# Full of sound and fury, but signifying something:

XVI International AIDS Conference,
Toronto, Canada, August 13-18, 2006

The biennial AIDS conference is often exhausting and irritating, but it offers a unique view of how science and society interact. It still deserves the support of basic scientists.

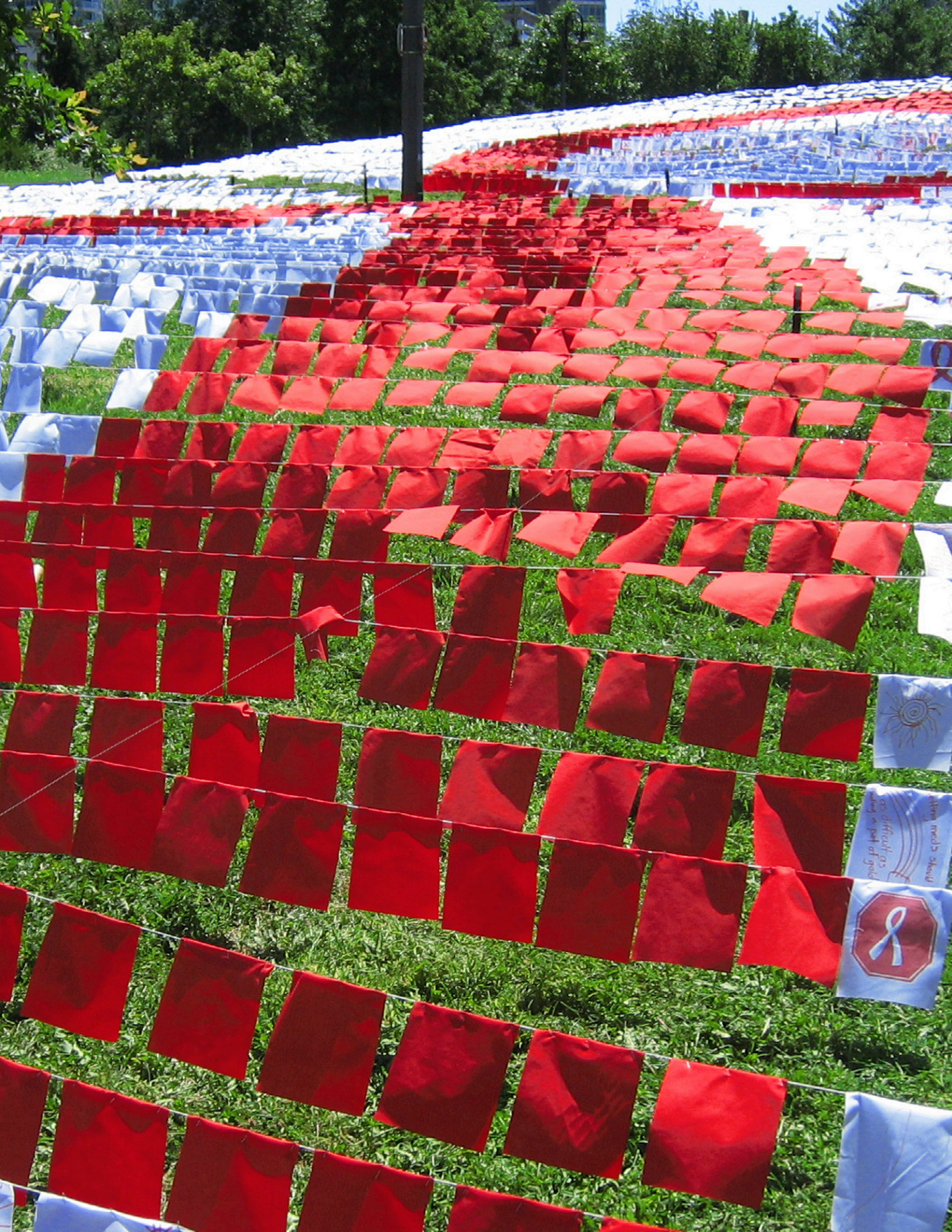
BY WILLIAM A. WELLS

For those seeking exposure to pure science, there are many reasons not to attend the circus that is the biennial AIDS conference. Some distractions are at least entertaining: Buddhist monks looking lost; a self-declared Prince from Nigeria; a posse of African grannies sponsored by Stephen Lewis (the UN special envoy for AIDS in Africa); and a fashion exhibit of dresses made entirely of condoms. Others—such as the four-hour wait to register, self-serving speeches by ministers of health, activists popping up on stage like yo-yos, and Clinton-related mobs—are more irritating.

Yet researchers willing to embrace the event in all its craziness are exposed to a richness of experience—and an intertwining of science and society—that cannot be had at any other science-related conference. "For basic science, I couldn't say it's better than going to a focused meeting," says Michael Tremblay (McGill University, Montreal, Canada). "But here it's important because the entire planet is talking about HIV/AIDS."

## The evolution of a conference

In the last 25 years, 25 million people



## The ABCDEFGHI of prevention

Dutiful applause breaks out regularly at AIDS conferences in response to expected platitudes. But the applause for Gita Ramjee's concluding statement was both heartfelt and hopeful. Ramjee (South African Medical Research Council, Durban, South Africa) was part of a session on HIV prevention, a field in which the mantra has been ABC for abstinence, be faithful, and use condoms. It has not been enough.

Fortunately, said Ramjee, there are other hopes on the horizon. "I would like to believe that HIV prevention soon will be more than ABC," she said. "We will add one more C for circumcision. We will add D for diaphragm, E for exposure prophylaxis, F for female-controlled options [such as microbicides], G for genital tract infections, H for HSV-2 suppression, and I for immunity, using vaccines."

Cue the applause. The focus came back on prevention for this conference because, as Kevin De Cock (director of the World Health Organization's Department of HIV/AIDS) said, "We can't treat our way out of this epidemic. We need to use our treatment successes to enhance prevention." And ABC has fallen short, said Cristina Pimenta (executive director of the Brazilian Interdisciplinary AIDS Association), because these approaches rely on "pure, individual responsibility" in an environment where vulnerability is "a product of social and economic exclusion." This is especially true for women, who need prevention methods that are under their own control.

**"SEX NICE, but de AIDS ting..."**
[from a T-shirt worn by a delegate from Montserrat, a tiny Caribbean nation]

The "I" in Ramjee's list is arguably most distant (see *The ultimate hope*), but there was encouraging news about many other prevention approaches. In one South African trial, circumcision reduced the risk of HIV infection by 60%. Also promising is the reported safety of using a single AIDS drug called tenofovir as a possible daily prophylactic. Efficacy is yet to be shown for this approach, because the education efforts in the first trial were so successful that they reduced new infections in both the treatment and control arms. Results are expected in 2007 for trials investigating the efficacy of diaphragms, HSV2 suppression, and so-called first generation microbicides.

The greatest hope is being put on microbicides, either applied directly or via long-acting vaginal rings. The first generation agents are primarily polymers that block surface attachment of viruses, but there is greater excitement about gel formulations of antiretroviral drugs. John Moore (Weill Medical College of Cornell University, New York, NY) has shown significant protection with microbicides in macaque trials, even when the monkeys were challenged several hours after microbicide application. Eventually, he said, the right mix of antiviral agents will emerge for microbicides as it did for systemic treatment of AIDS. "The case for combination microbicides, in my view, is absolutely obvious and almost inarguable," he said.

Pimenta sounded a note of caution, however, regarding "the present tendency to see biomedical interventions as quick technological, magical solutions to HIV/AIDS prevention." As with antiretroviral treatment, getting any given technology to the masses will be perhaps the greatest challenge of all, especially when the target audience is all of humanity. JEM

**Strike a pose.** Condom dresses designed by Brazilian Adriana Bertini were a sensation, but getting people to use condoms for HIV protection remains a challenge.

have died of AIDS, and approximately 40 million now live with HIV. Every day, an estimated 11,200 people are infected and 8,000 die. Although 1.65 million people are now receiving antiretroviral treatment, 70% of those in need still lack drugs. The epidemics that are most out of control are among intravenous drug users (especially in Eurasia), men who have sex with men (everywhere), and the generalized epidemic in sub-Saharan Africa.

The AIDS meeting is one response to this epidemic. From its humble beginnings in 1985 as a small scientific gathering, the conference has grown to a complex mixture of ~24,000 participants, including basic scientists, clinicians, epidemiologists, behavioral scientists, politicians, activists, and many who implement prevention and treatment programs in both developed and developing countries. Also present are 3,000 journalists from over 100 countries (see *Should journalists question science?*). At any one time there can be 12 concurrent sessions, official press conferences (three per hour, every hour), "global village" events put on by nongovernmental organizations (NGOs), and activist events.

The activists in particular can get creative. The threat of protests kept representatives of the drug company Abbott from manning (or even constructing) their intended booth at the conference. Activists were more than happy to take over the prime real estate, with a banner declaring "Abbott: Your booth is as empty as your promises." The group was protesting Abbott's pricing policy for Kaletra (lopinavir/ritonavir), a two-in-one, once-a-day pill that can be stored at room temperature and is thus perfect for developing country conditions.

Less raucous groups tried to get attention by forming Global Coalitions for Just About Anything You Can Imagine. (Right now, someone is preparing a PowerPoint slide in which they incorporate GCJAAYCI, which they will use happily without explaining what the acronym stands for. The only people who like jargon more than scientists are, it turns out, international policy professionals.) These groups vie with each other for more attention using seminars, press conferences, voluminous reports, and declarations.

This circus-like atmosphere was one

Just as the politicians have come, so have the researchers left

**The Bill effect.** Billionaire philanthropist Bill Gates and ex-President Bill Clinton both drew attention to new prevention technologies (left), and increased the general level of chaos (right).

reason that the International AIDS Society (IAS) created a second conference: the IAS Conference on HIV Pathogenesis, Treatment, and Prevention. This science- and clinical-only event is now held in odd years (the fourth will be next year in Sydney, Australia), whereas the original all-inclusive AIDS conference is held in the even years. The latter conference remains unique, as only here does science meet policy. Basic science is needed at both conferences, said IAS president Pedro Cahn, because it progresses more rapidly than the social science and field implementation.

But the adoption of a research-only conference may have accelerated the exodus of basic science from the original AIDS conference. Even outside of conferences, HIV scientists are constantly bombarded by interview and public speaking requests, and the opportunity to escape from the policy babble has been irresistible for some. By the 2004 Bangkok AIDS meeting, the reporter Laurie Garrett was declaring in the *New York Times* that the conference content was "the worst science ever presented at an AIDS meeting" with "top HIV laboratory researchers…finding it irrelevant." David Ho, director of the Aaron Diamond AIDS Research Center (New York, NY) chose not to attend this year because of the "general lack of new science" and a vaccine meeting occurring soon afterwards. "True or not," he said by email, "the general perception is that the meeting now serves a different purpose, which is to address policy and social sciences in the field. It is not regarded as a scientific or clinical meeting any more."

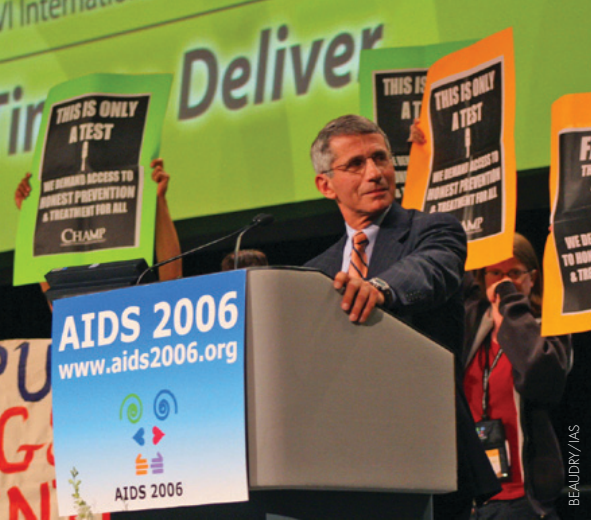
Even some of the researchers who attended agreed with this statement. Kelly MacDonald (University of Toronto, Canada) points out that the largest number of basic researchers are based in the United States, and yet the AIDS conference is never held in the US because US immigration policies restrict entry of HIV-positive individuals. That makes any AIDS meeting an expensive international meeting for US researchers. Adding that factor to all the others, she says, "This is dying as a basic science meeting."

## And yet...

It is certainly easy, with policy posturing getting more of the headlines than science, for the conference to be maligned. The local *Toronto Star* newspaper welcomed delegates with a cover story about the "AIDSerati" (Bill Clinton, Bill Gates, and friends), and then featured a piece by right-wing think-tanker Michael Fumento. According to Fumento's finely reasoned article, the whole thing is overblown. After all, a very early prediction of 50 million AIDS deaths in Africa by 2005 had never come to pass—it turned out to be only 20 million. Perhaps this is why Canadian Prime Minister Stephen Harper declined the conference invitation, choosing instead to tour a military base north of the Arctic Circle.

But as the *Toronto Star* and the rest of us observed the conference in action, it was hard not to be inspired, and on several levels. First, there was the fascinating assortment process by which issues and agendas were prioritized. The most obvious case of this prioritization was the consensus on the number one message from the conference. Like a jealous gaggle of fashion designers who somehow all end up showing aubergine-colored outfits for their Spring collection, the 24,000 participants interpreted this conference's generic official theme of "Time to Deliver" as requiring a renewed emphasis on prevention and new prevention technologies (see *The ABCDEFGHI of prevention*).

This process is not only intriguing in its own right but clearly relevant for the researcher wondering where the funding tides will turn to next. Is his or her general area now the hit of the year, and, if not, why not? Policy debates also address more nuanced questions, such as which drug classes are most in need of further research, based on feedback from the field on resistance, prices, licensing difficulties, or dosing difficulties.




**He's seen it before.** Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, waits out a protest.

The emphasis on new prevention technologies has also resulted in stronger connections between researchers and field workers, as the researchers rely on the field workers to explain how communication strategies can be best used in prevention campaigns to increase compliance. "There is a new engagement, and I think it is very encouraging," said David Cooper (University of New South Wales, Sydney, Australia). "It's very different from clinical trials where the science of clinical trials was well-known before HIV."

Interaction is also fostered by the shift from in vitro to patient studies, many of which are based in developing countries where NGOs may be important actors in the healthcare system. The early years of HIV research were concentrated on understanding the actions of individual HIV genes as revealed by in vitro assays. The newer research is focused on the immunological response to the virus. It was not always clear whether the conference was helping funnel community concerns from the field to those carrying out these studies in developing countries (see *Science on safari*), but at least the potential for interaction was there.

The connections to policy debates may be more obvious for clinical researchers, but there are other benefits for basic researchers. The conference gives everyone license to think not just about details of data but also more broadly about strategy. "It's getting so focused doing basic science," says Tremblay. "When you are always working in the same strain… maybe you are missing something."

### Keeping them honest

The presence of activists and scientists in one place results in a dialogue that "is very helpful both ways," said Sharon Lewin (Monash University, Melbourne, Australia). "Basic scientists need to know what is important globally. What we probably don't do well is to make [scientists and activists] intelligible to each other."

Ideally, those who wander into the universe of basic science can bring a refreshing change in perspective. One researcher presented a study on virus entry into (and inactivation by) oral epithelial cells. It was a nice piece of science but somewhat shrouded in talk of monolayer cultures and markers of transcytosis pathways. Then came the questions—most from scientists and some from nonscientists. An audience member who appeared to fall into the latter camp asked, "What happens when you add virus-infected breast milk?" The researcher seemed amused by the naïveté of the question. But the facts in the field are simple: we know that HIV does not appreciably infect via the oral route except in babies receiving infected breast milk. In this context, the simple question was the only relevant question.

Other questioners were more direct. After a presentation by a student whose ample enthusiasm was not matched by his

## Science on safari

Forget the occasional PCR machine sent to a random African country. Finally, with AIDS, real scientific alliances are being formed between research efforts in developed and developing countries.

Studies require numbers. The efficacy of a prevention technology can only be shown by contrasting the treatment arm with a control arm in which there are many new infections. The bulk of those new infections are in developing countries and so the bulk of the research is there too. It is from the developing world that we are seeing results on preexposure prophylaxis, vaccines, microbicides, and prevention of mother-to-child transmission.

There are many benefits from these collaborations. Researchers from developing nations have a greater presence at the AIDS conference than at probably any other major scientific meeting. And the prevention trials are happening in countries that need the successful products most. "What we are measuring is not efficacy but effectiveness—with the real constraints" of incomplete compliance in community settings, said Quarraisha Abdool Karim (Columbia University, New York, NY).

But clinical research does not translate seamlessly to a new location. In early trials, detailed investigations showed that "there was no way that placebo was understood," said Charles van der Horst (University of North Carolina, Chapel Hill, NC). With pictures and practice, "I think it is possible to get informed consent," he said, "but you have to work hard at it."

Other challenges come from the trial designs being too successful. Ethics require all prevention researchers to give those in both treatment and placebo arms the best in prevention counseling. As a result, "across almost all prevention trials… the incidence rates drop dramatically," said Karim. "So we have to do much bigger trials." If more prevention technologies are approved for use, this "problem" will only increase for future prevention and vaccine trials.

The need to integrate different prevention methods is clear, said Renee Ridzon of the Bill and Melinda Gates Foundation. "None of the prevention methods will be 100% effective," she said. "They all need to be used in the context of other prevention methods." That will increase the concern about risk compensation—the increase in one unsafe behavior (e.g., sex without a condom) in the mistaken belief that another prevention method (e.g., tenofovir prophylaxis) will take care of all risk. This concern holds for all prevention methods, but the criticism has been leveled primarily at those doing the tenofovir preexposure prophylaxis (PrEP) trials. "I think it's highly unfortunate that PrEP has been singled out," said Joep Lange (University of Amsterdam, Netherlands). Microbicide and vaccine trials are not held up to same standard, he said, probably because the backgrounds of most AIDS activists are in drug treatment. JEM

clarity, an audience member observed: "You mentioned several times that this was very exciting. Why?" For Killian O'Brien of AIDS Calgary (a service organization), his impatience with impenetrable science in a vaccine session was phrased more urgently. "I'm sure all this science stuff is very important," he said, shaking with nervousness. "But I'd like something to bring back to my clients. Sometimes we need straight English."

Some jargon will always be needed to communicate ideas that are buried deeply in a complex technological landscape of ideas. But that jargon need not preclude understanding by others. The AIDS conference featured perhaps the most science-literate nonscientists in the world—activists who tossed around names of cytokines and cell surface markers without a second thought. In O'Brien's defense, I was completely stumped by most of the talks in the session that prompted his comment.

"We adopt jargon far too much," agreed Kelly MacDonald, who chaired the symposium in question. With fewer big name scientists attending, the talks are often left to students, and many of them had clearly had insufficient guidance from their supervisors. "The [conference organizers] have set up for people to get tips on presentation… but the uptake has been very low," said MacDonald. "We're making this field completely inaccessible."

Restoring that access is vital both for the HIV/AIDS community and for the research community in general. Marilyn Chase of the *Wall Street Journal* captured very well the unique nature and social impact of what is now undeniably an HIV/AIDS industry:

> *"AIDS has, in a way, changed everything. It's changed the way we look at disease and its spread. It's changed the way we look at research, how research is conducted, how we share the fruits of that research with the people who volunteer for studies, how the developed world shares with the developing world. It's changed the way we look at treatment—its development, its pricing, its evolution, the way it's administered. It's changed the way we think about access to care. … AIDS, in short, is a kind of crucible in which old protocols and assumptions are melted down and remade."*

This remaking is one justification for the size of the AIDS industry. Other diseases are also important, but it is on the back of AIDS interventions that the possibilities of healthcare in developing countries are being redefined. Surely the scientific community should contribute to (or at least be aware of) this process?

The AIDS meeting is a place where researchers can witness, in one place, the winding path from basic discovery through clinical research to clinical impact in both familiar and less familiar environments. For those who are perceptive, it can give clues about how society prioritizes or fails to prioritize a particular research direction. At any one time there is at least one session that is purely basic science (see *Tidbits from Toronto*). The rest—the surrounding chaos of human contention—may not change the experiment that gets done tomorrow, but its long-term impact on personal motivation and research strategy should be profound. JEM

## Tidbits from Toronto

Some talks didn't necessarily fit into a big global picture, but nevertheless included some intriguing science. A few examples are outlined below.

**Receptor plus drug = entry**

Among the more recent anti-HIV drugs are the entry inhibitors, which block HIV from using its coreceptor CCR5 and thus keep the virus outside the cell. The viruses that escape from this inhibition do so by using a composite CCR5-plus-inhibitor complex as a key to entry, reported Pavel Pugach (Weill Medical College of Cornell University, New York, NY). Not just any CCR5 ligand will do, however. The mutant virus can actually be blocked from entering by the addition of RANTES, which is the usual ligand for CCR5 but has a different shape than the inhibitor drug.

**Prevention antibodies**

Tanawan Samleerat (Chiang Mai University, Thailand; and François Rabelais University, Tours, France) confirmed that the risk of mother-to-child transmission is far lower when mothers have neutralizing antibodies to HIV. This is one more hint that antibodies to HIV are not completely impotent.

**One virus begets another**

Infection with Herpes simplex virus type 2 (HSV2) is common and is associated with a threefold increase in HIV susceptibility in women, although many never experience genital ulceration. Anu Rebbapragada (University of Toronto, Canada) suggested that other, molecular factors may explain the increased susceptibility. She found that HSV2-infected female sex workers had more target cells for HIV infection: a 10-fold increase in DC-SIGN$^+$ immature dendritic cells and a threefold increase in CCR5$^+$ CD4$^+$ T cells. Thus, microbicides that target DC-SIGN and CCR5 may be particularly effective.

**A proxy for destruction**

Human endogenous retrovirus (HERV) sequences may help keep immune reactions to HIV alive, said Keith Garrison (University of California, San Francisco, CA). Garrison looked at regions of similarity between HERV sequences, which make up approximately 8% of the human genome, and HIV. Early during HIV infection, there were immune responses to these regions of similarity—probably because of immune reaction to HIV itself. But later there also arose immune reactions to the parts of HERV sequences that are dissimilar to HIV, indicating that the normally dormant HERV sequences had been reactivated. This is not surprising: HIV brings along the vif protein; vif inactivates APOBEC3G; and inactivated APOBEC3G can no longer suppress HERV sequences. The reactivation may also be of some use to the host, as it marks the cells containing HIV. The HIV epitopes mutate to escape immune attack, but HIV-infected cells will still be marked by invariant HERV peptides. If those peptides are truly specific to HIV-infected cells, they might make a good target for a vaccine. JEM

## Should journalists question science?

So many of the academic musings at an AIDS conference have life and death implications, and the session on "responsible journalism" was no exception. The underlying question, said Daniel Kuritzkes (Brigham and Women's Hospital, Boston, MA), was simple: "At what point can scientific controversies be considered settled?" The context was AIDS denialism—proposals such as those by Peter Duesberg (University of California, Berkeley) that HIV does not cause AIDS and by the Perth group (www.theperthgroup.com) that HIV may not even exist. As John Moore (Weill Medical College of Cornell University, New York, NY) stated: "This is dangerous stuff. AIDS denialism kills."

All participants agreed on this statement and its underlying logic: public doubt about links between HIV and AIDS have caused countless people to have unsafe sex, stop taking life-saving antiretroviral drugs, avoid getting screened for HIV, and avoid taking drugs to prevent mother-to-child transmission of HIV. The consequences have been the worst in South Africa, where HIV prevalence is now 30% among mothers attending antenatal clinics, and only approximately one in five of those who need antiretroviral drugs can get them.

In South Africa, President Thabo Mbeki and Health Minister Manto Tshabalala-Msimang have been criticized for their very public doubts about HIV's importance and the efficacy of antiretroviral drugs, and the vocal vitamin proponent Matthias Rath has loudly declared antiretrovirals to be toxic and multivitamins to be the correct solution to AIDS. The South African NGO Treatment Action Campaign (TAC) has led the fight against the government and Rath—in Toronto TAC stormed South Africa's exhibit to protest the display of garlic, beetroot, and lemon (a mixture often promoted by the health minister) alongside antiretrovirals.

> Scientists must be challenged, but not at the expense of accepted theories.

For the South African journalists on the panel, the question was how to cover this story without making things worse. "Does balanced reporting mean you give the lunatic fringe equal weight or rights—do they have right to reply?" asked Tamar Khan, from South Africa's *Business Day*. "[With] the AIDS dissidents… we don't cover blow-by-blow every activity they do. We try to be selective. But when these people are given an audience by your health minister, your readers need to know that."


**Imperfect messengers.** Occupants of the bustling press room at the AIDS conference must decide how much to challenge HIV researchers.

The evidence presented by the denialists is flimsy, according to Moore. They cite old, long-refuted papers, cherry pick data, use the evolution of scientific knowledge as evidence of errors, claim that acceptance of any research grant betrays a fatal bias in favor of the granting agency, and claim false affiliations to institutions that have long disowned them.

But the case is made worse by some journalists. Cited prominently was a recent *Harper's* article, which is the latest attack on AIDS researchers by long-time activist reporter Celia Farber. The view from South Africa on this work was clear. Most at fault are "journalists who think that by doing a few hours of research on the Internet they can overthrow… millions of person-hours of research done by scientists," said Nathan Geffen, policy coordinator at TAC. "That is a failure of ethics. That's an arrogance."

"Is it really the role of the media to challenge scientific consensus?" he continued. "Does the media have the expertise to challenge the scientific consensus? In my view, it doesn't."

This blanket statement drew a caution from Richard Horton, editor-in-chief of the *Lancet*. "Science is treated as truth—that anything that's published in a journal has to be right," he said. "That's wrong. We publish stuff that's wrong every day." Without a critical media, he said, the scientific establishment can be let off the hook in a way that no other group ever is.

The last word came from the journalist Laurie Garrett. "A lot of science writers do overly rely on the journals and basically translating things straight from the journals without much critical analysis," she admitted. But she sympathized with Geffen's description of "utter drivel that's published daily" in South Africa. "For us in North America, it's almost an intellectual debate," she said. But at the conference "we're trying to globalize this discussion and take it out of the comfortable place of Toronto into something larger"—into a place where it is a matter of life and death. JEM


**Down with Manto.** Activists take the stage during a session on "The Price of Inaction" to protest the policies of South Africa's health minister.

# THE ULTIMATE HOPE

"An AIDS vaccine is the only tool that can end the pandemic," said Seth Berkley, CEO and president of the International AIDS Vaccine Initiative (IAVI). As Berkley explained, the costs for antiretroviral treatment in developing countries will reach $3–9 billion per year for 2007, so a gigantic effort to develop a vaccine is certainly warranted.

The gigantic part, at least, is coming to pass. The effort is so large that it doesn't even need the word "vaccine" to be instantly recognized: it is called merely "The Enterprise." More formally it is the Global HIV Vaccine Enterprise, which acts as an umbrella for IAVI, CHAVI (Center for HIV/AIDS Vaccine Immunology; funded by the NIH), and the CAVD (Center for AIDS Vaccine Development; funded by the Bill and Melinda Gates Foundation). IAVI was founded in 1996 but its new friends are larger in dollar terms: CHAVI grants could total $300 million over 7 years, and CAVD recently announced its 16 grants totaling $287 million over five years.

**The general.** A lot of money and hopes are riding on the efforts of Barton Haynes, director of CHAVI.

Many observers are worried when the Enterprise is talked about in terms of simple engineering. But, said CHAVI director Barton Haynes, "we're not a Manhattan Project—theirs was a technical issue. We have to define the enabling technology." José Esparza, senior advisor on HIV Vaccines at the Bill & Melinda Gates Foundation, is also quick to reassure that more diverse lines of research will not be lost. "[The Enterprise] does not replace the creativity of individual investigators but tries to complement it," he said.

## Will science be heard?

Money does not guarantee success, however. "Up to now, the design of vaccine candidates has been mostly empirical design without enough scientific rationale," said Francoise Barré-Sinoussi (Institut Pasteur, Paris, France). The new consortia include their fair share of common facilities aimed at streamlining the empirical testing of vaccines, but they also include many projects aimed at generating new ideas. CHAVI investigators, in particular, are putting a great deal of effort into understanding the initial immune response to HIV. "By the time the immune response gets going," said Haynes, "there is such a reservoir of integrated virus and depletion of central memory cells that the battle is lost." He hopes that a vaccine that accelerates the early immune response might conquer the virus before it conquers the immune system.

Perhaps the biggest challenge is the lack of understanding about what kind of immune response is needed. "You don't have people that are infected and then cured," said IAVI's Berkley. "We don't have that natural model." There is even concern about activating the immune system too much (see *Too much of a good thing*). In one vaccine session a questioner noted that our best example of the control of HIV-like viruses is in certain monkey species, but even then the result has been a peaceful stalemate rather than victory. "How tremendous is the challenge to have [T cells] and antibody do something that evolution has not been capable of over thousands of years," he said.

> Developing an HIV vaccine is all the more difficult when we understand so little about the immune response to HIV.

The number of vaccine trials is increasing sharply, and some themes have emerged. It is probably better to present multiple HIV proteins and to stimulate both B and T cell responses. But vast gaps in the underlying immunology remain. Some of the approaches to this that were covered at the conference are described below. Based on the conference proceedings, it appears that knowledge about the immune response to HIV is still fragmented. Comprehensive surveys of all HLA types, all HIV peptides, and a wide range of immune responses (B cell, T cell, innate, and all their molecular subdivisions) need to be systematically correlated with resistance to infection, and speed of disease progression. In facing a question of such monumental importance, piecemeal studies are tantalizing but not enough.

## Models: HEPS, LTNPs, and macaques

If we made a successful vaccine, what would the winning immune reaction look like? Clues about these so-called "correlates of protection" come from various sources, including animal models, and people who are either highly exposed but persistently seronegative (HEPS; e.g., sex workers who have unprotected sex but remain uninfected) or long-term nonprogressors (LTNPs; people who are infected with HIV but do not succumb to AIDS).

Hope for an HIV vaccine got its biggest boost back in 2000 when macaques were protected from infection by infused antibodies. (The challenge virus was SHIV, which is based on simian immunodeficiency virus (SIV) but has the Env coat protein from HIV.) Ruth Ruprecht (Harvard Medical School, Boston, MA) emphasized that such primate models for immunization protection must mimic the process of human infection as closely as possible. She suggested challenging with heterologous viruses in repeated low doses. But others emphasized that testing everything in monkeys, while useful, was not enough. If we base our strategy on the results of monkey trials, said Kelly MacDonald (University of Toronto, Canada), "we could be discarding things

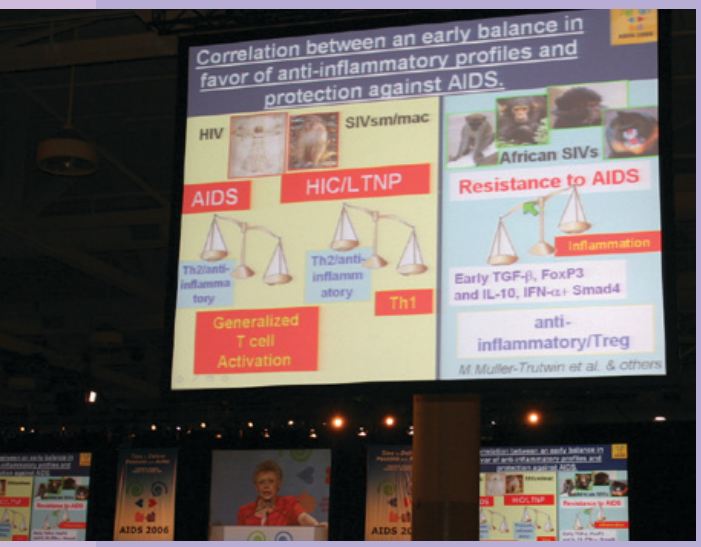
## Too much of a good thing

One of HIV's tactics is to exhaust the immune system by activating it in unproductive ways. "There is so much immune activation," said Photini Kiepiela (University of KwaZulu-Natal, Durban, South Africa). "It's like the immune system is hitting the dart board but not the bulls eye."

According to Angela Meier (Harvard Medical School, Boston, MA), one way that HIV does this is very direct. The ssRNA from HIV acts as a ligand for Toll-like receptors (TLRs), she said, leading to activation of $CD8^+$ cells.

This particular pathway need not always be negative, however. T. Blake Ball (University of Manitoba, Winnipeg, Canada) reported a study using peripheral blood mononuclear cells (PBMCs) from highly exposed persistently seronegative (HEPS) women. These PBMCs respond to TLR stimulation by producing more immunosuppressive IL-10 rather than immune stimulatory IFN-γ. The dampening effect of the IL-10 may help the women to avoid infection by reducing the target population of activated immune cells.

Negative regulation was also reported by Joseph Barbercheck (Tulane National Primate Research Center, Covington, LA). He found that the relatively less pathogenic SIV infection in African green monkeys correlates with a maintenance of inhibitory T regulatory cells, which were depleted during the more virulent SIV infection of macaques. Not reported was the situation in sooty mangabey monkeys, which show a greatly reduced response to SIV and a better outcome.




**Slow down.** Françoise Barré-Sinoussi, codiscoverer of HIV, explains the detrimental effects of excessive immune activation.

The overstimulation of the HIV-infected immune system can lead to replicative exhaustion. Telomerase has been shown to restore some of these lost functions to $CD8^+$ cells, and Calvin Harley (Geron Corp., Menlo Park, CA) reported at the conference that TAT0002, a drug candidate and telomerase activator, can do the same. The drug enhanced cytokine production by $CD8^+$ cells taken from three HIV-infected donors. With telomere restoration, "you may be taking these cells out of a DNA damage pathway and helping improve their function," said Harley.

The issue of overstimulation has attracted attention for years, and there have been limited trials with immunosuppressants. The results have been equivocal. One HIV-positive delegate did, however, ascribe his lengthy good health to his taking low doses of the immunosuppressant prednisone. If this is true, said monkey researcher Ruth Ruprecht (Harvard Medical School, Boston, MA) with a smile, "then you are like a sooty mangabey." JEM

**prematurely. The SIV–macaque is such a crummy model."**

**So the people are important. One of the biggest stories at the 1993 AIDS conference in Berlin was about a group of female sex workers in the Pumwani district of Nairobi, Kenya, who were seemingly resistant to HIV infection, despite repeated exposures. Rupert Kaul (University of Toronto) outlined the findings that have continued to emerge from this and similar cohorts of HEPS individuals. HIV resistance of HEPS individuals has been correlated with mutation of the CCR5 coreceptor, and the presence of specific cytotoxic T lymphocytes, neutralizing IgA antibodies, and genital innate factors such as the Trappin proteins. This diversity, he said, argues for larger and more rigorous studies to uncover all the means by which HEPS individuals escape HIV infection. It may then be possible to mimic these escape tactics (as was achieved by using CCR5 inhibitors) in the susceptible majority of the population.**

**Not quite as lucky as the HEPS individuals, but still very fortunate, are those who are LTNPs. The importance of HLA context for LTNPs was explained by Photini Kiepiela (University of KwaZulu-Natal, Durban, South Africa). Particular HLA types correlated strongly with either effective or ineffective HIV control. The favorable HLA types may grab hold of HIV peptides that make good targets for the immune system. Again, larger studies are needed to cover all the combinations of peptides and HLA genotypes.**

### Decoy responses

**The human studies rely on correlations to identify possible vaccine targets. But targeting HIV epitopes that look good based on simple correlations may turn out to be harmful, suggested Natasha Christie (University of Toronto, Canada). She found that HIV may be maintaining epitopes unchanged not because the epitopes are needed for replication but because they lead the immune system down the wrong path.**

**Epitopes that are targeted by the immune system are usually put into one of two categories. There are those that change to avoid the immune system,**

**Packing them in.** Approximately 24,000 people, from activists to scientists, attend the AIDS conference.

and those that cannot change because doing so would make the virus inviable. The latter group of epitopes would make good targets for a vaccine. But when Christie looked at some epitopes that do not normally mutate, and deliberately mutated them in vitro, she found that the resulting viruses were perfectly viable.

She suggested a very different explanation: these epitopes may be deliberately maintained by HIV because they engender detrimental immune responses. An example would be the phenotype seen by Yoav Peretz (McGill University, Montreal, Canada) in individuals with fast-progressing disease. These individuals' immune responses were more likely to be to HIV peptides that prompt secretion of interferon (IFN)-γ alone. Slow progressors, by contrast, responded to peptides that cause the immune system to make the more productive combination of IFN-γ and interleukin (IL)-2.

## Making a better immunogen

The one vaccine candidate that has been through phase III efficacy trials was the unsuccessful VaxGen vaccine. It was based on the gp120 surface protein of HIV. A better gp120 immunogen can be designed by pruning, said Ira Berkower (Food and Drug Administration, Bethesda, MD). He suggested that the key binding sites on gp120 are shielded by four protein loops. After he lopped off the loops, one such deletion increased antibody binding markedly. Entropy experiments suggested that the benefit came from a conformational change rather than the removal of a steric hindrance. "We removed something very essential [based on alanine scanning] and got back something that binds the CD4 receptor and binds antibody," he said. The resulting molecule may make a much better immunogen than gp120.

## Overlapping cycles

Appealing as the rational approach may be, "each of the successful vaccines that the world has made have been done in primarily an empirical way," said Wayne Koff, vice-president for research and development at IAVI. That means a lot of trial and error. "The challenge is to compress this down as absolutely far as we possibly can," says Berkley. Small trials in populations with high HIV incidence must be run quickly to get early clues to efficacy. To support this activity, "we need more clinical trial capacity in developing countries if we want to accelerate research," said Pontiano Kaleebu (Uganda Virus Research Institute, Entebbe, Uganda). "We need to conduct these trials in parallel."

Many early phase trials are underway, but the phase III trial data that everyone is waiting for will come in late 2007 or early 2008. This phase III trial is testing a Merck adenovirus vector carrying HIV *gag*, *pol*, and *nef* genes, and is designed to test the effect of cell-mediated immune responses. One observer of the field suggested that it would be "a miracle" if the vaccine candidates already in trials provided any meaningful protection, but other participants are putting on a brave face. "Either way, positive or negative, we'll learn a lot," said Haynes. He hopes the Merck vaccine will provide "a beachhead… of a vaccine that we can iteratively improve."

Whether HIV will succumb to a neat trick or to brute force is really anyone's guess. The one thing that we know for sure, said UN special envoy Stephen Lewis, is that the search for an HIV vaccine "is the most important quest on the planet." JEM