

# IAVI Report

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This special issue of the *IAVI Report* focuses on the evolving relationship between AIDS vaccine research and other efforts to control the pandemic through treatment and prevention. In 2004, this relationship is as close—and as complex—as it has ever been. AIDS vaccine trial sponsors are joining expanding global efforts to scale up antiretroviral therapy and other healthcare services in the developing world. At the same time the field is refocusing its goals to include partially protective vaccines that could blur the line between prevention and treatment, while it also considers the challenges and opportunities for therapeutic vaccines.

## Raising Hopes and Many Questions

*Vaccine trial sponsors' new approaches to providing antiretrovirals for trial volunteers*

BY EMILY BASS

**AIDS** vaccine research has long been seen as having scant overlap with treatment for people infected with HIV. But in 2003 several major AIDS vaccine trial sponsors effectively redrew the boundaries between the fields of AIDS vaccines and treatment with announcements that they would work to ensure the availability of antiretrovirals (ARVs) for volunteers who become infected through high-risk contact, such as unprotected sex, during the course of an AIDS vaccine trial.

The new commitments address a hotly-debated question that has hovered over the field since its inception: Are vaccine trial sponsors

responsible for treating people who become infected with HIV during the course of a trial?

The ARV issue looms largest for large-scale efficacy trials, where most infections are likely to be found. Infections are rare in small Phase I studies which generally enroll low-risk volunteers; Phase II and III studies are larger and take place in populations with higher HIV incidence rates. For example, in the recently-completed Phase III trial of AIDSVAX in North America and Europe, there were just under 300 HIV infections at the end of a 3-year, 5,000 person trial.

Volunteers in this study and the related Phase III trial that took place in Thailand were referred to

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## THERAPEUTIC AIDS VACCINES

*Are they feasible and is their development a separate endeavor from preventive vaccines?*

BY SIMON NOBLE

**D**eveloping an AIDS vaccine that will prevent HIV from establishing infection in a healthy immune system is a daunting enough challenge. But some researchers are working on what is almost certainly an even more formidable undertaking—developing therapeutic vaccines that are intended to boost the immune response to HIV in people who are already infected. Given that the target of HIV, the immune system itself, is

already compromised in these individuals and that established infection means high virus loads and diversity, as well as virus-infected cells, most AIDS vaccine researchers are highly skeptical that it will be feasible to manipulate the immune response in infected individuals to significantly improve their health status. Even so, many are convinced that there are still compelling reasons for trying to do so.

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government-subsidized ARV treatment programs.

But today several large-scale AIDS vaccine trials are planned for the developing world, in particular sub-Saharan Africa, where the vast majority of HIV-infected people do not yet have access to ARVs. In 2003 the process of planning for these trials helped fuel an intense re-examination of “the ARV question”—and ultimately resulted in the most explicit commitments to AIDS treatment that the vaccine field has ever made.

For the most part, these commitments are still in early development, with crucial details like funding sources, care providers and collaborating partners to be determined. The broad strokes, however, are clear: the US HIV Vaccine Trials Network (HVTN), the International AIDS Vaccine Initiative (IAVI) and the South African AIDS Vaccine Initiative (SAAVI) have all stated a commitment to ensure—either through direct funding or in collaboration with ARV programs—that volunteers have access to ARVs for a specified time (generally five to ten years) starting from whenever the volunteer becomes medically eligible for treatment. Merck is also taking this approach for its ongoing Phase I studies that are being conducted with the HVTN—although the company has not developed an overall policy. The US Military HIV Research Program has set its sights even higher, with ambitious plans to implement community-wide ARV treatment programs at all of its potential vaccine trial sites.

### **Revisiting a difficult dilemma**

The new stance on treatment came into focus during a year of heated debates between researchers, funders, and advocates from the AIDS vaccine field and other areas of HIV prevention including microbicides, behavioral science and mother-to-child transmission. Over the course of these discussions—which culminated in a WHO-UNAIDS sponsored summit, *Consultation on HIV Treatment for Participants in HIV Prevention Trials* in July 2003—participants revisited the reasons why AIDS prevention trials have generally not included ARVs as part of their trial-related care.

One primary concern has been the gross inequity that would be created if a sponsor were to provide ARVs to trial participants but not to other community members. In this situation, volunteers might feel pressured to share their medication with family members, reducing its benefit and possibly leading to drug resistance. The prospect of receiving ARVs should they become infected with HIV might also serve as an “undue inducement” for volunteers to enroll in the trial. The alternative of providing ARVs for all community members would tax the financial and human resources of some research projects, and perhaps derail them altogether.

Other longstanding questions include how long sponsors should pay for ARVs that should,

ideally, be taken for life; what to offer would-be volunteers who are identified as being HIV infected during the trial screening process; and how to ensure continuity of care if the research project ends and the sponsor is no longer active in the community.

In all of the meetings, there was unanimity that, in an ideal world, volunteers and communities would have access to ARVs. But participants returned again and again to the realities of the resource-poor communities where AIDS prevention research is taking place. “As we take elegantly-designed studies into the field, that’s where reality hits,” said Quarraisha Abdool Karim, head of the Women and AIDS Programme at the Centre for the AIDS Programme of Research in South Africa, at a 2003 consultation on trial-sponsored healthcare convened by IAVI and the Global Campaign for Microbicides. “The existing standard of healthcare in most countries is minimal. If you are doing research in that setting...anything you offer is substantially more than what is already available.”

In many of the discussions, participants referred to existing guidelines for research in human subjects, such as the Declaration of Helsinki ([www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)) and the Council for International Organizations of Medical Sciences (CIOMS) guidelines ([www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm)). These documents do not stipulate an ethical responsibility to provide ARVs for AIDS vaccine trial volunteers since they are healthy and uninfected with HIV at the time of enrollment, and since participation in the study does not cause or increase risk of HIV. The current CIOMS guidelines do state that provision of care for diseases contracted during vaccine trials is “morally praiseworthy” but does not mandate a specific level of care. The WHO UNAIDS guidelines *Ethical Considerations for Preventive AIDS Vaccine Trials* ([www.unaids.org/publications/documents/vaccines/vaccines/ethicsresearch.pdf](http://www.unaids.org/publications/documents/vaccines/vaccines/ethicsresearch.pdf)) also leave room for interpretation, stating that HIV-infected volunteers should receive some form of treatment, with “the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country.”

In the absence of a clear directive, ethicists have offered varying perspectives (see article, p. 3), while trial sponsors have developed packages of trial-related benefits that generally did not include ARVs. Although these packages were often developed in consultation with the community and local groups, they have occasionally been subject to fierce criticism, particularly in studies of HIV-discordant couples or mother-to-child prevention interventions that did not provide ARVs for HIV-infected participants. Trial planners say the past few years have been an often-turbulent search for solutions that meet local and international expect-

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# Ethics, Antiretrovirals and Prevention Trials

BY EMILY BASS

The recent decisions by several AIDS vaccine trial sponsors to ensure access to antiretrovirals (ARVs) for trial participants who become infected with HIV (see article, p. 1) come after years of debate and discussion about the ethical implications of providing—or not providing—these powerful medications to trial volunteers. Two of the central questions were: Is there an ethical obligation to provide ARVs to volunteers who become infected during the trial period through high-risk behavior? Is it unethical to provide these medications solely to a segment of the population, that is, trial volunteers, when other community members cannot obtain them? Perhaps surprisingly, the new policies do not provide definitive answers to these questions. Instead, they propose distinctions between obligations and options.

Many trial sponsors say that trial design considerations, not ethics, were a primary motivation for the decision to include ARVs in trial-related benefits. HIV Vaccine Trials Network (HVTN) head Larry Corey says that the need to learn about how vaccines impact on HIV disease in infected volunteers was a key consideration. Ensuring ARV access increases the likelihood that volunteers will remain in the study, and compensates them for their participation in a lengthy follow up period. “This is the right thing to do both scientifically and operationally,” Corey says. Seth Berkley, President and CEO of IAVI, takes a similar view. “In large part this is a protocol issue for AIDS vaccine trials; it is not a statement about what is or is not ethical.”

These pragmatic rationales have the most bearing on large-scale efficacy trials which will ask HIV-infected volunteers to participate in long-term follow-up studies. However, sponsors say that they will also extend the benefit to participants in small-scale trials.

These decisions have not supplanted the ethical considerations raised over the past several years. HVTN, IAVI and the South African AIDS Vaccine Initiative (SAAVI) all developed their policies in consultation with ethicists after review of the existing ethical guidance documents on research in human subjects. In South Africa this process led reviewers to the conclusion that, based on strict interpretation of ethical principles, vaccine trial sponsors are not obliged to provide ARVs to research participants who are not infected with HIV at the outset of the trial and who receive high-quality prevention counseling throughout. “It was hard for our committee to see why there was an ethical compulsion to provide ARVs,” says researcher Cathy Slack (University of Natal), a member of the South

African HIV AIDS Vaccine Ethics Group. “But it was possible to make a strong argument that providing ARVs was morally praiseworthy—an act of positive beneficence.”

This notion of ARV treatment as praiseworthy, rather than mandatory, is an important distinction to AIDS vaccine trial sponsors, as well as to sponsors of other prevention trials. While some international guidance documents do address the issue of AIDS vaccine trial sponsors’ responsibility toward volunteers who become HIV infected during the trial, none provide a clear directive on the issue. The 2002 CIOMS (Council for International Organizations of Medical Sciences) guidelines state that provision of treatment for the disease that a vaccine is designed to prevent is “morally praiseworthy” but not mandatory, and recommends that decisions be made in consultation with the host country and communities where research will occur. The WHO UNAIDS ethical guidelines for preventive AIDS vaccine trials state that at a minimum sponsors should provide the “highest level of care attainable in the host country.”

AIDS vaccine trial sponsors are aware that their actions will impact on other fields of prevention and perhaps lead to new expectations of all areas of research. This is particularly true for microbicide trials in which participants who become HIV infected are not followed for long periods of time since there is no presumption that microbicides will alter the natural history of infection. Microbicide researchers and advocates participated in many of the discussions leading up to the vaccine trial sponsors’ new policies. While there is growing consensus within the microbicide field that trial sites and sponsors will advocate for scale up of ARV access programs that will benefit volunteers, they have not yet committed to fund these programs themselves.

“Treatment should occur for all AIDS vaccine trials, but what do we do about other prevention trials, will we paralyze them? That’s a great fear in my mind,” says Berkley. “You have to be very careful not to condemn the future,” says Kevin DeCock, head of the US Centers for Disease Control and Prevention (CDC) program in Kenya. “If you’re very prescriptive about things, you can end up backing yourself into a corner. You can’t measure the effects of research that doesn’t get done.”

As trial sponsors begin to implement their new policies, ethicists continue to explore the principles and implications of these decisions and how they might affect other scenarios surrounding AIDS vaccine trials. A recent Clinical Trials Subcommittee meeting at IAVI to consider

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tations. “The ground has been moving under our feet for at least five years. It’s been like an earthquake on some of these issues,” says Kate MacQueen (Family Health International) who helped draft the HIV Prevention Trials Network ethics guidance document, and participated in several of the 2003 consultations.

### **New directions**

In the recent meetings, sponsors once again took stock of the landscape—and agreed that major changes had taken place. One focus of the discussion was the surge of ARV treatment initiatives in the developing world. The year was marked by commitments from governments and global health organizations. In January 2003 US President George W. Bush pledged billions of dollars for AIDS care and treatment in Africa and other developing countries; later in the year, the World Health Organization launched its “3 by 5” program that will support efforts to supply 3 million people with ARVs by 2005; the South African government took long-awaited steps to implement a national ARV treatment plan; and former US President Bill Clinton announced an agreement with manufacturers that would slash the price of ARV combinations to less than US\$150 per year. These and other activities have contributed to an atmosphere of optimism around expanding access to ARVs that, even among veterans of the AIDS epidemic, is positively heady.

“It sounds strange to say, but I haven’t been this excited since Kennedy announced that we would send a man to the moon,” says Colonel Debbi Birx, head of the US Military HIV Research Program.

These developments were a major influence on AIDS vaccine trial sponsors’ decisions to include ARVs in trial-related care. With ARVs becoming more available through other sources, this offering appears less likely to serve as an undue inducement to participate in trials. “The access movement has really changed our ability to have the conversation about ARVs for trial volunteers,” says IAVI CEO and President Seth Berkley. “Even a few years ago, there really would be a question of undue inducement if vaccine trial volunteers were offered ARVs.”

The four African countries with ongoing AIDS vaccine trials—Botswana, Kenya, South Africa and Uganda—all have national ARV treatment plans that are in various stages of planning and implementation. Thailand, which has just launched its second Phase III AIDS vaccine trial (see *Vaccine Briefs*, page 20), is also expanding its national program, which initially provided ARV treatment for 6,000 people.

“We can contemplate ARV treatment and that’s why we’re having this discussion,” says Paula Munderi, a Ugandan clinician who attended a November consultation on ethics and microbi-

cides research. “The cost barrier has been diminished, it has repeatedly been demonstrated that ARV therapy is feasible in resource-limited settings, and the numbers of patients who will require treatment in the context of prevention trials is really very small indeed.”

Further impetus for change came from within the vaccine field where the expanding scope of trials has led to an increased focus on a range of healthcare services, such as voluntary counseling and testing for HIV, family planning and treatment for TB and malaria, all of which should be in place before a large-scale trial can begin. As part of preparing for trials in rural sites, many sponsors are looking for ways to strengthen and develop these services, often in partnership with existing hospitals and NGOs. “For the vaccine agenda to move forward, the treatment agenda also needs to move forward,” says Nzeera Ketter, Director of Efficacy Trials at IAVI.

Sponsors also attribute their new stance on ARVs to shifting goal posts for the current generation of AIDS vaccine candidates, which induce primarily cell-mediated immune responses. One possibility is that such candidates will not prevent infection with HIV, but will instead provide some protection against HIV-related disease progression in vaccinated individuals. To test this hypothesis, vaccine trials will ask HIV-infected trial participants to return for multiple study visits over an extended time period to monitor the viral load, CD4<sup>+</sup> cell counts and clinical course of HIV disease—data which could provide clues about vaccine effects on HIV disease progression.

A vaccine candidate that improved health and slowed disease progression in HIV infected people would function as a form of treatment. (Almost all current trials are looking for such an effect in people who are healthy and uninfected with HIV when they receive the vaccine. Studies of “therapeutic vaccines” that might be used in already HIV-infected people are still in early stages. See article, page 1).

HVTN head Larry Corey says that this change in expectations for first generation candidates was “the tipping point” for the HVTN in its deliberations about whether or not to provide ARVs for its trial volunteers who become infected through high-risk behavior. “As we started developing vaccines that would be ameliorating disease rather than preventing infection, it became very clear to the HVTN that the distinction between prevention and treatment had been lost,” says Corey.

### **Treatment funds for future needs**

Having assembled compelling rationales—from feasibility to medical necessity—for providing ARVs, sponsors have set about devising strategies to meet trial participants’ treatment needs. IAVI, SAAVI and the HVTN have all proposed treatment funds, which would be established for each trial,

“For the vaccine agenda to move forward, the treatment agenda also needs to move forward.”

—NZEERA KETTER, DIRECTOR OF EFFICACY TRIALS AT IAVI

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# WEIGHING THE BURDEN OF DISEASE

## *How will other diseases affect AIDS vaccine trial design?*

BY EMILY BASS

WITH REPORTING BY MARK BOAZ

For the better part of the 20th century, vaccine development and testing was the province of the industrialized world. Many of today's vaccines, including those against polio and measles, were licensed based on data from efficacy trials in the United States and Europe. More recent vaccines, such as those targeting pneumococcal infections and hepatitis B virus, were evaluated in efficacy trials in developing countries including South Africa and Thailand. But there is still little precedent for the AIDS vaccine endeavor, which is focused on developing countries in sub-Saharan Africa, Asia and Latin America at every stage of vaccine testing—from small safety studies to large-scale efficacy trials. Throughout these regions, HIV is intertwined with other endemic infections, often called “diseases of poverty,” which include helminthic infections and intestinal parasites, malaria, tuberculosis and sexually transmitted diseases. These diseases add a layer of complexity to the already daunting task of finding an effective AIDS vaccine.

Licensed vaccines have a long history of being delivered in settings where health care is rudimentary. One dramatic example is the “Days of Tranquility” campaign in which El Salvador, Afghanistan and the Democratic Republic of Congo called cease-fires allowing tens of millions of children to receive polio vaccine. However there is a world of difference between administering a licensed vaccine and testing one against the background of poverty and endemic, untreated disease. This is one reason why many clinical trials, which require a rigorously controlled environment, have been conducted in countries with high standards of healthcare and sanitation, and low levels of endemic infections.

But limiting studies to the industrialized world is not an option for AIDS vaccine trials. Although HIV is increasing dramatically in some US and European communities, the most severe epidemics are in the poorest countries of the world. Vaccine trials in these countries will provide crucial information on how HIV genetic diversity impacts on AIDS vaccine efficacy, and on the acceptance of AIDS vaccines in different populations. In order to conduct efficacy studies that meet the stringent standards of regulato-

ry agencies like the US Food and Drug Administration, AIDS vaccine trial sponsors working in resource-poor settings must supply or strengthen a range of healthcare services, both as a benefit to the volunteers and to ensure that data on adverse events and efficacy can be generalized beyond the study community. “You can't get good data without providing good care,” says IAVI Medical Affairs Director Pat Fast.

HIV-related services such as voluntary counseling and testing, prevention interventions, and treatment and care for HIV-infected people top the list of trial sponsor priorities—and the issue of whether or not to include ARVs (antiretrovirals) in trial-related healthcare has only recently been settled by several vaccine trial sponsors (see article, page 1). But today, AIDS vaccine developers are paying increasing attention to diseases other than HIV. In doing so they are paying heed to warnings that have been sounded by researchers in other fields, notably parasitologists, who have warned that coinfection with common diseases of poverty could complicate analysis of trial data. This is a serious consideration, particularly for the AIDS vaccine candidates that will be evaluated solely based on efficacy trials in developing countries. Israeli parasitologist Zwi Bentwich (Rosetta Genomics, Rehovot, Israel) writes that, “Potentially good vaccines may fail in clinical trials if examined in the immune scenario presently existent in the developing world.”

### **Variable vaccine effects**

One of the most powerful arguments for considering the interaction between AIDS vaccines and diseases of poverty comes from studies of other vaccines, including rotavirus, BCG, polio and oral cholera, which have shown variable rates of immunogenicity in the developing, versus developed, world. For instance, a single dose of live oral cholera vaccine (CVD 103-HgR) induced vibriocidal antibody in 90% of vaccines in the industrialized world but in only 16% of Indonesian children. In many instances, this effect can be overcome by increasing the dosage of the vaccine—but the underlying mechanism is not clear.

One hypothesis suggests that the varia-

tions in vaccine immunogenicity are caused by helminthic infections, which infect 1.5 billion people—one quarter of the world's population—and are most common in the developing world.

The variety of small prospective studies that have tested the effects of helminth infection on immune responses to vaccines do show lower or less durable immune responses in people with intestinal parasites (see box, p. 17). A small trial that examined responses to hepatitis B vaccine in Egyptian children matched for age and other demographic characteristics found similar plasma antibody titers in children regardless of their *Schistosoma mansoni* status. However, by nine months post-vaccination the parasite-free control group had a significantly higher percentage of responders (97% versus 56%) and higher levels of antibody titers. Another trial randomized 60 helminth-infected Ethiopian adults to receive deworming therapy (albendazole) or a placebo prior to immunization with BCG vaccine, and found that the albendazole-treated participants had stronger cellular responses to tuberculin than placebo recipients (as measured by stimulation index or IFN- $\gamma$  production).

The precise mechanism of the proposed helminth effect is not known, but one theory points to the fact that chronic helminthic infection leads to persistent activation of Th-2 type immune responses, which are broadly characterized as anti-inflammatory responses. This bias may hamper the ability to mount a robust vaccine-induced Th-1 type response. Data from human trials and mouse model experiments show that helminth infections may also cause anergy and hyporesponsiveness in immune cells.

Several studies of differential vaccine effects in developing and developed countries concern orally administered vaccines, like cholera and polio, which are thought to work by inducing protective responses at mucosal surfaces such as the gut and lungs. This has led researchers to speculate that intestinal parasites could interfere with interactions between vaccine and antigen-presenting cells in the intestinal mucosa. However, other studies have shown an effect on parenteral vaccines such as BCG

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with the precise amount to be determined by the incidence rate, the current cost of ARVs, and the duration of the sponsors' commitment to funding ARVs. For example, the HVTN currently plans to set aside \$1,500 per person per year to cover five to ten years of treatment.

There are practical reasons for making this distinction: volunteers are not likely to need treatment until several years after the trial has ended (most people infected with HIV do not develop AIDS-related symptoms until five to seven years after infection), and may even move away from the trial site. In South Africa, volunteers will receive an identification card that can be presented to an insurance company, which will pay for care at the clinic of their choice.

Sponsors have varying views on who will provide the care. The HVTN has said that it will use the infrastructure at its vaccine trial sites for ARV provision, although the treatment fund could also subsidize care at a non-trial-related facility. IAVI hopes to fund treatment at independent programs. "The worst case scenario is if IAVI or another trial sponsor has to implement the care policies itself," says Seth Berkley. "We don't know whether we will be operating in countries five or ten years hence. What we would like is a system that is sustainable and locally-administered."

The treatment funds crystallize sponsors' commitments to volunteers at a time when international leaders, and individual nations, are pledging to implement sweeping treatment programs. And opinion is divided as to whether volunteer-specific commitments are a bold step—or a wrong move—for sponsors working in these changing times.

Solly Benatar, Professor of Medicine and Director of the Bioethics Centre, University of Cape Town, South Africa, says that the SAAVI policy will stand even though South Africa has recently taken steps to implement a national treatment program. "The fact that [state-funded] clinics are running means that there will be a back-up for the trust [treatment fund]. But we will insist that the trust continue. Treatment for volunteers shouldn't be solely the responsibility of a government that doesn't even have infrastructure set up yet. Sponsors' contributions will show a level of commitment to volunteers," says Benatar.

But there are also those who say that sponsors' volunteer-specific commitments are unnecessary, and that sponsors should work with local governments to supply the ARV benefit, rather than earmarking funds to pay for treatment themselves. One proponent of this view is the French research agency ANRS (Agence nationale de recherches sur le sida), which plans to conduct AIDS vaccine trials in West Africa, where it says host country governments will assume responsibility for post-trial care for participants, including ARVs.

"I know of no country in the developing world that has the infrastructure, medical staff and organizational ability needed to host a Phase I or II trial that is not a recipient of a grant from the Global Fund [to Fight AIDS, Tuberculosis and Malaria] (GFATM) or the World Bank, and that is developing a national treatment program," says Michel Kazatchkine, head of the ANRS and one of the most vociferous critics of the proposed treatment funds. "Countries like Kenya, Cameroon and Côte d'Ivoire all have funds to put several thousand people on treatment. Most countries that have applied to the Global Fund list participants in research programs as priorities for treatment when demand for ARVs exceeds by far the available number of treatments. I am sure they can save funds for the tens or hundreds who will become infected in a Phase I or II trial. I don't see why someone external should take responsibility for care. Clinical trials in the developing world should be conducted as a partnership between the North and the South, where benefits and burdens are shared by partners."

### **Toward a broader vision**

One reason that this debate has become so heated is that it is still too soon to tell when and how country-led ARV initiatives will develop. For the moment ARV programs are on the horizon in many countries and on the ground in very few. "In 2003 there were rhetorical and philosophical changes, but we won't know until 2004, or later, whether these shifts will translate into change on the ground," says Mitchell Warren, Senior Director for Vaccine Preparedness at IAVI. In this state of uncertainty, sponsors must decide whether it is more important for them to make volunteer-specific commitments, or to provide immediate support to programs that, if successful, will render treatment funds unnecessary.

For many sponsors, the answer is: Both. In addition to making volunteer-specific commitments, AIDS vaccine trial sponsors are, individually and collectively, embarking on a range of activities designed to support and accelerate scale up of ARV programs and related activities.

The US Military HIV Research Program has put forward the most ambitious plan. Bix and her colleagues hope to implement comprehensive healthcare packages, including ARVs, for all of the people living in the environs of a trial site, and have submitted multi-million dollar proposals to the Bush Presidential Emergency Plan for AIDS Relief (PEPFAR) to meet these goals. (Unlike the GFATM and the World Bank Multicountry HIV/AIDS Program [MAP] funding streams, the presidential AIDS initiative accepts applications from research entities.) Bix says that the Army proposals were developed with extensive local input and are designed to complement planned and existing national ARV initiatives.

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the implications of such healthcare provisions revealed disparate views among some of the experts in attendance, prompting *JAVI Report* editor Simon Noble to conduct an online debate between bioethicists Ruth Macklin and Charles Weijer. Their strong, sometimes controversial positions are illustrative of this dynamic field. ♦

**Simon Noble:** *There has been a lot of debate over the level of healthcare that AIDS vaccine trial researchers should be obligated to provide to trial participants who incidentally become infected with HIV during the course of the trial. Do you consider that there is a moral imperative for the trial researchers to provide this care, or is it simply morally praiseworthy to do so?*

**Ruth Macklin:** I believe there is a moral obligation to provide antiretroviral treatment to trial participants who become infected with HIV during the course of the trial. However, to say that a moral obligation exists is not to define precisely on whom that obligation falls. Quite clearly, it is beyond the ability of a research team alone to provide ARV treatment. It is also likely that many sponsors will be unwilling to do so. Nevertheless, the obligation to provide treatment derives from considerations of justice. Trial participants who become infected deserve something in return for their contribution to vaccine research for which they have volunteered.

**Charles Weijer:** HIV vaccine research in developing countries is morally vexing for the same reason that it is of great social importance. It is carried out in the face of global disparities in the distribution of healthcare resources. Many people with HIV in developing countries simply don't have access to life-saving HIV treatments. At the same time, the development of a successful HIV vaccine is one of the best hopes for lessening the burden of the disease in poor countries. Against this backdrop, the pressing nature of the question, "What do we owe participants in HIV vaccine trials conducted in developing countries?" is immediate. My answer to the question is this: We owe them no more or less than is owed participants in HIV vaccine trials in developed countries. It is well accepted that research participation ought not disadvantage the medical care of patients (e.g., *Declaration of Helsinki* 28, [www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)). Thus, HIV vaccine trials may only employ a placebo control so long as there is no effective HIV vaccine. Furthermore, should a safe and effective HIV vaccine emerge from a trial, it must be provided to all trial participants (*Declaration of Helsinki* 30, [www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)). But, the claim that researchers have an obligation to provide treatment for those who develop HIV while

enrolled in an HIV vaccine trial is both unprecedented and dubious. In moral theory, causation is a necessary condition of compensatory claims. Unless trial participation *per se* can be shown to have caused HIV infection (e.g., through the administration of an attenuated live vaccine), a compensatory claim upon the researcher is without merit.

*One of the biggest fears among AIDS vaccine researchers is that an obligation to provide funds for treatment of incidental HIV infection will divert research funds, slowing the pace of research and ultimately delay the discovery of an effective vaccine. With an estimated 14,000 new infections daily, any delay in the discovery process has profound ramifications. Doesn't this mean that the moral obligation should be toward the pace of discovery rather than treatment of infections that are not actually a research harm?*

**Ruth Macklin:** The two goals—providing ARV treatment to infected research participants, on the one hand, and proceeding with all due speed in the research endeavor, on the other—are not incompatible. First of all there is no evidence whatsoever that research funds will be diverted to pay for treatment. Today there are numerous possible sources of funds and newly forged collaborative relationships among researchers, industry, private philanthropic organizations, and the public sector. There is a sense in which this entire discussion is dated. The World Health Organization (WHO) has recently announced its "3 by 5" initiative—to ensure that ARVs are available to 3 million infected individuals in developing countries by the year 2005. Surely, individuals who became infected during preventive vaccine trials can be among that group, as it contains many fewer than 3 million people.

**Charles Weijer:** Global initiatives, such as WHO's "3 by 5" initiative, that seek to enhance the availability of ARVs to persons in developing countries further the cause of social justice and merit our support. The question in this exchange is whether it is prudent to saddle the research enterprise with this agenda of social reform. In its 1976 report on Research Involving Prisoners,

## Ethics, Antiretrovirals and Prevention Trials: An Online Debate



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the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research tied its recommendations to protect prisoners in research to an agenda of prison reform. Ostensibly to protect prisoners in research, the National Commission mandated 17 reforms to improve the living standards of prisoners, a suggestion greeted with enthusiasm. One ethicist, Nancy Dubler, who opposed research involving prisoners, commented at the time: “[S]imply imagine the strength of a lobby that would unite medicine, correctional officers and drug companies. It would be in the overwhelming interest of all of these groups to continue a system that would provide an unlimited supply of available, trackable, and willing subjects.” The end result of this initiative is well known. Research in prisons came to an end and conditions in prisons continued to deteriorate. HIV vaccine research offers perhaps the best hope of ameliorating suffering from HIV in developing countries. Tying such research to an agenda of social reform runs the risk of slowing the pace of discovery or, worse yet, bringing it to a halt.

**What do you consider are the obligations towards potential trial participants who are found to be HIV infected at the initial screening (and are therefore excluded from the trial)? Should those excluded be offered ARVs and, if so, is that not an undue inducement to volunteer for trial participation in the first place?**

**Ruth Macklin:** As the WHO’s ‘3 by 5’ initiative is rolled out, there will have to be a careful analysis of fair principles for allocation of ARVs. It will be impossible to provide access to the entire 3 million initially. Beginning with groups that have already been tested and found to be positive might be one good place to start, from the standpoint of efficiency. Therefore, those found to be infected at the initial screening, as well as those who become infected during a trial, could be among the first groups since the VCT (voluntary counselling and testing) process is already in place. As for the ‘undue inducement’ argument, it is a red herring. One worries about ‘undue inducement’ when research carries high

risks in an activity in which people would otherwise not choose to participate. But the current and proposed vaccine candidates are not risky. And people are eager to participate in the hope of being protected against infection. If anything could count as an undue inducement, it would be the vaccine itself, since that is what is hoped to provide the real benefit to uninfected people. But surely, we would not want to consider a preventive HIV vaccine an undue inducement, since in that case it would be unethical to conduct such research in the first place!

**Charles Weijer:** The conflation of an agenda of social reform and obligations to research subjects is clear in this response. Individuals found to be HIV infected at screening are ineligible for study participation and are not research subjects. Putative principles of reciprocity and maximizing research benefit thus do not support an obligation on the part of researchers to provide such individuals with ARV treatment. In the context of a community in which ARVs are not available, their provision to persons found to be HIV infected at screening or to trial participants who develop HIV during the course of study is obviously undue inducement to participate in the study. Only study participation gives access to ARVs that can forestall what is otherwise certain death from HIV. Under these circumstances, the voluntariness of decisions regarding trial enrollment would be enhanced by either (a) not offering ARVs to persons found to be HIV infected at screening or to trial participants who develop HIV, or (b) initiating a community HIV testing and treatment program in parallel with the trial. If wide-scale ARV treatment in a particular community is not available through programs such as WHO’s ‘3 by 5’ initiative, then the first option is preferred; if it is available, then the second option is preferred. Both options have the merit of mitigating undue influence and barring the injustice of treating trial participants preferentially to their neighbors not in the trial, whose right to treatment is equally pressing. ♦

*The full version of this exchange can be viewed online at:*  
[www.iavi.org/iavireport](http://www.iavi.org/iavireport)

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“We’re banking on this money. It’s the only way to move forward,” Birx says. “We need the infrastructure [associated with providing ARVs] to test vaccines. Providing treatment and care heightens awareness of our project and our staff in the community.” And, if ARV treatment is widely available, it will likely improve community attitudes to voluntary counseling and testing in general; since there will be treatment options available to those who are found to be HIV-infected there will be

some incentive to come forward to be tested. Consequently, vaccine trial sponsors will likely find that enrollment will be an easier task in an atmosphere where testing is more widely accepted.

Bill Snow, one of the founders of the AIDS Vaccine Advocacy Coalition, hopes that more US trial sponsors will take steps to link research projects and efforts to improve global health infrastructure. “Researchers are in a parallel but separate universe from scale-up activities; they should

all get together and apply for money," Snow says. "Right now, they are not looking at how to harness global activity and make it work for them."

So far, the US Military HIV Research Program is the only vaccine trial sponsor that is currently making a direct application to a global funding source. But other trial sponsors, including IAVI, hope that communities where research takes place can be prioritized to receive funds from the GFATM and other sources. MAP and GFATM grants require countries to state which groups—such as activists or research volunteers—will be prioritized for receiving ARV treatment; initially, most countries will not be able to provide ARVs to all those who are medically eligible.

In December IAVI and its Ugandan research partner the Uganda Virus Research Institute met with government leaders and the architects of the Ugandan national ARV plan to discuss ways that the government and IAVI could share responsibility for treating volunteers. Dr. Elizabeth Madraa, head of the Ugandan national ARV program, said that trial volunteers and research communities would be prioritized in the allocation of resources for ARV programs.

These efforts are key first steps according to Snow, who says that alliances between research projects and public health funders are not simple.

Snow has spent the past few months attempting to build support among AIDS vaccine and prevention trial sponsors for an inter-agency collaboration around fundraising for treatment and care. Snow has proposed that the networks submit joint proposals for funds which could be used to strengthen local treatment and care services at and near research sites. He says that many of the major networks have responded positively to the suggestion, but that there are still hurdles on both sides. "There's the skepticism among funders about funneling money through researchers," he says. "And researchers can be uncomfortable about simply applying for grants instead of proposing treatment protocols."

Snow sees these collaborations as a key way for the AIDS vaccine field to effect immediate change in access to prevention and care services—while pursuing its long-term goal of a preventive vaccine. Many trial sponsors agree, and say that the outcome of these efforts will have an impact that far exceeds that of any single trial-related policy. "I am sure that when Kennedy said we were going to the moon, it seemed a lot more outlandish than getting care and treatment to Africa," says Birx. "But it is going to take the same level of commitment—and a lot of work. I don't know where we're going to end up—but isn't that the responsibility of us all?" ♦

**In 2003**, IAVI Report launched a new monthly bulletin, **VAX**.

VAX includes shorter, nontechnical versions of IAVI Report articles and has been designed to make topics more accessible to non-scientific audiences, particularly in community-oriented efforts that include potential AIDS vaccine trial volunteers around the world.

VAX features glossary definitions for the few technical words used in these articles, along with "Primers" answering key questions critical to understanding AIDS vaccine development such as:

- ◆ How are AIDS vaccines tested?
- ◆ Why are there so many different versions of HIV?
- ◆ Why do vaccines need to be tested in different populations?



VAX has enjoyed great success to date and four issues are available, each one in English, French, Spanish and Portuguese. VAX is currently reaching an audience of several thousand with online subscription growing by the week.

VAX has begun establishing in-country print and distribution centers, with French and English versions currently being printed and distributed for East Africa (Kenya, Rwanda and Uganda), and South Africa and Botswana. Coming soon—Brazil will have its own print and distribution center.

**How to receive VAX:**

VAX can be downloaded as a pdf in Portuguese, French, Spanish and English at the IAVI Report website: [www.iavi.org/iavireport](http://www.iavi.org/iavireport)

VAX is also available in a plain-text email format in Portuguese, French, Spanish and English. To subscribe to VAX via email, please send a request including language preference to [vax@iavi.org](mailto:vax@iavi.org)

Limited numbers of print copies of VAX are also available for AIDS vaccine trial sites and community organizations involved in AIDS vaccine education. If your organization would like to receive print copies, please send a request to [vax@iavi.org](mailto:vax@iavi.org)

# Treatment in Vaccine Trials and AIDS in Brazil

## AN INTERVIEW WITH

**Mauro Schechter, MD, PhD, is one of the leading figures in the field of AIDS in Brazil, and his renown spreads beyond his home country to the international sphere. He is Head of the AIDS Research Laboratory at the Universidade Federal do Rio de Janeiro, and was one of the first Brazilian scientists to commit to setting up a preventive AIDS vaccine clinical trial site, as well as being instrumental in setting up the first Community Advisory Board in the country. Schechter also plays a continuing key role in developing and updating the treatment**

**guidelines for Brazilian AIDS patients and is seen as one of the country's leading AIDS physicians. His international standing has led to his inclusion on a number of influential global health panels, including the International AIDS Society's Consensus Panel on Antiretroviral Therapy and the Scientific Advisory Committee of IAVI. Recently Schechter spoke to IAVI Report editor Simon Noble about healthcare implications around AIDS vaccine trials and the current situation in Brazil.**

## Mauro Schechter



**The AIDS vaccine field is currently tackling the question of the level of healthcare that should be provided to vaccine trial participants who become infected during the trial period. Do you consider that there is a moral imperative to provide a certain level of healthcare to these participants, or is there a lesser qualification on the issue? Is it more a case of simply the right thing to do?**

Well, there is a moral imperative to provide to trial participants care for whatever happens to them that's trial-related. And I think no one would argue about that. What I think is more difficult is what to do with regards to treatment of incidental infections, which are not trial-related damages, what do you have to do for these persons? Is there a moral imperative to provide treatment for them in an environment where there's no treatment, or is providing treatment just a nice thing to do? And once you provide

treatment to these persons, how far do you go? Is it OK that these persons are getting treatment for the virus while their next-door neighbors who did not join the trial are not? So the short answer is that I don't know. From this perspective you may argue that although you thought that you were doing good, that you had the best intentions, you may actually be doing harm. I don't feel I'm really qualified to say what's right and wrong there. Clearly, we have to do everything that's directly trial-related, to ensure responsibility. But then after that sort of general broad statement, one has to decide what is really trial-related.

**In the past it hasn't been incumbent upon vaccine researchers in other disease settings to provide such care. Why do you think that AIDS vaccine research is now being held to a different standard?**

If you look back at the whole history of HIV treatment, the standards of care that HIV researchers were held accountable to have always, arguably, been different from what other areas were. Basically, I think, because HIV hit originally the gay community in the US. So the whole activism changed the way society deals with medical research, which I think is good. When I started working with HIV in the 1980s, there was no community input, non-medical individuals weren't participating in the design of trials and criticizing trials. And then HIV came about, with the whole idea of having a Community Advisory Board (CAB). You didn't have a CAB for a diabetes trial or a trial for hair loss. Until there was HIV and it rightly became the standard—holding HIV research to higher standards was a good thing. I think HIV research is not the higher ground, just the beacon that tells everyone that eventually you have to do things as you do with HIV research.

**Do you think there is a fear that diverting funding towards surrounding healthcare—which can mushroom to community-wide coverage rather than just trial participants—will impact upon the speed of scientific discovery, and then ultimately impact on the speed with which an effective preventive vaccine is available to the community?**

That's again a situation in which one is trying to do good and may end up doing harm, even though, again, one had the best intentions. I think it comes down to determining what's the difference, if any, between your responsibilities as a researcher and your responsibilities as a citizen. And it's always very difficult to decide where one ends and the other one starts. So we have to find ways of equipoise and at the same time not divert efforts and funds from the trial itself.

**One concern about the healthcare provision is that this will impact adversely on other avenues of prevention research. And these**

**fields, especially microbicides, have relied on doing research trials without surrounding costs. Do you think that will impact upon microbicide research?**

Well, yes, we cannot have double standards. But on the other hand, we're trying to do this off futurology. By the time most of these trials are ongoing, with the '3 by 5' WHO initiative, hopefully in two or three years' time we'll have millions of people on treatment, then the situation will be totally different from today, where very few are on treatment. It will be a different equation.

**What do you think of the idea of getting independent funding for the healthcare provision and making it, in some respects, independent of the vaccine trials? Essentially you will create 'seed' populations at the vaccine trial site but will be treating the wider community. Do you think that's a valuable concept?**

I think that's a valuable concept, and that might be a more efficient way of doing two things at the same time. Considering that you will not be able to scale up treatment for everyone at the same time, you have to at some point or another decide you have enough capacity to, say, treat a million people next year. So then you have to decide whether these people will be in North, South, East or West Kenya, for example. Then you could tie that up to where the trials are happening. So, you answer more than one question, probably being much more efficient. In a way, the NIH is going through the same discussions now; they have several networks that do different things, and they are discussing how to do them more efficiently, because these networks need to be complimentary. At the moment they aren't, sometimes they appear to be working in a vacuum. On a global scale, for example, we have the 'Enterprise' initiative for the vaccine, which should somehow tie up with the Global Fund and with '3 by 5', and so make the process more efficient.

**In the past you've advocated for treatment of opportunistic infections and other risk factors that impact on HIV disease, and that this is as important as antiretrovirals. Could you expand on that a little?**

I think a lot of thought goes into antiretroviral therapy, because that was a major success story and people like novelties and sophisticated treatment. On the other hand there's plenty of data to indicate that mortality was already going down before we had these drugs, and there is also plenty of data to show that this decline is probably due to adequate prophylaxis for opportunistic infections, which are generally very cheap, and have an enormous impact not only on the incidence of these infections but also on

overall HIV-related mortality. The other side of the story is that people tend to think that providing antiretroviral therapy needs a very sophisticated infrastructure. It doesn't. Basically, if people take the drugs, they work. The doctors on the ground don't have to all be PhDs from Johns Hopkins. Someone can tell patients, 'You take these drugs when the sun rises. You take these drugs again when the sun goes down. You'll be OK. And if you don't feel good, just come to me, otherwise you'll be OK.'

**What do you think are the first practical steps that can be taken to roll out access to antiretrovirals?**

What you need to begin with, which the WHO has done, is to have simple 'cookbook' guidelines—and we can learn from tuberculosis—which tell people how to treat, in very simple ways. Simple guidelines that you get everyone to follow, in which you say, 'if someone is HIV infected and presents X, Y, Z conditions, which are simple to evaluate, than you give drugs A, B, C.'

**Is there still a 'clade question' in Brazil? Or is there the attitude that perhaps is becoming dominant, that clades shouldn't be seen as important because we need to know about protection across clades?**

From the scientific point of view in Brazil, the discussion of clades is everywhere. You can argue forever whether clades matter or clades don't matter. From a practical point of view, because Brazil is mainly a clade B country the issue does not arise to the same extent as, for example, in East Africa where you have lots of clade A or southern Africa with clade C. Since most of the vaccines being developed at the moment are actually clade B vaccines, in a way they are perceived as matching Brazil, although they may not be, because in some areas up to a third of infected Brazilians may have subtype C. Early in the epidemic there were a lot of vocal people saying that we needed a vaccine tailored for Brazil. Now we don't hear that as much.

**In the past, there have been suggestions that the 'clade question' is related to people's fears that they're going to be used as a testing ground for somebody else's vaccine. Do you think that attitude has waned?**

I think there was an attitude in the early 90s that you could only test a vaccine in a developing country if you had done the Phase I in the US, but I think that has changed. At least the scientific community really wants to be part of Phase I trials. And you have countries now that really want to be part of a mismatched trial. They should be commended for this.

I think it all goes back to the guinea-pig issue. I feel that this will never die out. On the

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other hand I think that in the last few years AIDS has produced a working relationship between community activists and scientists, in Brazil at least. I think there is an unprecedented degree of understanding, of mutual trust. But that has only changed in the last several years. In the community, maybe 10 years ago, there was a lot of mistrust.... And now both sides can say, 'Well, we disagree on several things, but the fundamental thing is that I think you're trying to do good. We might have different opinions but you're not intrinsically a bad person.' I think that has changed a lot.

***The Brazilian example is being adapted by the WHO as the model for expanding access to ARVs and other forms of HIV-related care. What do you think are the most important lessons you've learned from your experiences in Brazil that might come into play in other communities?***

There is always this tension—do you need to build the infrastructure before you supply the drugs, or do you supply the drugs and then build the infrastructure? And Brazil showed that we could do both at the same time. And it worked. That is *the* basic lesson. There are those who say, 'Well, if we cannot do CD4 counts and viral loads everywhere we shouldn't even think about giving treatment.' So, these people think that we can only treat patients if they live in Manhattan. And what Brazil proved was that even if you live in rural Brazil, wherever you are, provided you take your drugs, they will work. Obviously it would be better if we had very sophisticated monitoring systems and very sophisticated doctors everywhere. One would obviously prefer to save the lives of 99% of the people, but, on a population basis, if you save the lives of 95% of the people, you're doing extremely well.

***Is there a lesson there for the AIDS vaccine effort?***

There's a difference because one knew that the drugs worked. It's not a matter of you have a vaccine that you know works and now you're trying to see how you will vaccinate people in the world. We don't have a vaccine. ARVs in Brazil was a different thing. You had the drugs, you knew they worked, and you had to decide how to make these drugs available to everyone. If one day, hopefully, we have a vaccine then we will have to decide how to make it available to everyone. What Brazil showed is that if you have efficacious drugs, to scale up is not that difficult; it's a matter of political will. All you need is to commit the resources and have the willpower to do it.

***What about the fears expressed that because of lower adherence levels in developing nations we're going to see resistant viruses emerging?***

That's complete nonsense, and for two reasons. First, there is the misconception that in developed countries adherence rates are very high and failure rates are very low. It has been shown time and again that if you go anywhere, in the US, in France, a large proportion of patients will have 'failed,' because the definition of failure many use is 'if your viral load is detectable, you've failed,' which I think is a bad definition. But if you use that definition, you get about 50% failure rates everywhere. Second, there are several small studies done in developing countries that show that adherence rates are at least as good as, if not better than, in developed countries. Basically, I think one of the reasons is that people in developing countries value and treasure what they get much more than the average person living on the Upper West Side. What's a thousand dollars to these Upper West Siders? You can't even buy a new Armani coat. But to someone whose annual income is far less than a thousand dollars.....

***And they're seeing their family members die.***  
Yes.

***To finish, what is the mood in Brazil these days regarding the national response to AIDS?***

I think there's a general sense of pride in the Brazilian AIDS program. And rightly, I think, that people look at it not as the work of a particular party or a particular government. They look at it as an AIDS program, developed by several governments and mostly by the same group of people; it's not because party A, B, or C was in power that the program worked. So there's a sense of pride, of national achievement, not a party achievement, a demonstration that Brazilians can accomplish important things. ♦

“...in developing countries... adherence rates are at least as good as, if not better than, in developed countries.”

It is still far from clear in HIV infection precisely what are the “correlates of protection”; that is, the relative importance of the immune parameters (neutralizing antibody, CD4<sup>+</sup> and CD8<sup>+</sup> T cells, plus many others) that need to be stimulated to give a robust immune response against HIV. Many within AIDS vaccine research think that, beyond any potential benefit to infected individuals, investigations into therapeutic vaccination modalities are likely to give indicators as to what is required for a preventive vaccine response.

“A therapeutic vaccine as an adjunct to HAART to counter re-emerging virus is a perfectly reasonable idea, but the task of a therapeutic vaccine is more difficult than a prophylactic one—the amount and diversity of virus it will have to counter initially is greater in a therapeutic setting,” says John Moore of Cornell University, “you might as well try and make a prophylactic vaccine because it would seem to be easier.” The requirement of HAART is an important qualifier, and he says it is difficult to “even contemplate using [a therapeutic vaccine] in the absence of virus suppression by HAART because you’re just making the [virus] escape even more inevitable.”

#### **Progress to date**

There has been a long history of therapeutic vaccine strategies that have proven ineffective at improving clinical outcome, although a number of studies have shown moderate positive effects on some HIV-specific immune responses. A whole inactivated HIV immunogen called Remune, made from whole HIV particles depleted of gp120, has been tested in combination with incomplete Freund’s adjuvant in a number of clinical trials involving HIV-infected patients receiving HAART. Cumulatively, results have indicated that this agent can induce some improvement in several HIV-specific immune responses, including CD4<sup>+</sup> cell responses, but there has been no suggestion that these can affect patients’ disease progression. Similarly, recombinant gp160 and gp120 have been tested in a total of six Phase II efficacy trials in asymptomatic patients with early-stage HIV infection, again with no effect on clinical outcome.

More recently, some of the more promising immunogens that are being tested in preventive vaccine trials are now going into human trials in therapeutic settings. The Adult AIDS Clinical Trials Group (AACTG) focuses on therapeutic approaches generally, and now has a number of therapeutic vaccine trials planned or underway. One trial that begins next month will test Merck’s Ad5-gag adenovirus construct in 120 patients whose virus is well-contained by HAART in a randomized, placebo-controlled trial. These patients will be immunized, their HAART suspended and then they will be monitored to see how well virus replication can be controlled.

But it is still far from certain, given the biolog-

ical unknowns, that an effective therapeutic AIDS vaccine can be developed. As Emilio Emini of IAVI says, “the nature of [HIV] infection is a balance between the virus and the immune system and the ongoing interaction between the two during the course of persistent infection. From a prophylactic vaccine perspective, the objective is to alter that balance clearly in favor of the immune response during the early stages of infection. Studies performed in monkeys, as well as anecdotal human observations, suggest that once that balance is established it’s very difficult to alter the equilibrium, even under a situation in which virus replication is being suppressed with antiviral chemotherapy. Therefore, the unknown with regard to therapeutic vaccination is whether or not the damage that’s caused to the immune system during the initial phase of HIV infection is essentially irreversible and unlikely to be enhanced by anti-HIV immunization.”

#### **Goals**

The initial goals of therapeutic vaccines will be to try to increase the durability of HAART regimens (that is, increase the time to virological failure when drug-resistant virus emerges) and to allow patients “drug holidays,” the off-therapy periods that mean patients can relax from the strict adherence that can compromise quality of life. If therapeutic vaccines prove particularly effective these goals will become more ambitious, with the removal of all ARV therapy being the ultimate, but presently very distant, goal.

This reliance on HAART means conducting therapeutic vaccine trials in developing countries would be extremely difficult right now. “I think this is a case where you really do have to do the first trials in settings where ARV drug treatment is freely available, so that you don’t induce volunteers to participate by the offer of free treatment—you have the full range of drug treatment available for people who participate in the trials just the same as if they hadn’t participated,” says Andrew McMichael of John Radcliffe Hospital, Oxford. “I think it would be very hard to set this up in many developing countries at this stage, but if [therapeutic vaccination] looked promising then it would be very important to do it in developing countries.”

#### **Need for new interventions**

Particularly in the last six months, a great deal of attention has centered on antiretroviral (ARV) treatment and sweeping pledges have come from many quarters to provide funds to improve global access to these powerful drugs. Many preventive AIDS vaccine trial sponsors have committed to ensure that ARVs will be made available to trial participants who become infected with HIV (see article on p. 1). This progress has raised hopes that some of the grave inequities in ARV access might finally be addressed. But McMichael still thinks that, if an

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effective therapeutic vaccine can be developed, “therapeutic vaccination may be one of the few hopes for effective therapy in developing countries, where it’s unlikely for a long time that lifelong treatment with ARVs is going to be available for everybody.”

Those fortunate enough to have access to these powerful ARV regimens can effectively manage disease progression, possibly for up to twenty years, but lifelong adherence is not easy and virus suppression comes at a price. Some patients experience severe adverse effects of therapy, including lipodystrophy, myocardial infarction and mitochondrial toxicity resulting in neuropathy and myopathy. And even when patients don’t suffer these toxicities, drug-resistant viruses often emerge which means they have to switch to alternative regimens. Eventually they may run out of options.

Alexandra Trkola of University Hospital Zurich works with patients who are controlling their virus with HAART and is familiar with the associated problems. She is investigating therapeutic approaches that require patients to come off their ARV regimens periodically. “Patients, sadly enough, are very keen in getting some off-time from taking drug therapy, some take every chance they can for a ‘drug holiday,’” she says. “Some patients don’t want to go back on therapy even though they are urged to because of the rise in viral load.”

#### **Feasibility of therapeutic vaccines**

There is some scientific evidence that the immune system of HIV infected individuals can be manipulated to improve their immune response to HIV, although it’s widely agreed that this evidence is only suggestive. A number of trials have looked at structured treatment interruption (STI) where patients who are receiving HAART to suppress their virus have their treatment periodically withdrawn under strict, often weekly, clinical monitoring. The rationale is that the HAART-induced suppression of virus allows the immune system to recuperate and then, when HAART is stopped, the virus load rebounds (the virus begins to replicate again) and it acts as an “auto-vaccination”—it is hoped that the cells of the immune system again encounter the virus and can respond to mount an improved immune response. Early studies enrolled patients who had initiated HAART during the primary acute phase of their HIV infection, and some patients could effectively control their virus load for prolonged periods after the suspension of the HAART regimen.

However, follow up studies in patients who had begun HAART during the chronic phase of infection did not derive any benefit from STI, and viral load set-points after the STI protocol were comparable to the initial set-points before HAART was first initiated. This suggests that preservation of the immune system (and also possibly suppression of viral diversity) by early intervention with ARV

chemotherapy is crucial. The vast majority of patients do not begin their ARV therapy in the acute phase of infection, meaning that STI is unlikely to be a practical therapeutic approach to boost HIV-specific responses.

Since the ARV regimen in STI is intermittent and consequently sub-optimal, another concern raised is that this approach could lead more readily to the emergence of drug-resistant virus. But in a wider context, “what STI showed is that the immune system can help you even in HIV disease. If you can do that then it’s functionally possible to design a vaccine that could induce a more robust response and therefore be able to suppress viral replication below a certain level,” says Roger Pomerantz of Thomas Jefferson University.

One of the most promising strategies in preventive vaccine modalities in recent years has been the prime-boost approach. The prime vaccine, often a DNA plasmid encoding HIV epitopes, is given to trial participants and then, some weeks later, a boost vaccine is given, most usually an attenuated viral vector expressing HIV proteins. The scientific mechanism behind this approach is still not fully clear, but most immunologists think that the prime activates a broad repertoire of T-cell clones that the boost then selectively amplifies to give what is hoped will be a robust and appropriate immune response against HIV antigens. McMichael, a pioneer of this approach in preventive AIDS vaccines, is planning to use his preventive prime-boost vaccine in a therapeutic vaccine trial setting, and suggests that “it may be easier to boost the immune response in someone who is already well primed by natural infection than in somebody in whom you’re trying to use the vaccine to prime the immune response.” But he is keen to stress that he thinks both preventive and therapeutic vaccine approaches should be pursued.

Jeff Lifson of the AIDS Vaccine Program, SAIC Frederick, Inc., at the US National Cancer Institute also thinks there may be some reason to be optimistic. “The most important thing is that there are some indications that, at least under some circumstances, these viruses can be controlled by some individuals. The question is how are they doing that and is there a generalizable mechanism, and can we induce such a mechanism in a broader segment of the population?”

And he cautions against dismissing the potential of therapeutic vaccines too soon. “The [HIV] field can have a relatively short attention span, relative to the timeframes required to actually figure any of this stuff out, so an idea like therapeutic vaccination will go from heresy to dogma to common wisdom to rejected paradigm before anyone has really had chance to systematically explore the idea at the level of actual data.”

But Lifson goes on to qualify any optimism. “My intuitive feeling, based on the cumulative available data, even if [a therapeutic vaccine] does work

it is probably only going to work in a meaningful way for a very small subset of patients, presumably those who have been treated relatively early in the course of disease and have limited cumulative immunological damage.”

In studies that support this more cautious stance, patients whose virus loads were suppressed with HAART were given a standard vaccine, like diphtheria toxin, and their subsequent immune responses measured. The strength of the immune response to the standard vaccine correlated with the time interval between their CD4<sup>+</sup> cell count nadir and the initiation of HAART. In other words, HAART must be initiated soon after CD4<sup>+</sup> cell counts reach their lowest levels in order to preserve the immune system so that it can subsequently mount a good immune response. Again, like the STI studies, this suggests that there is a progressive negative effect on the immune system over time.

Lifson further points out that “emerging data on superinfections in individuals who seemed to be controlling their original virus suggests that immune control may not be as robust as we’d hoped. So certainly there may be limits on what might be achievable with therapeutic vaccination.”

#### **Experimental approach**

Trkola, together with Huldrych Günthard, is conducting a passive immunization trial at the University Hospital Zurich. Analogous passive immunization strategies have been tried before, most notably using HIV-specific immunoglobulin (HIVIG) obtained from chronically HIV-infected asymptomatic donors. In those studies, HIV-infected patients were infused with HIVIG and monitored, but again no clinical benefits were seen.

Trkola’s study is different in that it will use well-defined human monoclonal antibodies that have unusually high and broad neutralizing activity against HIV. Patients on HAART are given a cocktail of three neutralizing monoclonal antibodies (called 2F5, 2G12 and 4E10), HAART is then suspended and they are infused weekly with the cocktail, after which their virus load and CD4<sup>+</sup> cell count are closely monitored. The goal is to look for improvement of clinical parameters in the individual patients, but it is also a proof of principle trial to try to determine the importance of humoral immunity in the management of disease progression. “We are trying to mimic a therapeutic vaccine that elicits neutralizing antibodies. Such a vaccine isn’t available so we have to use passive immunization,” she says. Although passive immunization is unlikely to ever be a feasible long-term treatment option (it’s far too costly to produce the antibodies), the outcome will suggest whether or not antibodies are a vital component of the immune response in infected individuals. Trkola is also keen to see if antibody-dependent cellular cytotoxicity is an important mechanism.

This typifies the approach that those engaged in therapeutic vaccine research are adopting; the primary goal of any therapeutic clinical trial must always be the amelioration of an individual’s disease, but if designed appropriately, these experimental approaches offer a secondary advantage: lessons might be learned regarding which immune parameters are important in an effective immune response against HIV.

This experimental attitude is endorsed by Pomerantz: “I look on it like chicken soup—it may not help but if it couldn’t hurt, why not? It’s important to think how therapeutic vaccines could hurt people, because it might be worth setting up these [therapeutic vaccination] studies, as long as you’re not going to hurt anyone.” Harriet Robinson of Emory University agrees, “I think the most promising current preventives should be tested in the therapeutic arena and find out how they do and build on that for long-term control.”

“There is a school of thought that you could use HAART-suppressed individuals as a ‘vaccine test-bed,’ as a way of testing [preventive] vaccine efficacy in a small number of patients in a short period of time. You have HAART-suppressed individuals, you vaccinate them and then take them off HAART and you can get some idea of vaccine efficacy. It’s an idea that’s worth considering,” says Moore. He emphasizes an important qualifier; an improvement in an individual’s HIV-specific immune response would be an important result, both for the patient and for vaccine development, but a negative result would not rule out that a vaccine candidate might have better efficacy in a prophylactic setting where it would be directed at a pristine immune system.

The most sophisticated therapeutic vaccine clinical trials clearly illustrate that this experimental philosophy is at the fore. Nina Bhardwaj of New York University is taking dendritic cells from volunteers, incubating these cells with a mixture of HIV-derived peptides and then infusing them back into the volunteers. These dendritic cells are antigen presenting cells; their role is to “show” virus antigens in a particular context to lymphocytes, which subsequently go on to initiate a full immune response. Bhardwaj is conducting a trial that will compare the immune response induced in non-infected volunteers to that in infected patients who began their HAART early in infection. The primary goal is to augment HIV-specific immune responses (and ultimately improve the clinical outcome) in the infected patients, but she is also “teasing out the immune components that are important for inducing immunity—the longer term goal is to figure out how to activate these cells *in situ*, without having to pull them out of the body.” She is also conducting a two-arm study under the AACTG which is comparing the effects of therapeutic vaccination with canarypox AIDS vaccine vectors with or without a dendritic cell component.

“... an idea like therapeutic vaccination will go from heresy to dogma to common wisdom to rejected paradigm before anyone has really had chance to ..explore the idea...”

—JEFF LIFSON, AIDS VACCINE PROGRAM, SAIC FREDERICK, INC., US NATIONAL CANCER INSTITUTE

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and tetanus toxoid. In one Kenyan study, schistosomiasis or filarial parasitic infection in pregnant women was shown to correlate with lowered responses to BCG vaccine among newborns.

These data are suggestive but by no means conclusive. Not all parasites have been linked to Th-2 type bias, and it appears that different types of worms have varying effects on the immune system. It's difficult to forecast the implications for AIDS vaccines, since they could be tested in populations infected by or exposed to multiple parasites. To complicate matters further, in the absence of reliable correlates of protection it is impossible to know if changes in immunogenicity—such as those potentially caused by helminthic infections—will have a bearing on vaccine efficacy data.

Some researchers suggest that AIDS vaccine trials gather parasite epidemiology data during trials and keep the potential effects of parasites in mind. “I think it would be worth knowing people's helminth status in vaccine trials and, if the hypothesis is confirmed, doing some work on when is the best time to deworm people,” says Allison Elliott (Wellcome Trust), who has conducted several studies on the interaction between helminthic infection and HIV disease progression in HIV-infected Ugandans. Elliott explains that deworming immediately prior to immunization also has immune consequences—including sudden increases in anti-worm responses which might also impact on vaccine efficacy.

Zwi Bentwich agrees, saying that “it is imperative to evaluate and follow the immune profile in vaccinees before and following vaccination, because of the potential interference of background immunity with the ability to generate specific responses to the vaccines.”

#### **Taking stock of multiple factors**

Although helminthic infections may be a contributing factor, it is unlikely that all differential vaccine effects can be attributed to a single facet of life in resource poor settings. Poor nutrition, chronic or recurring infection with other diseases like malaria, and host genetic background all play a role in immune profiles on an individual and community level. Sexually transmitted infections other than HIV could also compromise the efficacy of AIDS vaccines. Since these infections compromise the integrity of the genital mucosa, a vaccine which affords protection in the context of an intact mucosal membrane might be less effective if these physical barriers have already been compromised by other infections.

It's impossible to predict which, if any, of these factors will affect AIDS vaccine efficacy, either in preventing HIV infection or in protecting against HIV-related disease in trial participants who become infected with HIV through high-risk behavior. But in order to identify potential confounding variables, sponsors need a clear picture

of the common diseases and immune profiles of volunteers and potential recipients of a licensed vaccine.

Perhaps surprisingly, this information is hard to come by. One of the paradoxes of disease in the developing world is that, while it is omnipresent, it is also—from an epidemiological standpoint—ill-documented. Although some epidemiological studies have been done in potential AIDS vaccine trial sites, there are also sites where there is relatively little precise data on prevalence, incidence, recurrence or immune effects of various coinfections.

Today many sites are undertaking studies designed to fill in these gaps. At the Soweto Vaccine Evaluation Unit at the Chris Hani Baragwanath Hospital, Guy De Bruyn of the HVTN and principal investigator Glenda Gray conducted a prevalence study of helminthic infections in over 100 potential AIDS vaccine trial volunteers. “There is very little recent prevalence data on helminthic infections among adults in the places in South Africa where trials will take place,” De Bruyn explains. “This is an initial look to see if we can even answer a question about helminth-vaccine interactions in this population.”

By mid-2004, De Bruyn and Gray will have preliminary prevalence data. If the prevalence is high, De Bruyn says the next step will be to screen people who are participating in trials to determine whether immune responses differ in people who are dewormed prior to vaccination compared to people who are parasite-free at the time of vaccination.

This paucity of data is also a stumbling block for evaluating vaccine efficacy in protecting against HIV-related disease. AIDS vaccine trial designers are now attempting to define a “composite endpoint” that could be used to evaluate vaccine impact on the course of HIV infection. This will be measured by changes in CD4<sup>+</sup> cell count and viral load in vaccinees and placebo recipients. It may also be measured in terms of clinical conditions including AIDS-related illnesses. Although there is considerable data on AIDS defining illnesses in the industrialized world, much less is known about HIV-related illnesses in resource-poor settings, particularly in the early stages of infection.

“Actually, and incredibly, the data we need to answer these types of questions are extremely few. Good information on early clinical course of HIV infection in the developing world is one of the major gaps in our knowledge,” says HVTN statistician Steve Self.

#### **Trial design considerations**

How should information about the rates of various infections influence trial design? Coinfections raise different issues at each stage of clinical testing. In Phase I studies participants are

rigorously screened prior to enrollment and asymptomatic conditions such as eosinophilia (which is associated with helminth infections) or anemia may be used as exclusion criteria. During the trial it is crucial to make precise rather than presumptive diagnoses in order to definitively rule out a vaccine-related side effect. So, for example, a feverish Phase I trial participant from a malaria-endemic area would undergo a confirmatory blood test before receiving treatment that might ordinarily be prescribed based on clinical symptoms.

In Phase II and III studies there are different issues. Participants in these trials will be clinically healthy, but will not be tested for asymptomatic conditions; there is also less intensive medical surveillance of trial participants. Jimmy Whitworth (London School of Hygiene and Tropical Medicine) thinks that this is the point at which trials should begin to gather data about interactions between co-infections and vaccine effects. Data on disease effects are "probably best accrued in later-stage Phase II trials," he says, and suggests that substudies within Phase II trials could compare vaccine-induced immune responses in individuals with and without background infections. While small, these substudies would be able to detect a major effect on immune responses and could provide some guidance about inclusion and exclusion criteria for Phase III or expanded Phase II studies. While randomization safeguards against bias due to background infections in either trial arm, it will not protect against misinterpretations of data that could arise if a background infection skews immune responses to the vaccine itself.

"If coinfections have only minor effects on immune responses then I feel we should not screen them out from a Phase III or expanded Phase II study because of issues of generalizability," Whitworth says, referring to the fact that excessively stringent exclusion criteria could limit the relevance of trial data to other populations with different disease burdens. "However if coinfections have major immune effects I think, though I am reluctant to say so, that we would have to screen them out at enrollment and possibly throughout the trial. Otherwise we may miss important vaccine effects."

Practically speaking, it would be nearly impossible to incorporate treatment for all potentially confounding asymptomatic infections into large-scale trials. Taking helminthic infections and intestinal parasites alone, it would be a mammoth undertaking to collect and analyze stool samples and administer treatment to all infected participants in a large-scale efficacy trial. Different intestinal parasites respond to different medications; some can be eliminated with a single dose while others require multiple treatments to eliminate, and reinfection is common. This complexity precludes administering universal deworming treat-

## Parasitic Infections and Vaccines: A Bibliography

Bassily S, *et al.* **Immunogenicity of recombinant hepatitis B vaccine among infants of mothers with active schistosomiasis.** *Am J Trop Med Hyg.* 1997 Aug;57(2):197-9.

**Study population:** 385 Egyptian infants born to HB-negative mothers

**Key findings:** Maternal schistosomiasis (n=191) had no effect on levels of anti-Hepatitis B antibodies in infants at 9 months following HB immunization at 2,4,6 mo.

Cooper, *et al.* **Albendazole treatment of children with ascariasis enhances the vibriocidal antibody response to the live attenuated oral cholera vaccine CVD 103-HgR.** *J Infect Dis.* 2000 Oct;182(4):1199-206. Epub 2000 Sep 08.

**Study population:** Ecuador (age range 6 – 13 years), n = 233

**Key findings:** Significantly greater rates of seroconversion and geometric mean antinbody titer in the albendazole group (in subjects with non-O ABO blood groups) as compared to placebo group. (Loss to follow up exceeded 50% in both groups, complicating the analysis of this data).

Cooper, *et al.* **Human onchocerciasis and tetanus vaccination: impact on the post-vaccination antitetanus antibody response.** *Infect Immun.* 1999 Nov;67(11):5951-7.

**Study population:** Ecuador (age range 5 – 80 years), n=193

**Key findings:** Concurrent infection with *O. volvulus* did not prevent the development of a protective antitetanus response, although heavier *O. volvulus* infections were associated with lower increases in TT-specific IgG levels.

Elias D, *et al.* **Effect of deworming on human T cell responses to mycobacterial antigens in helminth-exposed individuals before and after bacille Calmette-Guerin (BCG) vaccination.** *Clin Exp Immunol.* 2001 Feb;123(2):219-25.

**Study population:** Ethiopians (18-24 years old), n = 240

**Key findings:** BCG immunization resulted in significantly improved PPD responses (measured by T cell proliferation and interferon gamma production) in participants who were de-wormed prior to vaccination but not in the control group.

Ghaffar YA *et al.* **Hepatitis B vaccination in children infected with *Schistosoma mansoni*** *Am J Trop Med Hyg.* 1990; 43(5): 516 – 9

**Study population:** Egyptian male children (age range 8-12 years), n = 80

**Key findings:** Three months after vaccination, no difference in responders versus non-responders in otherwise matched children w/ and w/o *Schistosoma*-positive stool samples. At 9 months, control group had significantly higher percentage of responders, and higher levels of HBs antibody.

Kilian HD, Nielsen G. **Cell-mediated and humoral immune responses to BCG and rubella vaccinations and to recall antigens in onchocerciasis patients.** *Trop Med Parasitol.* 1989 Dec;40(4):445-53.

**Study population:** Liberian children, n = 629

**Key findings:** Conversion rate three months after BCG vaccination was significantly lower in children with onchocerciasis (48%) than in controls (85%).

Kilian HD, Nielsen G. **Cell-mediated and humoral immune response to tetanus vaccinations in onchocerciasis patients.** *Trop Med Parasitol.* 1989 Sep;40(3):285-91.

**Study population:** Liberians (2-29 years old), n = 326

**Key findings:** Diminished cell-mediated immune responses to tetanus toxoid immunization in matched vaccinees with and without onchocerciasis infection; no alteration in humoral responses between two groups.

Malhotra, *et al.* **Helminth- and Bacillus Calmette-Guerin-induced immunity in children sensitized in utero to filariasis and schistosomiasis.** *J Immunol.* 1999 Jun 1;162(11):6843-8.

**Study population:** Kenya, n=25 infants

**Key findings:** Mean level PPD-driven IFN- $\gamma$  at 10–14 mo of age was greater in BCG-immunized infants who were not sensitized to helminthic infection in utero ( $p < 0.01$ ).

Thanks to Guy de Bruyn, MBBCh and Allison Elliott, MD for their assistance in compiling this bibliography

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## ◀ **WIEGHING THE BURDEN OF DISEASE** *continued from 17*

ments to all volunteers.

The challenges do not end with efficacy trials. Phase III studies still represent a controlled environment compared to the “real world” in which a vaccine will be used. “In the context of a clinical trial, conditions like ulcerative STDs that could change vaccine efficacy will be checked for and treated—at higher than average standard of care. But this may not be how people who eventually get the licensed vaccine will get care,” says Nzeera Ketter, head of efficacy trials at IAVI.

Once a vaccine has shown efficacy in a large-scale trial, vaccine developers will devise follow-up “bridging studies” to learn more about vaccine

effects in populations with more complex health issues; bridging studies will also involve adolescents, who have different disease profiles and immune parameters than adults.

For now, scientists say that it is crucial to learn more about the potential confounding effects of coinfections. “It’s somewhat black box immunology,” says De Bruyn. “It’s very unclear what the immunological mechanism of helminth interference with vaccines might be, and whether this effect will be seen with AIDS vaccines. Then again, we’re still uncertain about what AIDS vaccine effects will be protective against infection.”◆

## ◀ **THERAPEUTIC AIDS VACCINES** *continued from 15*

Investigators are also looking at other novel strategies to try to augment any therapeutic vaccine-induced immune responses, and further innovations will probably be important. Cytokines are at the forefront now, but others like co-stimulatory signals may be beneficial, and again these approaches may well give indicators as to what’s required for a preventive vaccine response. Better understanding of the basic immunology governing these signals may increase their utility in the future.

### **Separate endeavor?**

Beyond the challenges that come with an established infection and a compromised immune system, is there going to be any qualitative scientific distinction between an effective preventive and therapeutic vaccine? Lifson says that “according to immunological dogma, in a therapeutic vaccine setting antibodies may play a helpful role but cellular responses are probably going to be more important. And although we don’t know how to achieve it with any of the current prophylactic vaccine immunogens, the data [in monkey models] for passive immunization with monoclonal antibodies suggests that you can achieve sterilizing protection with antibody.” But he adds the caveat that “there may be scientific differences [between therapeutic and preventive vaccines] but still there are no compelling data that tell you what you ideally would want to control the virus in one setting or another.”

In the absence of hard evidence, should the two approaches really be seen as distinct? “There shouldn’t be two fields, we should be trying to make an effective prophylactic vaccine and if it works, therapy may be an additional use of it,” says Moore.

Emini agrees: “Given the present state of knowledge, it seems likely that no distinction will exist between vaccine-elicited immune responses that may be effective in either a prophylactic or a therapeutic setting. Of course, the two settings are not identical, but there is a high probability that studies performed in one of these settings will substantially inform the other.” He also thinks that, given our current understanding, there is “nothing qualitatively different regarding the development of the immunogen itself in

terms of what you would do prophylactically or therapeutically.”

But some researchers give more weight to the suggestive evidence available so far, and think there might be important distinctions to be drawn between preventive and therapeutic vaccine approaches. McMichael emphasizes that a therapeutic vaccine will “need to stimulate T-cell immunity rather than antibody immunity, which is probably different from what you need to do for prophylactic immunity,” and points out that cell-mediated immunity “is a major player in controlling infection for 10 years in people who are untreated,” referring to the isolated cases of long-term non-progressors who are infected but show little sign of disease.

Robinson thinks that inducing CD4<sup>+</sup> helper T cells will be the crux in distinguishing the two. “The difference is that the preventive [vaccine] is going to be able to use the normal mechanisms that a host has for providing CD4 help, but a therapeutic [vaccine] is going to have to use novel mechanisms for providing the CD4 help,” referring to the innovative strategies like cytokines that are still in early assessment.

### **A whole new paradigm**

Most researchers are unconvinced that a highly effective therapeutic vaccine that will significantly improve HIV-infected patients’ disease progression can be developed. However, that doesn’t mean they think the effort will be fruitless. Given our lack of understanding of the basic biology of HIV disease, a therapeutic vaccine may perhaps turn out to be feasible. And it’s still not clear that the search for a preventive and a therapeutic vaccine are separate endeavors; lessons learned from one setting will most likely benefit the other.

Still, most researchers agree that developing a therapeutic AIDS vaccine is a much more difficult undertaking than a preventive one. As Pomerantz points out, “there is no such a thing as a therapeutic vaccine in any infectious disease, we’ve never made one. So we’re not only designing a new vaccine, we’re designing a whole new paradigm. It’s a tall order.”◆

# TO OUR READERS: A FAREWELL

BY PATRICIA KAHN

I'm writing to say adieu from my perch at the IAVI Report. In August 2003, after three years as editor of the newsletter, I left IAVI to resume freelance writing, editing and teaching. My successor at the Report is Simon Noble, a virologist by training and most recently an associate editor at *Nature Medicine*, where he was responsible for selection of the journal's AIDS-related research papers (among many other topics). Simon will write to you separately in the next issue. Suffice it to say that he and the Report team will continue to bring you news and analysis of the global AIDS vaccine effort, through the vehicles of the newsletter (and *VAX*, its new sister publication for non-technical audiences), Clinical Trials Database and revamped website.

As I thought about what to write in taking leave, I've been leafing through past issues of the Report. What struck me was how they reflect a clear dichotomy in the field, one that has become more pronounced as the afterglow of the landmark Durban conference in July 2000 gave way to both an expanded global vaccine effort and some familiar frustrations in moving forward.

Leaving Durban, it was hard not to feel a heady sense of optimism that maybe, finally, the world would commit to a comprehensive response commensurate with the scale of the epidemic and its devastating consequences. Some of that optimism extended to vaccines, where things were looking up after many long, slow years. The development pipeline was beginning to expand and diversify; a ramped-up, more internationalized effort was taking shape; and vaccines were increasingly being seen as a key weapon in the fight against AIDS, rather than as a backwater populated mostly by scientists from developed countries. And the tendency to pit prevention and treatment against each other, branding the former more "cost-effective," was starting to abate as recognition grew that the two are inextricably linked.

It's heartening that most of these trends have continued since Durban—although more would certainly be better. But in other crucial areas, progress is excruciatingly slow. One huge uncertainty concerns the basic premise behind nearly all candidates now in the clinical pipeline: that vaccines which fail to block infection but can suppress viral load will delay HIV disease and reduce transmission significantly. Until efficacy data on one or more good candidate tells us whether this concept holds water—data we won't have for at least another four years—the entire crop of current candidates is essentially stuck in limbo.

At the same time, there's been little headway made on most of the longstanding scientific challenges to AIDS vaccine development—with the result that there's no new generation of candidates (based on different concepts) poised to enter the pipeline any time soon.

The list of these obstacles is well-known, but I'll mention two that are crucial for designing this next generation of products, however long it may take.

One is to figure out how to induce broadly neutral-

izing antibodies, which will hopefully yield candidates able to block HIV infection. It's a goal that continues to elude vaccine developers, although efforts and progress are now clearly accelerating.

Another is to determine whether immune responses at key mucosal sites are among the long-sought correlates of protection. Mucosal tissues are not only ports of entry for HIV (via the genital tract in sexual transmission and the gut in breastfeeding), but also key targets: the gut is home to the vast majority of the body's lymphocytes (as compared with about 2% in blood) and is a primary site of both HIV replication and early pathogenesis, regardless of initial infection route. So a vaccine that prevents HIV from establishing a beachhead at crucial mucosal sites might profoundly impact the course of HIV infection. Yet, while the issue of mucosal immunity is often raised on vaccine agendas, it tends to be quickly dismissed for a well-worn (albeit valid) list of reasons, from the difficulties of evaluating mucosal responses in humans, especially in a clinical trials context, to a lack of information on which (if any) mucosal sites and responses really matter and which vaccine designs and delivery routes best induce them.

It goes without saying that big issues loom beyond the science, such as creating the right context for vaccine efficacy trials in developing countries. These trials represent an important opportunity to help shore up local capacity to provide AIDS testing and counseling and other prevention services, along with treatment and improved healthcare (see article on page 1). Seen another way, unless they do, it will prove difficult to raise the local support without which these trials cannot succeed.

That brings us back to the issue of commitment and where we are today. Clearly one of the greatest post-Durban disappointments is that the global response has not matched the high hopes this conference generated. While potentially groundbreaking programs and proposals are in the air and prices for ARVs (antiretrovirals) have plummeted, severe underfunding and other obstacles mean that little has changed at the bottom line: for example, no more than 2% of people who need immediate ARV treatment in Africa are now receiving it. So it also goes with vaccines (and microbicides, and other elements of the response to AIDS), where the level of resources remains far below the needs.

Helping to close this gap is one place where news and information have a critical role to play. On that note, I leave with a profound sense of gratitude for the support we at the *IAVI Report* have received—from our readers, whose interest in the publication has sustained it; from the many people in the field who shared their insights, experience and (often unpublished) data with us; and to IAVI, for supporting a unique operation dedicated to collecting first-hand information on AIDS vaccine development. It has been immensely humbling and inspiring to bear witness to this global battle which, difficult and discouraging as it is, we can't afford to lose. ♦

## IAVI Report

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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.

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# vaccine BRIEFS

## IAVI AND INDUSTRY/ACADEMIC PARTNERS BEGIN TWO PHASE I AIDS VACCINE TRIALS IN DECEMBER

IAVI, in partnership with industry and academic research centers, began two separate AIDS vaccine human trials in December 2003. The trials were designed to test two distinct investigational vaccine products for the prevention of HIV/AIDS in non-infected individuals.

The first trial is a collaboration of IAVI and the Aaron Diamond AIDS Research Center (ADARC), an affiliate of Rockefeller University. The vaccine being tested is a new DNA vaccine called ADVAX and contains genetic material from clade C, the most prevalent HIV strain in the world. Clade C HIV is largely distributed in China, India and in sub-Saharan Africa. This Phase I trial will involve 45 healthy non-infected volunteer men and women over the next few months and will test the safety and immunogenicity of the vaccine. ADARC and IAVI have agreed that if ADVAX proves effective, it will be made available in developing countries at reasonable cost.

The second trial is currently underway in Belgium and soon to be in Germany, and is a collaboration of IAVI, Targeted Genetics Corporation and Columbus Children's Research Institute. This candidate vaccine, called tgAAC09, containing clade C HIV sequences, uses Targeted Genetics' rAAV (recombinant adeno-associated virus) and is designed to elicit both humoral and cell-mediated responses. In studies to date, non-human primates that received the rAAV-based vaccine showed robust and durable antibody and T-cell responses, and also had reduced viral load when challenged with a virulent strain of SIV, the non-human primate equivalent to HIV.

## MERCK AIDS VACCINE RESEARCHER EMILIO EMINI JOINS IAVI

In January Merck's Senior Vice President of Vaccine Research, Emilio Emini, PhD, joined IAVI as Senior Vice President and Chief of Vaccine Development. Emini will spearhead IAVI product development activities and lead efforts to accelerate the most promising of these candidates into large-scale efficacy trials and eventual licensure. During his 20-year tenure at Merck, Emini helped lead the company's AIDS vaccine program that brought several candidates into human trials and is currently focused on a candidate based on the replication-incompetent adenovirus (Ad)-5 vectors. Ad-5 candidate vaccines are currently being tested both alone and in combination in several ongoing clinical trials. Emini also led the Merck team that developed Crixivan (indinavir), the first protease inhibitor, a potent antiretroviral therapy against HIV.

## CHIRON STARTS PHASE I AIDS VACCINE TRIAL

On 15 January, Chiron Corporation announced the initiation of its first Phase I clinical trial of a preventive AIDS vaccine strategy. The study, HVTN 049, will be conducted by the US HIV Vaccine Trials Network (HVTN); it is funded by the US National Institute of Allergy and Infectious Diseases (NIAID) and Chiron. The trial will evaluate the safety and immunogenicity of a prime-boost strategy. The DNA priming immunization consists of clade B *gag* and *env* plasmids delivered in cationic poly(lactide coglycolide) (PLG) microparticles. The study will boost with a novel oligomeric, V2-deleted gp140 with an MF59 adjuvant (used in an influenza vaccine licensed in Europe) designed to enhance the production of broadly neutralizing antibodies.

## VAXGEN ANNOUNCES RESULTS FROM THAI AIDS VAX TRIAL

On 12 November 2003, VaxGen announced the preliminary results from its randomized, double-blind, placebo-controlled Phase III clinical trial in Thailand to evaluate AIDS VAX B/E, an investigational vaccine (monomeric recombinant gp120) for the prevention of HIV infection. The study of 2,546 injecting drug users found that the vaccine offered no protection from HIV infection or disease. The North American and European Phase III trial of a highly similar candidate also found no overall protection. Thailand recently launched another Phase III trial that will test AIDS VAX B/E together with the canarypox candidate ALVAC vCP1521 in a prime-boost regimen (see below).

## THAI PRIME-BOOST TRIAL LAUNCHES AMID CONTROVERSY

On 29 September 2003, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) launched a Phase III efficacy trial in 16,000 volunteers of a prime-boost regimen consisting of AIDS VAX B/E and Aventis Pasteur's canarypox candidate ALVAC vCP1521 in Thailand. The US\$119 million trial has since been the subject of criticism from a group of prominent scientists, including HIV co-discoverer Robert Gallo. Writing in the 16 January issue of the journal *Science*, the group expressed concern over the trial saying that while the original aims of the trial "remain fundamentally worth addressing, [they] doubt whether these immunogens have any prospect of stimulating immune responses anywhere near adequate... [to] prevent infection and/or lead to the immune control of HIV-1 replication postinfection."

The prime piece of the vaccine is the canarypox vector ALVAC from Aventis Pasteur, which these critics claim is "poorly immunogenic" as determined in "multiple Phase I and II clinical trials. The AIDS VAX gp120 component has shown no efficacy to date in two independent Phase III trials in the United States and Thailand." Dr. Prasert Thongcharoen, chairman of the Thai National AIDS Commission's subcommittee on HIV Vaccine Development, told the *Associated Press* that their aim in this trial is to test the effect of the two vaccine components in combination.

John McNeil of the Walter Reed Army Institute of Research and a key player in the current Thai trial, told *Science* last November that in small human trials, the prime-boost approach has triggered a "much broader" immune response expanding HIV-specific CD4<sup>+</sup> T helper cells. NIAID is preparing a formal rebuttal to the letter for publication in *Science*.