations – NGOs, Community-Based Organizations (CBOs), international agencies and other relevant stakeholders – working in the communities;
- Integrating Nigerian efforts into the African HIV vaccine program initiated with the Nairobi Declaration of 14 June 2000 (see *IAVI Report*, Sept.-Nov. 2000, p. 6).

Key to the success of these ambitious plans will be raising sufficient funding. NACA is looking at potential collaboration with existing programs like the Nigeria AIDS Prevention Initiative, which recently received a US\$ 25 million grant from the Bill and Melinda Gates Foundation. That program will be implemented by the Harvard AIDS Institute and includes several activities which overlap with goals of the vaccine community, such as training Nigerian scientists to screen populations, analyze HIV strains and develop HIV/AIDS prevention and treatment strategies. UNAIDS and other donors are also seen as crucial to realization of the Nigerian plans. A further boost could come from the April 2001 Organization of African Unity (OAU) meeting where HIV/AIDS in Africa will be one of the major issues on the agenda. ♦

*Akin Jimoh is a medical correspondent for The Guardian newspaper in Lagos, Nigeria. He is spending the 2000-2001 academic year at the Massachusetts Institute of Technology on a Knight Science Journalism Fellowship.*

reported that the CTL assay often correlates with ELISpot but with exceptions in both directions, suggesting that these assays detect overlapping, non-identical cell populations. The HVTN is now embarking on a large, systematic analysis – also including the ICC and proliferation assays, and comparing fresh and frozen cells – in the newly launched HVTN 203 Phase II trial (canarypox vaccine with or without gp120 boost) with 330 volunteers.

Another issue, raised by Francis Gotch (Imperial College, London) at IAVI's latest meeting, is the potential differences in immune responses and assay performance due to immune status of the study volunteers in different countries. Gotch spends time at the UVRI in Entebbe, where volunteers generally have a high infection load, particularly with helminths (intestinal worms). They also tend to have higher background levels in some of the immune assays, increases that are not seen in Africans living in London – suggesting that they stem from a more highly activated immune system. Gotch recommends that volunteers for HIV vaccine trials get treated beforehand for worms – a simple, inexpensive procedure that also provides immediate benefit to participants.

Observations like these bring the focus back to the bottom line: understanding how to best use these assays in the settings where they are needed most. ♦

# Perspectives on AIDS Vaccine Research: An Interview with Jaap Goudsmit

*Jaap Goudsmit has worked in the AIDS field since the epidemic's early days, when he and several colleagues began studying progression to full-blown AIDS in cohorts of gay men and intravenous drug users – now the longest-standing HIV cohorts in the world. His virological studies of HIV led him to an interest in vaccines, where he has helped mobilize several international vaccine efforts, including IAVI. Goudsmit now chairs IAVI's Scientific Advisory Committee and serves on its Board of Directors, and last year became co-chair of the European Union–sponsored EuroVac project. He has an M.D. and Ph.D. from the University of Amsterdam and is Professor of Virology at its Academic Medical Center.*

**Let's start by talking about IAVI's vaccine development program. With several different candidates now in the works, what will be the basis for deciding which ones are good enough to push forward?**

IAVI now has four projects. Let's assume that we picked the best ones, initially. What is always going to happen is that, while a vaccine candidate is being developed, other candidates come along that look even more promising. But what you learn from industry is that you cannot go back. You have to move the vaccines into people and see what they do.

We have to look closely at the individual products resulting from these projects and begin testing them in different combinations. In other words, how can we best work with these individual components?

## **Mix and match?**

Exactly. Take DNA vaccines, for example. The scientific problem is clear: their expression levels vary in different cell types, depending on which construct you're using. So IAVI will need to compare three or four DNAs head-to-head, say in monkey models. You have to figure out which antigens to include, what is the best DNA expressing system, what is the best way to administer the vaccine. Then you combine your best product with your best delivery system.

The next step is to get lots of vaccine into vials on the shelf. You need enough of each to do several Phase I trials, plus parallel monkey studies.

My point is, you may or may not have the ideal constructs, but by mixing and matching, you can use them optimally.

## **What should the criteria be for evaluating these data?**

The go/no-go decisions depend totally on whether there are other products available which are better.

Say that one criterion is T-cell immunity as measured by a particular assay. Your vaccine gives 30% CTL at one or more time points during the trial. That is not especially high. What do you

do? I would say, since this is about the highest you see with canarypox, my product should do a little better. Say 40%. I'd consider 30% too low for moving into a Phase IIB trial.

On the other hand, I don't think we should throw this product out. We should ask whether it can be improved, whether it is useful in any combination. I would pretty much exhaust my product in monkeys, and only give up when there is not a single good idea on how to make it more useful.

**How good a vaccine do you think is realistic? Or, to ask another way, what do you think a vaccine will be able to achieve?**

I expect we will get vaccines that do two things. They should delay disease as long as possible – just like a therapy. On top of that, they should lower transmission rates.

**You don't mention preventing infection.**

Of course we want to get sterilizing immunity. But that will take much longer.

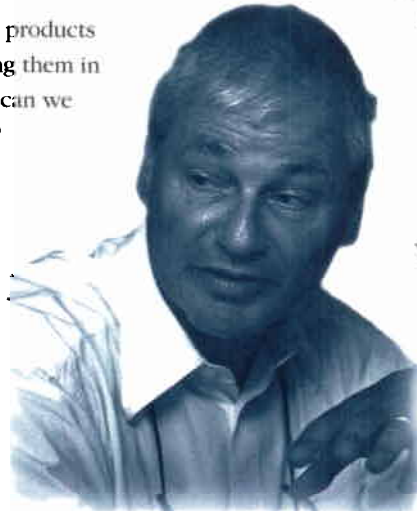
**How well is the vaccine effort going at this point in time?**

In the T-cell field, things are moving now that we have testing systems. Again, compare this to therapy. The initial breakthrough was not a therapy. It was identifying viral load as a predictive marker for disease, and measuring it accurately. It was learning that the more virus people have, the worse off they are. So we knew that we had to bring down load.

**In other words, a correlate was identified.**

Yes. In a similar way, my feeling is that we're close to figuring out in monkeys how much viral load reduction you get from what T-cell response levels or affinities. I think we will also find this out for humans.

So I'm optimistic that there will be good approaches within a short time frame – especially in the DNA field, because you can make new DNA vaccines so fast. There will be good T-cell immunity-based, partially protective vaccines out there, which work by reducing viral load.



There is one caveat, though – CTL escape. We have data showing that nearly everyone with low viral load at setpoint – less than 1000 copies per ml – loses control of viremia after ten years or more. This tells me that we need longer follow-up in monkey challenge studies with load-reducing vaccines.

Antibodies are much harder. No one has a way to induce humoral immunity effectively. Even in a natural infection it isn't easy to get neutralizing antibodies – they appear only very late. My bias is that this will be difficult without long-term expression of the viral envelope, using persistently expressing vectors and perhaps also modulating the envelope structure.

### **How should vaccine designers choose an HIV isolate?**

#### **How important is clade?**

That's a terrible question to have to answer. Of course, we don't really know.

First of all, we shouldn't restrict ourselves to clades in thinking about HIV diversity and vaccines. To me, the overriding issue is the biological properties of the isolate. So it might be a lot more important *when* you take your isolate and how you culture it than which clade or exactly what genotype it is.

What properties do I mean? It's easiest to grow an aggressive bulk culture. If you biologically clone it, you see that it is a mixture of slow- and fast-replicating strains. Depending on its origin, it might also be a mixture in terms of receptor use – CCR-5 only, or mixed CCR-5 and CXCR-4. Early cultures tend to be fairly homogeneous in their genotype and their replication properties, while later cultures are more mixed. We don't know if immunogenicity is affected by long versus short culture, or by culture in different types of cells.

Beyond the culture history, we should also pay more attention to the clinical history – when an isolate was taken relative to seroconversion. This is usually poorly documented, even in our own programs. I don't know which of these is the best starting point for a vaccine.

### **So, since different vaccines are made from different types of isolates, we could be comparing apples to oranges when we evaluate these products.**

Yes. People spend very little time on this. They mix all these strains into one bag, although we don't know if any of these differences matter. I think this is an undervalued issue, and an important one.

Maybe a good starting point is an early strain from a long-term non-progressor with high levels of broadly reactive neutralizing antibodies and CTLs. I hope that IAVI can help promote standardization and compatibility.

### **With all the discussion on clades, is there some experimental approach – short of having Phase III trial data – that could help resolve the morass?**

One way would be to characterize immune responses in people infected with each of the different subtypes – say, people one year after infection who still have intact immune systems. You could simply ask exactly what parts of HIV – which epitopes – they recognize. Then you look at whether these epitopes are the same or different among the clades.

A nicer experiment would be to make a peptide set of overlapping 15-mers for a whole viral genome from each clade. Then you would look at the T-cells of, say, clade A-infected individuals one year after seroconversion and see which peptides they recognize. If someone with subtype A recognizes certain T-cell epitopes from B, C, D and E, then you have hard information about whether you need a multivalent vaccine. With antibodies, cross-clade neutralization – even including HIV-2 – is well-documented in sera of infected people.

I'm doing a study on CTL escape and natural history of infections. We do it exactly this way. We make overlapping peptides from people with a given HLA type and look for escape in certain anchor residues. Bruce Walker is also doing this type of study. He sees that, although certain HLA types recognize slightly different epitopes, overall they

are reasonably conserved. So you can easily map this for infection. Of course we don't know if it would be the same for protection.

The point is that we need to build a data set to counteract the political arguments, which go farther than ever these days. It's even beyond clades – some people are saying, we need a national vaccine. They don't accept the same clade from another country.

### **How is the AIDS vaccine effort doing in Europe, in terms of political support and funding?**

It is clearly gathering momentum. We started with EuroVac, which was launched last year on EU funds (see *IAVI Report*, Sept.-Nov. 2000, p.9). The idea was to create a structure so that European scientists can work together on vaccines. EuroVac is basically a collaborative system made up of units – T-cell people, mucosal immunity people, neutralization people. The scientific goal is to develop poxvirus candidates and get them through Phase I testing in combination with gp120 vaccines. The program was awarded €8.8 million (US \$8.1 million), which is the biggest grant the EU ever gave for such a collaboration.

We're now waiting to hear about a second EuroVac grant, to develop vaccines based on naked DNA and on SFV (Semliki Forest Virus). That project is pure product development, without the basic science that the first grant has. I'm keeping my fingers crossed that it will get this type of EU research funding.

---

*It might be a lot more important how long after seroconversion you isolate virus, and how you culture it, than which clade it is.*

---



But what is very positive is that the EU's science directorate, DG Research, is now totally aware of the need to create new funding mechanisms, and there is real movement. Marc Girard and I went to the leadership and said, "What if our Phase I project is successful? Will there be money to take it further?" At the moment there is no mechanism to pay for Phase II or III trials. The EU recognizes this, and the sense is growing that we should do something about it.

### **Are there any concrete plans?**

Yes, there is a plan on the table. We call it the EU action plan for HIV vaccine development, and it's being discussed at the level of the European Commission and the commissioner for science. It calls for a minimum of €150 million (US \$138 million).

The plan is aimed at moving several preventive HIV vaccine candidates, chosen from national and institutional research programs within Europe, into Phase II and III trials. The selection will be handled in a technical steering committee, which has to establish the criteria for moving products forward. My hope is that this can be done in conjunction with IAVI.

So the plan involves selecting candidates, building a network for clinical trials, producing clinical lots and performing the trials. It's not for building capacity. Somebody else should do that.

### **What vaccines would be eligible?**

Criteria will be of two kinds. Eligible candidates will have proven their safety and immunogenicity in Phase I studies. They will also have to show feasibility of production within a few years into a product suitable for large-scale use.

We have done an inventory of European products currently in the pipeline. There are the EuroVac vaccines – DNAs, the NYVAC poxvirus and hopefully SFV. The first of these should be through Phase I in 2003. The ANRS (French government research funding agency) and Aventis Pasteur in France have the ALVAC canarypox products and a lipopeptide vaccine. Then there are the Oxford MVA and DNA candidates that IAVI is supporting now in Phase I studies, which should be finished next year. We don't know exactly what SmithKline will do, but it will probably involve protein plus an adjuvant. And there is the *tat*-based vaccine from Ensoli's group in Italy, and presumably DNA vaccines from Britta Wahren and her group in Sweden.

### **How and where would Phase II and III trials be organized?**

This will build on existing bilateral collaborations between European and developing countries. For example, in Holland we work with scientists in Ethiopia. The French have funding for several countries, including Vietnam and Senegal, the Italians work in Uganda, the U.K. in Gambia, Uganda and South Africa, and the Swedes in Tanzania. It might take some extra money to get these

sites fully ready for vaccine trials, but the basic structure is there. So are mechanisms to train people from these institutes.

We are also exploring the possibility of building cohorts of IDUs and homosexual men in Europe. Our Public Health Service in Amsterdam is thinking about organizing Phase III trials in Europe with these types of cohorts, alongside the womens' cohorts.

### **Where, specifically?**

Besides Amsterdam, there are possibilities in France, Spain and Italy. The incidence in these groups is above 2%, which is enough. We would need 5,000 to 10,000 people. The logistics might be a challenge, but not a bigger one than for Phase III situations in the developing world. The VaxGen Phase III study in North America, Canada and Amsterdam shows us that it is feasible.

In the end we are aiming for national vaccine trial centers linked in a network we're calling the EVTP – European Vaccine Trial Platform – with sites in each participating country.

### **Is there support for this plan at the national level?**

Yes, absolutely. And not only from scientists – there is also a broader context. Europeans want to see their efforts as enhancing development. That's why national governments in Europe are incorporating AIDS vaccines into their development programs. It's also the reason some EU countries are giving money to IAVI – as a way to invest in this problem, to get focused money out there. All the European money to IAVI has come from developmental funds.

So there is broad support for national and EU-level activity on AIDS vaccines. The UK's MRC supports this idea. The ANRS supports it. In the Netherlands our situation is different – we don't have an MRC or ANRS structure for linking our efforts to the medical area. So I'm working for an alliance with the malaria and TB people and entering from the development angle, trying to set up a Netherlands Center for poverty-related diseases. It would also involve universities, NGOs and the EU.

### **It all sounds great. What has to happen for these plans to be adopted and implemented?**

The EU action plan would have to be implemented in 2003 so that vaccine candidates now in the pipeline can keep moving.

The plan was developed by a group of scientists under the auspices of DG Research. It was produced with the help of DG Research staff, who are very supportive and willing to help until 2003. That's exactly the starting point for the EU's next funding program, the 6th Framework, which is not yet written. So we scientists are now trying to influence that process, to integrate vaccine action plans – for AIDS, malaria and TB – into the 6th





# Cohorts, Communities and HIV Vaccines: On the Ground in Africa

As a growing number of HIV vaccine candidates enter the development pipeline, more attention is going to the mammoth task of planning and preparing for the large clinical trials down the road – the Phase III efficacy studies that test whether an experimental vaccine actually protects people against AIDS.

Many of the trials will take place in developing countries being devastated by the AIDS epidemic, adding to the complicated mixture of political, scientific, human and logistical issues surrounding these studies.

The *IAVI Report* has covered vaccine trial preparations in the past from a variety of different angles. Here we take a new one, profiling three African sites that face these complex issues each and every day. Based on visits to the sites as well as off-site discussions and research, we describe on-the-ground experiences of researchers who are managing to do good science in settings of extreme poverty and a lack of basic resources and services. Key ingredients of their success: establishing trust and rapport with local organizations, scientists, communities and governments.

First, a caveat. The three sites we present here were chosen exclusively as representing different “evolutionary” stages in this type of research. Many other communities and projects, both within and outside of Africa, are deeply committed to similar types of work and will play key roles in large-scale vaccine trials. We will present some of them as we continue this series of profiles throughout the year, focusing in the next issue on Hlabisa, South Africa – the site of vaccine preparedness work since the mid-1990’s, and a pioneer of early, intensive community involvement.

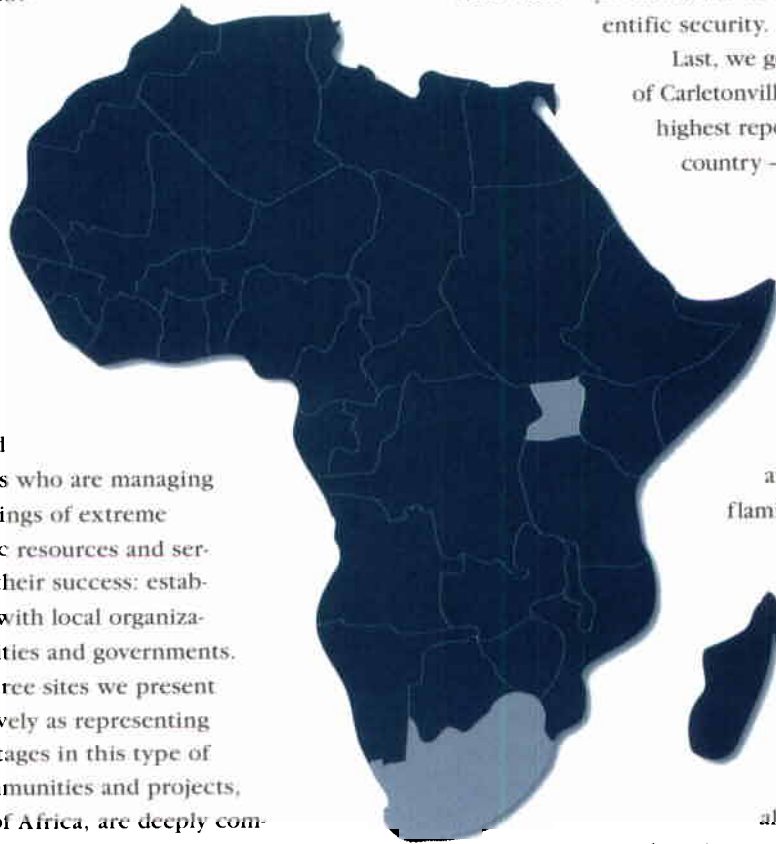
This time, we begin at the Perinatal HIV Research Unit (PHRU) in the township of Soweto, South Africa. With over a

dozen clinical trials of HIV therapeutics and prevention strategies already under its belt, the PHRU has a well-developed infrastructure, patient care clinic and strong community support – essential building blocks in their effort to expand into HIV vaccine work, in collaboration with several South African partners.

We then move to the Rakai region of Uganda, where a Ugandan-US collaboration begun in the late 1980’s has established a prospective cohort of over 15,000 people, completed several major research projects on HIV epidemiology and interventions and is now conducting vaccine preparedness work – yet continues to struggle for financial and scientific security.

Last, we go to the mining community of Carletonville, South Africa, home to the highest reported rates of HIV in the country – if not the world. Although there are no concrete plans for HIV vaccine trials at this point, the intervention research described here illustrates how scientists were able to establish community-based projects and garner local support at a flaming hotspot of the epidemic.

Although these projects all involve different populations and circumstances, they share a similar grass-roots philosophy in which communities are viewed as early and key allies. “The challenge is how to make science really work in the developing world,” says Brian Williams, a South African epidemiologist who heads the Carletonville project. “The point is to work very closely with the local community and look at good science in the context of real peoples’ lives. Any projects that aren’t rooted in an established community or just give lip service to community involvement are simply asking for trouble.”





# Soweto: A Seasoned Clinical Trials Site Looks To Vaccines

by Anne-christine d'Adesky

A short drive from the modern metropolis of Johannesburg lies the sprawling, bustling, impoverished township of Soweto, best known to outsiders as the site of fervent anti-apartheid activism in the 1970s. Today Soweto is the largest residential area in South Africa, a place where the smoke from cooking fires at dusk leaves a haze over the new housing projects that stand beside the tin and cardboard shanties of squatter settlements. This is the legacy of apartheid: a high rate of unemployment and a lack of basic services, including health services, for many. Add to the list skyrocketing rates of HIV infection, which threaten to erode the hard-won progress of the recent past.

Less well-known to outsiders is that Soweto is also home to a well-established HIV research and clinical trial facility: the Perinatal HIV Research Unit (PHRU) of the University of Witwatersrand's Chris Hani Baragwani Hospital, said to be the largest hospital in the world – and perhaps soon to be a new entrant into the HIV vaccine arena.

Much of the needed infrastructure is already in place. Besides its hospital setting that provides clinical services for many thousands of HIV-positive women and their babies, the Unit and its close collaborator at the Chris Hani, the Reproductive Health Research Unit (RHRU), have carried out 15 Phase I, II and III trials of agents to treat or prevent AIDS. Through these trials and other joint studies, the PHRU has worked with a wide range of multilateral and national agencies, major pharmaceutical companies and scientists around the world. Along the way it has built up a research staff of nearly 100 people, a variety of study cohorts and expertise in conducting large, scientifically rigorous trials. Meanwhile it has built community involvement, support and outreach programs, and become a passionate advocate on behalf of the community it serves.

The PHRU was born through the efforts of its two directors, obstetrician James McIntyre and his colleague Glenda Gray, a pediatrician. The two have been working in the AIDS care field for over ten years, and alongside their clinical and research work, helped draft South Africa's National AIDS Plan – in particular the chapter on perinatal HIV. Before their scientific careers

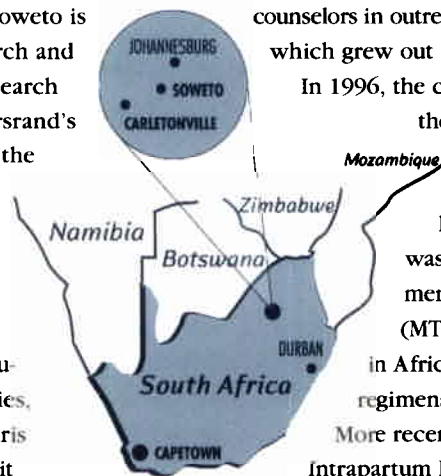
began, they were political activists involved in desegregation of the health sector and in helping the African National Congress formulate health policy. "We've always been part of the AIDS community," says McIntyre, who was also co-chair of the national AIDS consortium for many years. The result, adds Gray: "People trust us. You have to earn that trust."

They started by setting up a perinatal HIV clinic in 1991, "as a response to bad treatment," says Gray, who adds that HIV testing of mothers in their hospital actually dates back to 1987 – making it one of the first facilities in South Africa set to offer HIV testing and counselling in a maternity setting. It was also among the first to emphasize STD management and to train midwives and counselors in outreach to the surrounding community – activities which grew out of early links with NGOs.

In 1996, the clinic expanded to become a research unit of the University of the Witwatersrand and has produced a steady stream of scientific and policy work around HIV and reproductive health. The PHRU's international reputation was launched by its early clinical trials of treatments to prevent mother-to-child transmission (MTCT) of HIV. It was one of five PETRA trial sites in Africa that compared the effects of different AZT regimens on lowering maternal HIV transmission.

More recently, it participated in the South African Intrapartum Nevirapine Trial (SAINT), which proved that nevirapine offers a cheaper, more effective alternative to AZT.

In both cases, the community played an important role in shaping the trials. "We've never had a top-down approach that a lot of researchers have," states Gray. She cites placebo trials as a case in point. In September 1997, the *New England Journal of Medicine* published an editorial that strongly criticized the PETRA study for including a placebo arm, since a 14-week course of AZT given to HIV-positive pregnant women was already known to reduce MTCT – although the duration and price of this treatment put it out of reach for the developing world, including South Africa. "The moment there was a furor about it we called the community, the NGOs, the people in the trials and we discussed it," Gray says. "We allowed them to decide." The consensus: Go ahead. And the results: unambiguous validation of the shorter, cheaper regimen – and a community's empowerment.





To Gray, these trials also reaffirmed the crucial importance of serving the community throughout the research process. "Our mother-to-infant trials were a success because we run good support groups," she says. Aside from quality medical care, the PHRU also offers mental health services, counseling for men by male counselors, and affordable milk at half the retail price, to name a few perks. Now the unit is embarking on another nevirapine trial, backed by a 4.5 million rand (US\$ 690K) grant from Bristol Myers Squibb's 'Secure The Future' project.

And they are preparing to tackle another hot issue: extending nevirapine treatment to a small number of pregnant women outside the trial, with funding from France's International Solidary Fund. A recent South African government report found that MTCT treatment would save up to 50,000 lives a year and save the country 270 million rand (US\$ 45 million). But a government decision on whether to fund treatment for HIV-infected pregnant women has been delayed in the wake of President Thabo Mbeki's controversial positions on HIV and AIDS therapies. But the Soweto group is forging ahead and has secured endorsements "at every single level within the health service nationally," says

McIntyre. Again, the community provided the moral compass. "Now that we have gone to the communities," Gray cuts in, "their response is, 'What took you so long?'"

### Vaccine Plans

The escalating incidence of new HIV cases in Gauteng Province, especially among women, has spurred the duo to move into vaccine work. Together with two other groups, they are mapping out a proposed consortium that could test HIV vaccines, and looking for ways to make it happen.

One partner is the hospital's Reproductive Health Research Unit (RHRU), directed by Helen Rees, which brings its own extensive experience in international trials and partnerships – for instance, as a reproductive health research site for the World Health Organization and a participant in the UNAIDS-sponsored Phase II multicenter study of nonoxyl-9 as a microbicide. The RHRU also works with HIV-negative cohorts in several different provinces of South Africa, thus adding a key component for vaccine trial capacity. Chief among them is the Palesa Study cohort, based in the Orange Farm squatter camp outside Soweto, a region with soaring HIV rates: seroprevalence is at 22% and seroincidence is 5%. The project, which will recruit and follow 2,000 HIV-negative women to examine whether injectable progestin contraceptives affect their risk of acquiring HIV, has strong community support, according to

McIntyre. The RHRU also maintains several HIV-positive cohorts in which the screening process could be adapted to help build new negative cohorts or expand existing ones, such as the PHRU's serodiscordant couple cohort.

The third potential collaborator is the AIDS Unit at the National Institute of Virology in Johannesburg, headed by Lynn Morris, whose newly-established southern African Regional Laboratory would carry out most of the immunological studies. Under the direction of Clive Gray, the Regional Laboratory is now involved in a study (HIVNET 028) with other NIH-sponsored southern African sites to identify strong neutralizing antibodies and dominant CTL epitopes in people newly infected with HIV subtype C, the main subtype in sub-Saharan Africa.

From a research perspective, the proposed HIV vaccine plan emphasizes an important and under-researched question: Does infection with tuberculosis (TB) or an STD affect an individual's responses to an HIV vaccine? Every year in South Africa, 350 new TB infections are reported per 100,000 people – and up to 600 per 100,000 in Soweto, both underestimates of the true number. Several studies have found that people co-infected with HIV and TB show an enhanced state of immune activation, including altered levels of certain cytokines and increased CD8+ T-cell activation, which could affect HIV

viral load. Researchers suspect that it could also impede immune responses to HIV vaccines. Given the importance of this question for developing world populations, many of which are experiencing explosive TB and STD epidemics, the partners hope to tackle this issue by testing vaccines in cohorts of people with TB or STDs.

Right now the collaborators are looking for funding to take the remaining steps in vaccine trial preparedness, working on a small one-year grant from IAVI to flesh out their plans. That includes more detailed planning for cohorts, a small expansion of their on-site laboratory, training additional counselors and nurses, and community outreach and mobilization.

The group has already done some preliminary work to probe community attitudes, relying on Florence Ngobeni, the unit's seasoned community coordinator, to lead the effort. A poised, outspoken, HIV-positive woman, Ngobeni provides a role model, sounding board and advocate for many women who are afraid to reveal their HIV status. Incorporating vaccines into their community work will mean tackling a new set of issues, from educating people on HIV vaccines to probing the informed consent issues they raise to making decisions on

---

*Researchers hope to tackle a key question for the developing world: Does infection with TB affect immune responses to an HIV vaccine?*

---



treatment and care in the context of vaccine trials. And if there's one thing Ngobeni says she's learned as an outreach worker, it's never to assume she knows what communities will say or feel when it comes to HIV.

All this leaves the PHRU ready for the challenge of HIV vaccines. "We've come a long way in terms of what is good science and what is good ethics," says Gray. "Our patients are

sophisticated enough to understand the research process, and our researchers are good enough to conduct good science."

*Anne-christine d'Adesky (acd66@hotmail.com) is a New York-based journalist who has covered AIDS since 1992. From 1998-2000 she was founding editor of the magazine HIV Plus. She is currently launching a global HIV treatment and care newsletter.*

## Rakai: Twelve Years of Work, Hopes and Uncertainties

by Emily Bass

James Ludigo stands in front of a crowded room in a spare, concrete-walled church in a rural village in the Rakai district of southwestern Uganda. He wears a baseball cap and T-shirt from his employer, the Rakai Project. The shirt is emblazoned with an African scientist peering into a microscope, above the slogan, "Improving Health through Research." The crowd is rapt as Ludigo administers a light-hearted quiz. First off: "Name five things you don't like about the Rakai Project." An audience member raises his hand: "What if I can't come up with five things?" Ludigo widens his eyes in mock anger. "Well then," he says. "Your points will go down." The room erupts in laughter.

Ludigo demands the criticism with confidence. The Rakai Project has been a familiar presence in the district since 1988, when the first cases of HIV, then known as "slim," began to appear in clusters on the Tanzanian border. Over the past 12 years, Rakai Project researchers have tracked the course of the epidemic in an open cohort which has grown to include over 16,000 men and women in 56 communities. The Project's mobile clinics rove the district, visiting each village once every 10 months or so and providing care to all comers, whether they are participants in the research or not.

On this blustery day last September, a group of first-time attendees and experienced community leaders have gathered for a "sensitization" meeting that is part of the Rakai Project's latest undertaking: a two-year HIV vaccine preparedness effort to build capacity for conducting Phase III trials, in collaboration with the US Military HIV Research Program (based in Rockville), the Walter Reed Army Institute for Research (WRAIR) and the Henry M. Jackson Foundation. The Project follows on the

heels of Uganda's first foray into clinical vaccine work – an NIH-sponsored Phase I study in Kampala in 1999–2000 – the first HIV vaccine trial on African soil.

The experience gained in that trial, along with strong support for vaccine development from the Ugandan government, bode well for the Rakai Project's future. So do the years of field work there and in a few other Ugandan communities. Yet none of this shields the Project from tough challenges ahead in keeping the cohort together and ensuring a role in future Phase III studies. Chief among them is securing long-term support for the cohort from international funders, who have usually favored time-limited grants for hypothesis-driven research over continuous support for basic infrastructure. (That should begin to change, however, with several international funders – including NIH, IAVI, the European Union and the US Military Program – now preparing to invest more heavily in supporting cohorts and trial infrastructure in developing countries.) Another is coordinating the agendas of the many Rakai collaborators, both within and outside Uganda, so they work synergistically and avoid conflict and overlap.

### The Early Years

The groundwork for the Rakai Project was laid in 1987, when David Serwadda and Nelson Sewankambo, researchers at Makerere University in Kampala, first traveled to the district to identify people with a mysterious new disease. In 1985, antenatal surveillance data showed a seroprevalence of 11% among pregnant women. By 1990, the figure had soared to 30%, and Uganda was considered the epicenter of the epidemic in sub-Saharan Africa. The Rakai District, with prevalence rates as high as 40% in some areas, was ground zero.





As Serwadda and Sewankambo began their investigations, Uganda was embarking on the course that would make it a leader among African nations confronting AIDS. Instead of turning a blind eye, President Yoweri Museveni engaged religious and community leaders, doctors and health-care workers in a carefully-planned prevention campaign. This early response has had some success: by the end of 1999, national seroprevalence was 8.3%. But this figure masks sobering trends – for example, HIV prevalence among military recruits rose from 16% in 1992 to 27% in 1996, while infection rates now exceed 30% among men and women attending STDS clinics, according to UNAIDS.

In 1987, Columbia University's Maria Wawer, a public health expert with extensive experience in Africa, traveled to Rakai to meet with Serwadda and Sewankambo and explore possible collaborative projects. The commitment of Uganda's government and of its leading researchers convinced her that meaningful research could be done even as the country was recovering from decades of oppression and human rights atrocities under Idi Amin. "The infrastructure was in terrible shape but the human infrastructure was great," says Wawer. "People wanted to do good work and nothing was going to stop them."

The Rakai Project was born out of that initial meeting, using leftover funds from one of Wawer's grants as seed money. Then a four-year grant from the US National Institutes of Health (NIH) allowed the project to start in earnest; in 1988 the team began monitoring rates of new infections (seroincidence) and the proportion of infected people (seroprevalence) in the region and surveying local residents' knowledge, attitudes and behaviors surrounding HIV. At first the scale was small and simple: at night, Wawer recalls, they returned to a bare-bones local hotel where they processed the day's blood samples, often by candlelight, using a hand-cranked centrifuge. Over time the cohort was expanded and the Project lined up lab support for HIV testing from the Uganda Virus Research Institute (UVRI) in Entebbe.

Data from the cohort's early years provided a detailed picture of a mature epidemic. Seroprevalence for adults ages 15-59 hovered around 20% in 1990-1992, with wide variations among different communities – particularly trading centers (40.9%) versus agricultural villages (13.4%). Amid these soaring rates were some declines, for instance among pregnant women (from 25.4% to 20.1%). But that seemingly good news was dampened by the finding that seroincidence remained stable (at 2.1 infections per 100 years of person observation, or PYO), indicating

that the reduction stemmed more from increased mortality among infected people than from declining infection rates.

The first NIH research grant ended in 1992, leaving the Rakai Project without support. And because there were no potential funding sources for the cohort's basic infrastructure or operations, says Serwadda, the only way forward was to frame a new research question. After a difficult year, that strategy paid off: NIH awarded the team a five-year grant to study the effects of STD management on HIV transmission. Johns Hopkins University joined as sponsors of the Project, with researchers Thomas Quinn and Ron Gray as new team members. The new study not only reinstated support for most of the original cohort but also funded a rapid scale-up, eventually enrolling over 15,000 volunteers.

The STD prevention study was the Project's first randomized control trial, giving participants and communities first-hand experience with concepts such as blinding, rigorous follow-up schedules and informed consent in the setting of a clinical trial.

It also further strengthened the capacity of the Project's UVRI laboratory to conduct HIV and STD screening.

#### **Trial by Fire**

The results of the study drew widespread attention to the Rakai Project, for two very different reasons. The first was scientific. Unlike a similar

1995 trial in Tanzania, which found a 42% drop in HIV transmission associated with STD management, the Rakai study found no reduction in the treatment arm. This apparent contradiction was not only puzzling scientifically, but raised questions about the value of STD treatment in HIV prevention efforts. Yet a closer look at the two studies revealed several possible explanations. Chief among them are that STD control is likely to have far more impact on an immature epidemic like Tanzania's than on a mature one like Rakai's and that the trials differed in whether they provided STD treatment continuously (Tanzania) or intermittently (Rakai). Another possibility is that low overall risk for treatable STDs in the Rakai population, together with a high prevalence of bacterial vaginosis, overwhelmed the potential effects of the interventions.

The trial also landed Rakai investigators at the center of an ethical maelstrom. The controversy was sparked when the *New England Journal of Medicine* published a retrospective analysis of data on HIV transmission between serodiscordant couples, with Thomas Quinn of Johns Hopkins Hospital as lead author. In an accompanying editorial, Marcia Angell,

---

*Starting from studies of "slim disease"  
in 1987, the Rakai Project  
now monitors 16,000 adults  
in 56 communities*

---



then editor-in-chief of the *Journal*, criticized the ethics of the trial, particularly that HIV-negative partners had not been informed of their partners' status and that HIV-positive volunteers did not receive antiretroviral therapy. Major media, including the *New York Times*, picked up the story.

Yet the uproar that followed took place almost entirely outside of Uganda; domestically, the government, local scientists and Rakai residents remained supportive. Both of the criticized points had been extensively discussed locally via town-hall style meetings with participating communities, and the local ethics committee and the Data Safety Monitoring Board had also signed off on the trial. What's more, the decision not to disclose the volunteers' HIV status to their partners not only had strong local backing but was a key condition of participation for many volunteers, given the tremendous stigma surrounding HIV. "I know that in the US, physicians are permitted to inform people about the risk of sex with an index partner," says Rakai Project field director Noah Kiwanuka. (The US has partner notification laws in 32 states.) "But if you did that here, you'd be in very, very hot water."

And on the standard-of-care issue, Sewankambo pointed to gaps between vaccine trial participants and the general population as a decisive ethical factor. "By providing the ultimate, say, 'Boston' standard of care to experimental trial participants, are you making the standard way, way out of reach for nonparticipants?" he asks. "If you're doing that, it becomes very unethical."

Trial participants questioned by journalists following Angell's editorial also emphasized another point: the Project's positive impact on the community. "The community sees the Project as very Ugandan," says Wawer. "All of the senior management is Ugandan, and it was initiated by Uganda. So there is a real sense of pride in the community that they are part of it."

In the end, there were some hard lessons learned. The experience of being caught off-guard and scrambling to respond to criticism underscored the importance of being well-prepared for controversy. "It's like being accused of murder," says Rakai investigator Fred Wabwire. "Even if you are subsequently cleared, you still have the stigma of being accused. When the controversy arose, we had no media team. We spent months doing media instead of science." To Peter Mugenyi, head of Kampala's Joint Clinical Research Centre (and investigator in the earlier canarypox trial), the episode highlighted the need to emphasize

to outsiders that the trial design was discussed and approved locally. It also pointed to the role that a standing community advisory board, which does not exist in the Rakai Project, could play in addressing contentious issues in the future.

### The New Challenge: Becoming a Phase III Trial Site

The current vaccine preparedness work in Rakai was launched in 1999 and has two components. The smaller one, the Molecular Epidemiological Research (MER) nested sub-study, is gathering data on the biological and immunological profiles of newly-acquired HIV infections in a group of 600 age-matched HIV-positive people and negative controls. It also tracks trends in recombination. To date, Francine McCutchan of the Henry M. Jackson Foundation has analyzed 40 full-length sequences from the region and identified the main subtypes and recombinants in circulation (see table).

While MER fills in the molecular details, the Community Health Epidemiological Research project (CHER) takes on the big picture, examining community awareness, interest, and assumptions about vaccines and trials. Of 10,848 respondents in the first CHER survey, according to Kiwanuka, 99% had heard of vaccines in general and 84% were vaccinated against at least one infectious disease.

Some of the most striking findings involved gender: for example, over 90% of those surveyed believed that vaccines were useful for women and children, but only 27% thought that they were also for men. Women were less likely to report knowledge of HIV vaccines, perhaps because of limited access to radio and other forms of news, and a slightly lower level of education than men.

Two more CHER surveys will be completed within the coming year. In addition, the US military HIV research program will establish a vaccine research center at Makerere University, to include clinic suites and a laboratory for T-cell assays, including flow cytometry, as well as HIV testing and viral load monitoring.

Beyond 2001, the US military will continue to work with the Rakai Project, says Merlin Robb, chief of the military program's vaccine research department and head of its Africa program. But its activities will probably be limited to targeted subsets of the population rather than to the entire cohort – a scale-back necessitated by the Army's small AIDS vaccine program and its ongoing involvement in Kenya, Tanzania and Thailand, in addition to Uganda.

SUBTYPE OR RECOMBINANT	% OF TOTAL ISOLATES
D	52.5
A/D	22
A	17.5
A/C	8

A/C was found only in samples from newly-diagnosed individuals, suggesting it is on the rise.  
No full-length subtype C has been isolated in Uganda.



## Facing the Future

Looking ahead, the Rakai Project faces a challenging period. There are still no concrete plans to test a specific vaccine in the region. One potential candidate – still a few years off, and dependent on early trial results – is the subtype A HIV-canary-pox construct under development at Aventis Pasteur, slated to enter Phase I studies in Kampala in the last quarter of 2001 under US military program sponsorship. Robb says that favorable results from the ongoing VaxGen trial could also affect the military's plans in Uganda. "Should [the gp120 vaccine] prove efficacious, that would certainly change our strategies and timelines for East Africa," says Robb. Another issue, ironically, could be the falling seroincidence: at 1.5 PYO, it is approaching the lower threshold for conducting efficacy trials, according to Don Burke, director of the Johns Hopkins Center for Immunization Research and an experienced hand in developing country vaccine trials – although other strengths of the Rakai Project could justify running larger trials to accommodate a lower rate.

Perhaps the biggest looming uncertainty is how to fund the cohort once the Army cuts back and other short-term grants, including one from the Gates Foundation, run out. "We'll be able to keep activities and research going," says Maria Wawer. "But the fundamental follow-up of everybody in 50-odd villages, so we can look at HIV dynamics – I don't necessarily see the way clear after the next couple of years."

One possibility is to continue research work on prevention interventions, under the auspices of NIH's HIV Prevention Trials Network (HPTN). Currently, the Rakai Project is conducting an HPTN-funded study of improved penile hygiene as a strategy for reducing transmission, and Project investigators are seeking funds for other prevention studies. Yet such HPTN funding would not guarantee support for the whole cohort – although it would keep the Project integrated into the US government-funded vaccine effort.

Another avenue for Rakai would be acceptance into NIH's HIV Vaccine Trials Network (HVTN). Peter Mugenyi at the JCRC is also pursuing this option, since his NIH funding ended when the canarypox trial wound down. But both the Rakai Project and the JCRC have been invited by NIH to respond to the next Request for Proposals, and Mugenyi is hopeful that a strong application will improve their prospects.

Yet by turning to a mixed bag of potential funders, the Project will continue to face the difficulties posed by shifting

international partners, each with their own research priorities. "It gets more complicated the more collaborators you have," says Nelson Sewankambo. That's why the ability to manage multiple partners is emerging as a key survival skill for Rakai. "It helps when local collaborators set the terms and say, right from the word go, that room should be left open for other collaborators," Sewankambo adds, so they can avoid being limited by the priorities of a single partner. Beyond that, the Ugandans are looking to their US collaborators to keep one another informed and to coordinate their agendas, rather than merely tolerating one another, he says.

Americans in Rakai and at home echo the need for more effective collaboration. The large institutions, including the US Centers for Disease Control and Prevention (CDC), NIH and US military programs, are each pursuing their goals with "little effective communication" according to Burke. "There is courteous exchange of what is already largely public information, but as far as I can tell, no serious attempt to plan together," he says. In his view, better communication could also help the Rakai Project develop future sources of support – such as the vaccine program of the CDC, which supports epidemiology and infrastructure-building.

Burke also believes that more coordination is needed within Uganda. He points out that "the elements of Phase I/II capability are disconnected from Phase III – they've been supported by different funding streams and treated as separate projects. So one of the first things to do is to improve coherence in-country." That will require increased collaboration among Uganda's leading institutions, including the JCRC, UVRI, Makerere University and Mulago Hospital and the British Medical Research Council.

The Ugandan government is currently revising its 1992 national vaccine strategy plan, with a focus on increasing such coordination. These changes are promising. Still, open questions about the cohort's future fuel a sense of urgency. "Our need is a vaccine. In Rakai, we are ready for a Phase III trial," says Fred Wabwire. "We wanted it yesterday. We have tried our best to occupy the cohort by doing some other studies, but as soon as possible, we need to get a vaccine and use the infrastructure while it is still optimal."

*Emily Bass is Senior Correspondent for the amfAR Treatment Insider, and a former senior writer for HIV Plus magazine.*

---

*"We have tried our best to occupy the cohort with other studies. But we need to get a vaccine and use the infrastructure."*

---

*– Fred Wabwire, Rakai researcher*

---





# Carletonville: Research in the Eye of the Storm

by Anne-christine d'Adesky

It's easy to see why Carletonville has become an epicenter for South Africa's AIDS crisis. Every day, some 70,000 migrant miners work grueling shifts in the largest gold-mining complex in the world. Many emerge after sunrise from the bowels of the mineshaft and spill into the cramped quarters of ten single-sex male hostels nearby, where up to 15 miners share a room. Before sleep, they often wander over to makeshift food-stalls or to the shebeens – informal shacks where home-brewed beer is sold along with sex by commercial sex workers. It is in these “hotspots,” as they are known, that the HIV epidemic has taken off, fueled by the intertwined factors of poverty, alcohol, violence, and the miners' fatalistic attitude about their own survival. “The miners say, quite correctly, that in 10 years the rocks or dust will kill us, so why should we worry about HIV?” explains Brian Williams, a South African epidemiologist who heads the Mothusimpilo (“Working Together For Health”) HIV/AIDS Outreach Project there, under the auspices of the Council for Scientific and Industrial Research. “In the meantime we might as well have a good time.”

There are 12 mines in the Carletonville district, a 25 kilometer-square area that includes the historically white town of Carletonville (population 20,000), the largely black township of Khutsong (population 150,000) and smaller residential areas where migrant squatter settlements have also emerged as HIV trouble-spots. Williams began working there in the mid-90s, when he was hired to study overall health conditions among miners.

What he found was a skyrocketing HIV epidemic that flourished in a setting of poverty, danger and sex, along with rampant, untreated STDs. HIV prevalence was 4-5%, he says. By 1998, 22% of the mineworkers he sampled had HIV, while an astonishing 50% of the 24-year old local women also tested positive. For local males, the peak comes later, but the outcome is similar: 8% are positive by age 20, and by age 32 that figure has climbed to 45%. Among Carletonville's commercial sex workers, some 70% are now infected. Combine this with the fact that 90% of the miners are migrants – some from neighboring countries of Lesotho, Mozambique and Botswana – and it becomes clear why HIV spreads so fast from this mining hotspot.

The Carletonville Project springs from a 1995 meeting that brought Williams together with mining and union officials, mine workers, community leaders, and professional colleagues such as

Catherine Campbell of the London School of Economics and Liz Floyd, director of the AIDS program in the greater province of Gauteng. It led to the Mothusimpilo Project, launched in August 1997 to develop a sustainable, community-based intervention to evaluate the impact of STDs and HIV in Carletonville.

Participants of the first meeting formed a skeleton advisory group for the project; Campbell and Floyd became teammates. With US\$1 million in grant money from USAID and the British Department for International Development (DFID), they reached out to others with a stake in the local community, such as the national and provincial health departments, mine management, research organizations and local NGOs, a strategy meant to ensure community “ownership” of the project. Their immediate goal was to provide syndromic management of STDs while working closely with traditional healers. They also wanted to recruit miners and “hot spot” sex workers into a sustainable HIV peer education and condom distribution project.

The first phase of their work involved assessing community needs and identifying potential outreach workers. Next came the epidemiological surveys of HIV and STD rates. Once a year, they did anonymous cross-sectional surveys of 1,500 people aged 15 to 30, including 1,000 miners and 100 sex workers from the hotspots. The surveys included screening for HIV and STDs (carried out at the South African Institute for Medical Research in Johannesburg) and administering an extensive questionnaire adapted from one used by UNAIDS for its multicenter studies elsewhere in Africa. The last phase, now being completed, is an analysis of the project's successes and shortcomings.

When they began there was little AIDS awareness in the Carletonville community; in its place was fear, stigmatization and denial. “No one was interested in HIV,” Williams says bluntly. Nor did anyone know much about community attitudes and behavior around HIV. “So we spent the first two years talking to sex workers, and learning a lot.” What was urgently needed, they found, was HIV support groups, counseling for rape, alcoholism and pregnancy, and job training and housing assistance – areas where local NGOs had a role to play.

With four major ethnic groups in Carletonville, the team also learned how to tailor educational messages in culturally sensitive ways, and to scrutinize how those messages are received. By recruiting and training miners and sex workers, they have developed a committed team of outreach workers.



"It's very basic stuff," Williams says of the peer training program. "You give them a two-week course on STDs and physiology, and at that level it's working."

But their biggest success has come from the intense focus on STDs. "We've had a fairly dramatic effect because the women realized early on that they were no longer getting STDs," he says – a major incentive for community involvement in the project. Tens of thousands of condoms later, the safe-sex message is spreading and is being carried into high schools by youth peer educators. But success has not been uniform: while the highest-risk women have developed a very active program of peer education, reports Williams, "peer education among mine workers has been less successful, mainly because the industry is unwilling to allow men time off work to be trained." He's more hopeful about school-based interventions – the project's new frontier, born out of the early, unexpected findings that adolescents, primarily females, have such high rates of infection.

The clear link between treatable STDs and HIV has also been incorporated into their strategy. Earlier this year, with the backing of USAID and the Population Council's Horizons Project, the Carletonville team initiated Presumptive Periodic Treatment (PPT) of STDs, using a mobile health unit to treat those at high risk

for STD re-infection before they become symptomatic. A similar program at the gold fields of the Free State province showed that PPT of sex workers has led to a substantial decline in STDs among mineworkers.

The PPT program will run until August 2001 and be evaluated immediately afterward. But results are already encouraging. "STD rates are going down dramatically in sex workers," reports Johannes van Dam, deputy director of the Population Council's Horizons Project, which funds the PPT program. To him, the program's other achievements are the "enormous increase in condom distribution" and the greatly increased awareness of HIV/AIDS in the community at-large.

Perhaps the biggest measure of success is the local community's desire to now manage the Carletonville project. "It has always been our expectation that the intervention site be taken up by local groups," says van Dam. "That shows they have become self-sufficient." While it may take months for the various players to sort themselves out, one of two mining groups has agreed to fund the next phase of activities, and local and municipal authorities are signing on. Plans include a trial to examine the effect of male circumcision on HIV transmission

and a study of who young girls are having sex with, and why – an attempt to find out "where the chain of infection is vulnerable to intervention," says van Dam.

Turning to HIV vaccines, van Dam says there's no active discussion of possible trials in Carletonville now, but that it is potentially "a very attractive site" given the high rates of HIV and the community infrastructure in place. With teenage girls at such extreme risk, "they are one of the groups you want to test a vaccine on," he states. "By the time they are adults, it will be too late." Williams agrees, suggesting that vaccine advocates begin tackling the thorny ethical issues of testing HIV vaccines in adolescents. He also points to the need for preliminary groundwork to assess community attitudes towards vaccines and trials.

But the capacity and trust built up over the years would provide a strong foundation. "We've built up a cadre of very committed people. Giving them additional training in vaccine work would be quite straightforward." For his part, Williams hopes to test an experimental genital herpes (HSV-2) vaccine there and is seeking funding for such a trial. That could also provide a stepping stone to future HIV vaccine trials, in terms of preparing the community and the laboratory and logistical infrastructure.

What about miners as a potential vaccine cohort? Here, there are special challenges and clear advantages. "The mining industry is a bit of a law unto itself," Williams says ruefully. "They can be very controlling." But from a research perspective, the mines are well-financed, private entities that offer free, high-quality medical care to workers in mine hospitals equipped with state-of-the-art technology and drugs. And "logistically the mines are an absolutely ideal place to do a vaccine trial," notes Williams. Adds van Dam: "The mining houses have labs as good as they get around here, but they could be really upgraded to do vaccine research."

Yet on the ground in Carletonville, every day without progress towards a vaccine can seem like another step towards the dark scenario projected on Williams' computer, in the numbers and logarithmic waves of infection. "You're sitting in Carletonville where nearly 70% of all 25-year-old girls are HIV-positive and they are going to die in the next five to ten years," Williams sums up darkly. "We need something unbelievably drastic if we're going to save even half of them. If you cannot protect them, then everything is lost. It's an almost unimaginable situation." ♦

---

*"We need something unbelievably drastic if we're going to save even half of the young people here. It's an almost unimaginable situation."*

*– Brian Williams, Carletonville epidemiologist*

---

Framework. In the meantime we will hopefully also have some money from DG Development for capacity building.

We're also discussing the plan with the European Parliament, because that's where the allocation and appropriation process takes place. If they decide they want to allocate a billion euros to an EU action plan, they can do it. Then the EU directorates have to figure out how to distribute the money.

#### **How will this program mesh with other global efforts?**

I see a sort of natural growth in the field now, where the different players are finding their niche.

The US invests heavily in basic research, which fuels the ideas. Now they're adding the Vaccine Research Center (VRC) under Gary Nabel, to focus on early vaccine studies. I'm sure good ideas will come out. NIH is also beefing up investment in product development and clinical trials. The ANRS in France is investing in similar areas, on a smaller scale.

IAVI is an organization that can make a product on the fast track and push it into humans. Over time, more money will go towards trials, probably including Phase III studies, and to access issues.

Now we see the EU planning to focus on Phase II and III, and also on access. And downstream there's UNAIDS, working on the political and far back end – licensure issues, how to deliver vaccines to the world.

The only people we have to stimulate to do more is industry. And I think that's starting to happen. At least they're more enthusiastic – there's buy-in from Merck, Aventis Pasteur, which was always involved, is getting more active. GlaxoSmithKline are slowly but surely getting into the game.

So the whole global picture is not so bad. It is a long way from where we were five or ten years ago – even two years ago. ♦

#### **GATES FOUNDATION PLEDGE** continued from page 1

the power of our global network to help find a solution," said Yahoo! co-founder David Filo.

The new commitment by the Bill & Melinda Gates Foundation extends through 2006 and will help underwrite IAVI's support for eight to 12 vaccine candidates, as outlined in IAVI's "Scientific Blueprint 2000: Accelerating Global Efforts in AIDS Vaccine Development." According to Wayne Koff, who leads IAVI's research and development effort, the new funds will help cover some of the most costly aspects of the work: scaling up production of promising candidates, developing clinical trial infrastructure and vaccine cohorts and, if necessary, supporting Phase III efficacy trials. While IAVI's hope is that candidates which yield promising results in Phase I and II trials will be taken up by pharmaceutical companies for efficacy studies, the Gates gift helps provide contingency funding should such support fail to materialize for worthy vaccines.

IAVI has four ongoing Vaccine Development Partnerships (VDPs) involving African nations and is finalizing plans to work in India and in China. The first VDP has moved a vaccine into Phase I studies in the UK and Kenya (see p.3). A second vaccine will enter trials in South Africa later this year.

The new commitment from the Gates Foundation is in addition to its previous US \$26.5 million grants to IAVI. ♦

# IAVI REPORT

*Editor*  
Patricia Kahn

*Founding Editor*  
David Gold

*Editorial Advisor*  
Victor Zonana

*Writers*  
Akin Jimoh, Emily Bass, Anne-christine d'Adesky, Mike Isbell, Richard Jefferys, Bonnie Levings, Jasmina Omerovic

*Design Advisor*  
Stephen de Francesco

*Layout & Graphics*  
Robert Fiedler

*Copy Editor*  
Michael Hariton

*Editorial Assistant*  
Rozsa Szappanos

*Production*  
JMR 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, or to notify us about a change of address, send name and address by e-mail to: [iavireport@iavi.org](mailto: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 and Melinda Gates, Until There's A Cure and Vincent P. Belotsky, Jr. Foundations, as well as the U.K., Dutch, Canadian, Irish and US governments, the World Bank, UNAIDS, the National AIDS Trust and Fondation Marcel Mérieux. IAVI has also received support from Crusaid, the Elton John AIDS Foundation, Levi Strauss International, and other generous corporate and individual donors around the world.



# Vaccine Briefs

## New US Administration

HIV vaccine advocates, like other interest groups, witnessed the US Presidential inauguration in January 2001 without a clear sense of where the new president may be headed. Following a truncated transition and a campaign in which AIDS issues did not figure prominently, observers were left to discern hints from the political tea leaves.

Reports indicate that Secretary of State Colin Powell has shown particular interest in the impact of AIDS in Africa, while it seems likely that the Bush administration might adopt the enthusiasm of Congressional Republicans for long-term increases in biomedical research spending. Tommy Thompson, the new Secretary of Health and Human Services, supported energetic HIV care initiatives in his home state of Wisconsin, although he was reportedly less supportive of spending for behavioral prevention interventions.

Despite these early signs, important questions remain. The administration is reviewing former President Clinton's executive order that prohibited US government intervention to prevent developing countries from using compulsory licensing or parallel importation to expand access to HIV drugs. It is also unclear how much emphasis will be placed on foreign aid, especially the sort not tied to traditional geopolitical notions of American self-interest. According to Washington insiders, the details of the President's first budget may not emerge before April.

## Search for US OAR Head Underway

The search for a new director of the Office of AIDS Research at the US National Institutes of Health (NIH) is underway, with a search committee now reviewing candidates. The post became vacant when Neal Nathanson retired in September 2000. Observers say it could be difficult to replace the well-respected Nathanson who, in the opinion of many, combined a sterling academic reputation with a pragmatic approach to moving research forward. Nathanson, a strong advocate for AIDS vaccine research, is returning to a professorship at the University of Pennsylvania. He also serves on NIH's AIDS Vaccine Advisory Committee and IAVI's Scientific Advisory Committee.

## Australia Approves Therapeutic HIV Vaccine Trial

On 28 November 2000, Australian regulatory authorities approved a Phase I/II therapeutic vaccine trial of a recombinant fowlpox vector (rFPV) containing the HIV *gag* and *pol* genes. The study will compare rFPV alone to rFPV co-expressing the human cytokine interferon (IFN)-gamma and to placebo, examining both the safety of these regimes and their ability to enhance HIV-specific killer T-cells during the early stages of infection. The trial will enroll 36 recent seroconverters on anti-retroviral therapy.

The vaccine was developed by Ian Ramshaw (Australian National University, Canberra), David Boyle (CSIRO, Geelong)

and Stephen Kent (University of Melbourne) and is licensed to Virax Holdings in Melbourne, which is funding the study. The trial will be conducted at three sites under the auspices of the National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales and is expected to start in February or March 2001.

The same constructs will also be used as part of a preventive vaccine being developed with NIH funding. That strategy uses a DNA prime + rFRV boost approach, with or without co-expression of either IFN-gamma or IL-12 in the boost.

## Controversies Keep Thai Remune® Trial Hanging

Plans for a 10,000 person efficacy study of Remune®, a whole-killed HIV therapeutic vaccine developed by the late Jonas Salk, are on hold following questions over interpretation of earlier trial data and concerns of financial conflict of interest for its principal investigator. Permission to conduct the trial was sought from Thai authorities by Vina Churdboonchart on behalf of the Trinity Medical Group (TMG), which licensed commercial rights to Remune® (from the California-based Immune Response Corporation) in several Asian countries.

Trouble began when the subcommittee questioned differences between Churdboonchart's analysis of a 300-person study of Remune® given without anti-HIV drugs to HIV-infected Thai volunteers. While she claims that increases in CD4 counts among Remune® recipients are statistically significant, Harvard statistician Steve Lagakos sees only a trend in this direction.

Another controversial study comparing HAART plus Remune® to HAART alone reported no additional benefit of Remune® (*JAMA* 284, 2193, 2000). Yet some scientists have criticized the study design. Bruce Walker of Massachusetts General Hospital said the study "does little to resolve issues related to effectiveness of Remune® [since] the endpoints called it a failure if there were any minor increases in viral load in those receiving the vaccine." In his own recent treatment interruption trial - which succeeded in getting "a significant fraction" of volunteers off therapy thus far, viral load initially increased before the immune system kicked in. "All of these subjects would have been considered failures by the criteria of the JAMA paper," said Walker. Although skeptical of using therapeutic vaccines without concurrent anti-viral treatment, he warned that therapeutic vaccines should not be evaluated by the same criteria as HAART, as this could lead to "prematurely dismissing an agent that may ultimately be of some benefit."

That leaves the Thai trial still hanging. With the conflict-of-interest issue apparently resolved, Thailand's subcommittee on vaccine evaluation will revisit the scientific questions at its next meeting. ♦