



IAVI Report

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Groundhog Day

HIV researchers of many stripes convene at the annual Keystone meeting and discuss some familiar obstacles

by **Kristen Jill Kresge and Simon Noble**

The Whistler-Blackcomb Mountains form one of the world's premier ski resorts, the largest in North America, and provided the backdrop for the 2007 Keystone Joint Symposia on HIV Vaccines: From Basic Research to Clinical Trials and Molecular and Cellular Determinants of HIV Pathogenesis. Whistler got its name from the whistling calls of the marmots that populate the alpine area, and this year's conference did have something of a 'Groundhog Day' feel to it—the same familiar scientific obstacles and a field waiting for that vital breakthrough.

There are now more than 30 ongoing clinical trials of AIDS vaccine candidates but one thing they all have in common is that none are expected to induce the much sought after protective antibody response capable of neutralizing a diverse array of HIV isolates. The consensus among most researchers is that, at best, the cellular-mediated immunity (CMI)-based candidates might significantly lower the viral load in vaccinated individuals who do become HIV infected, delaying disease progression and reducing the risk of transmission.

This would be no small accomplishment—such a first generation, partially-effective AIDS vaccine would help curtail the global epidemic and perhaps reduce the number of years that an HIV-infected person has to take antiretrovirals (ARVs). But just what researchers can expect from this pipeline of candidates is still unclear and may remain so until results are available from the first test-of-concept trials with CMI-based vaccines in a few years time.

Merck expects results from one of their first Phase IIb trials with an adenovirus serotype 5 (Ad5) candidate vaccine at the end of 2008 or early 2009. In 2011 the Vaccine Research Center (VRC) at the US National Institute of Allergy and Infectious Diseases (NIAID) anticipates having results from their soon to begin test-of-concept trial known as PAVE 100, which will administer DNA and Ad5 candidates as a prime-boost. Even then, as some researchers point out, there is little agreement about what the parameters are for success of these vaccines. Bruce Walker of Massachusetts General Hospital urged the field to come to a consensus regarding what level of reduction in viremia would constitute success with a CMI-based vaccine.

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Going public

Public health campaigns to raise awareness about HIV/AIDS can be very effective and are needed more than ever

by **Catherine Zandonella**


A Swiss girl's birthday party is attended by three scantily-clad prostitutes, symbolizing that the girl's father has some lingering worries about his HIV status. A Malawian high-schooler turns away from three male friends and says, "sex can wait." Chinese basketball star Yao Ming, a player for the US team the Houston Astros, lends his 7-foot 6-inch presence to the message

"HIV/AIDS will not affect our friendship."

Public health campaigns to educate people about HIV and AIDS take distinctive forms in different cultures and are an essential part of efforts to fight the pandemic. Anti-stigma and behavior change messages delivered through media outlets and trained communicators often serve as a first exposure to much-needed facts, dispelling rumors, myths, and

misconceptions, and empowering people to take control of their own lives. And there have been some outstanding success stories—in Uganda and Thailand, for instance, many credit public health campaigns with making huge inroads to reduce the number of new HIV infections.

The high prevalence and incidence rates of HIV show that such public health cam-

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Processing antigens

In the meantime, AIDS vaccine researchers are intensifying efforts into fundamental immunological questions rather than advancing too many new CMI-based candidates into clinical trials. Jonathan Yewdell of NIAID gave a highly entertaining and thought-provoking talk on the first evening of the conference, starting out by emphasizing the truism that there are still many unknowns in immunology and plenty of scope for much more basic research. His research group is initiating studies in neuroimmunology—an intriguing field he admitted “doesn’t have the best reputation”—looking at the involvement of sympathetic innervation on antiviral immunity. They have found that CD8⁺ and CD4⁺ T-cell responses can be increased up to 4-fold by ablating sympathetic neurons.

Yewdell then switched to a topic that he and colleagues Jack Bennink and Luis Anton have pioneered. Class I peptide complexes can reach sufficient levels to trigger CD8⁺ T-cell activation within an hour of adding virus to cell culture. Since these viral proteins must compete with a pool of billions of already translated cellular proteins, this suggests that there must be an active sampling mechanism in place to direct such a rapid presentation process. He and colleagues hypothesize that the peptides presented by MHC class I molecules originate from defective ribosomal products (DRiPs) that arise from imperfections in transcription, translation, post-translational modifications, or protein folding, and are trying to define the contribution to antigen processing. Provocatively he declared, only partly tongue in cheek, “we’re not here to refine our favorite model to the nth degree, we’re here to overturn the appplecart.”

In its latest incarnation, the DRiP hypothesis further postulates that there is a subset of ribosomes that purposely generates DRiPs for antigen presentation; the ‘immunoribosome.’ Yewdell pointed out in his talk that protein translation is much more intricate than generally appreciated, that different mRNAs and different tissues use different tRNAs, and that 451 tRNAs have been annotated in the human genome. He also pointed out that the largest locus for tRNAs is in the HLA complex, suggesting that the immune system and viruses probably exploit tRNA heterogeneity, and presented evidence that virus infections induce misloading of tRNAs with the wrong amino acid, perhaps to better generate DRiPs. He ended by predicting to the audience that “tRNAs are in your future.”

Program updates: CHAVI

A new development at this year’s Keystone Symposia was a session of HIV Vaccine Program Updates that gave representatives from some of the major research programs the opportunity to describe their respective approaches and progress. Bart Haynes of Duke University kicked off this session with an update on the progress of the Center for HIV/AIDS Vaccine Immunology (CHAVI), of which he

is director. The CHAVI Grant was awarded by NIAID in July 2005, and Haynes began by giving an overview of the infrastructure that has been put in place that, as of March 2007, includes 94 investigators at 51 institutions or sites in Africa, Europe, and the US.

He then gave an update on the progress of three of CHAVI’s Discovery Teams, beginning with the Genetics Discovery Team that is looking genome-wide for human gene variants that affect early virus set-point. They are using a microarray chip that can check 550,000 single-nucleotide polymorphisms (SNPs) to study their EuroCHAVI Consortium cohorts in five European countries and Australia. Preliminary results from these studies have confirmed the strong link between the HLA*B5701 allele and low virus set-point, calculating that this allele accounts for 8% of the total variability in set-point. The team has found

other polymorphisms associated with set-point, two of which are genome-wide statistically significant, and are now further evaluating these SNPs in additional cohorts.


Another Discovery Team is conducting studies in patients with acute HIV-1 infection in cohorts in South Africa and the US to look for signatures and functional characteristics of transmitted viruses to eventually develop new immunogens. The analysis strategy is to align over 4000 B-clade *env* sequences from 103 acutely-infected individuals to identify transmission signatures, and Haynes reported on two initial signatures in the *env* leader sequence and gp120. Functional and immunogenicity studies are underway.

The B Cell Discovery Team is looking to define viral and host mechanisms that affect antibody production during acute HIV-1 infection. Haynes presented some ideas as to what might account for the delay between the initial infectious event and the peak antibody titers against Env, and hypothesized that some species of broadly neutralizing antibody may be under the control of B-cell immunoregulatory events. Published evi-


dence indicates that there is also massive apoptosis occurring during HIV infection, and the team has now looked at apoptosis during the time of viral load ramp-up in acute HIV infection. They do indeed see elevated levels of apoptosis markers (FasL, TNFR1, and TRAIL) in plasma that is temporally associated with the initial viral load increase, and postulate that this may mediate immune suppression of early B-cell responses.

Program updates: IAVI

Next up was Wayne Koff, Senior Vice President of R&D at IAVI, who said the theme of his presentation would be fostering innovation in AIDS vaccine discovery and development. The scientific priorities for IAVI are to design, develop and advance to efficacy trials vaccine candidates that (i) elicit broadly neutralizing antibodies against HIV or (ii) control HIV infection to a similar degree that live attenuated SIV protects against pathogenic SIV challenge. IAVI has three main scientific consortia working on these goals—Neutralizing Antibody Consortium (NAC), Vector Design Consortium (VEC),



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Jonathan Yewdell

Control of HIV/SIV-Live Attenuated Consortium (LAC)—in addition to the IAVI Vaccine Development Laboratory at State University New York, Brooklyn, and the IAVI Human Immunology Laboratory at Imperial College, London, as well as a product development infrastructure and a network of partner sites in developing countries.

Koff first talked about the NAC and the neutralizing antibody problem. In designing immunogens to elicit broadly-neutralizing antibodies, one of the current major roadblocks is screening candidates for immunogenicity. IAVI has been using large-scale automated neutralization assays with pseudotyped virus for some time, and is also now conducting a study called Protocol G, a large-scale screen of sera looking for broadly-neutralizing monoclonal antibodies (MAbs). Newly-identified MAbs will then enter the new robotic platform at The Scripps Research Institute to accelerate crystallization and structural studies that will in turn inform immunogen design.

Koff briefly talked about the Control of HIV/SIV-LAC, specifically identifying antigenic targets for HIV control in human elite controllers who spontaneously control their HIV infection below undetectable levels, as well as some exciting data coming out of the LAC with SIVmac239 Δ *nef* (see below, Watkins).

The various research groups that make up the VEC are now developing novel virus vectors that seek to induce persistent immunity—cytomegalovirus (CMV; see below, Picker), reovirus, and paramyxovirus—or chimeric virus vectors that mimic the live attenuated SIV vaccines—Venezuelan equine encephalitis virus/HIV, and vesicular stomatitis virus/HIV.

With regard to clinical trials, Koff reported that in addition to 13 completed AIDS vaccine clinical trials and 4 ongoing, IAVI also has a series of clinical research studies completed, underway, or in development to test everything from HIV prevalence and incidence to acute infection and vector seroprevalence. One of these he described in some detail, Protocol D in 2400 participants in Uganda, Kenya, Zambia, and Rwanda to determine reference ranges for a number of clinical parameters relevant to the immunological and general health status of trial volunteers in developing countries. He presented data on eosinophil and neutrophil counts and showed that these values deviated extensively from the ranges found—and currently universally used in clinical trials—in ‘Western’ populations. These datasets will be published this year in a series of papers.

IAVI is collaborating with the HIV Vaccine Trials Network (HVTN) and US Military HIV Research Program (USMHRP) in the ongoing Phase I/II multi-site evaluation of the VRC DNA and Ad5 AIDS vaccine candidate. IAVI is conducting the trials at sites in Rwanda and Kenya, and Koff presented data showing that 72% of vaccinees given 10^{10} particles responded by interferon (IFN)- γ ELISPOT assays. When segregated by

pre-existing anti-Ad5 antibody titer, 78% of vaccinees with titers <1000 were responders, compared to 57% of vaccinees with higher titers. This compares favorably with the data previously obtained in relation to the Merck Ad5 AIDS vaccine candidate currently in Phase IIb trial.

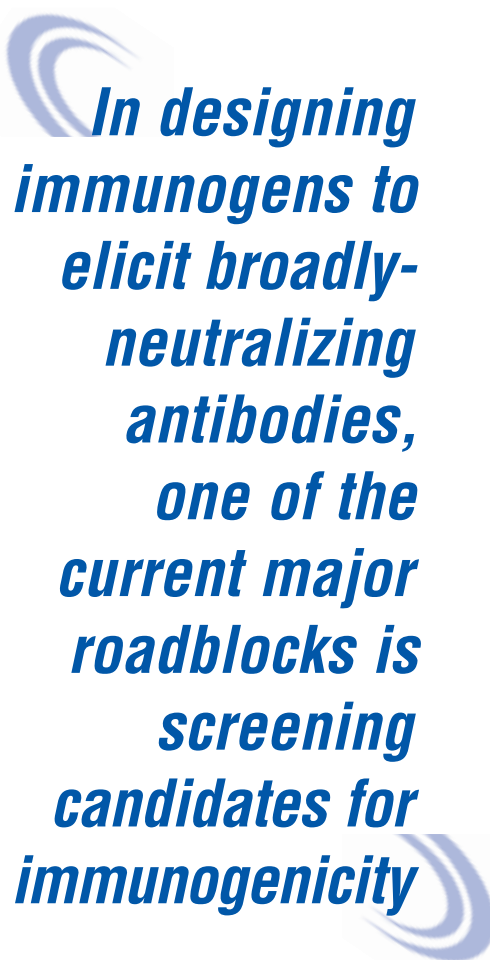
In response to the potential of pre-existing immunity to Ad5 to compromise any immunogenicity or efficacy of Ad5-based candidates, IAVI has been developing and testing AIDS vaccine candidates based on adenovirus serotypes with low seroprevalence, including human Ad35 and chimpanzee Ad7 (C7), the latter in partnership with GlaxoSmithKline. In rhesus macaque immunogenicity studies Koff showed that heterologous C7 prime/Ad35 boost elicited the highest T-cell responses.

Koff finished his presentation by talking about Phase II Screening Test of Concept (STOC) trials, a novel clinical trial paradigm that would garner preliminary efficacy data on promising vaccine candidates in a short period of time and in fewer trial participants. A series of these trials could rank the most promising candidates in a relatively rapid timeframe, rather than test them all in lengthy, expensive Phase III trials in >10,000 volunteers. Koff’s suggested numbers for STOC trials were 30 incident HIV infections to detect a 1 log suppression of viral load, which would require a 4% incidence and 500 subjects with 18-month post-vaccination follow up. STOC trials might also have utility in systematically testing other parameters such as different immunogen combinations in a specific platform or delivery routes.

Program updates: VRC

Gary Nabel, Director of the VRC at NIAID, then followed with a comprehensive update on the VRC multiclade AIDS vaccine candidate that Koff mentioned that is being tested in the Partnership for AIDS Vaccine Evaluation (PAVE) collaboration. Nabel began by explaining that the DNA/Ad5 prime boost platform was the most potent currently available for inducing CD8⁺ T cells, and that the candidates contained—in addition to the internal Gag, Pol, and Nef antigens—Env antigens because evidence suggested they could increase the breadth of immunity and potentially diminish viral escape. He presented data that indicated that the DNA/Ad5 combination elicited more polyfunctional (as measured by the number of cytokines produced) HIV-specific CD4⁺ and CD8⁺ T cells than either candidate alone, and that DNA/Ad5 but not Ad5/Ad5 showed efficacy against SIVmac239 challenge in macaques.

Nabel then talked about the PAVE 100 Phase IIb efficacy trial that will further test the VRC candidate subsequent to the Phase I/II trials currently underway. The multi-site collaboration between HVTN, USMHRP, IAVI, and the US Centers for Disease Control and Prevention (CDC) will enroll 8500 participants in North and South America, the Caribbean, and eastern and South Africa starting later this year, with results available in



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2011. Nabel then went on to discuss potential outcomes and what should be done to best respond to those outcome scenarios.

If the VRC DNA/Ad5 candidate is a complete success then it will be necessary to identify the most expedient way to obtain licensure, and Nabel expects that would be no sooner than 2013, and probably more likely around 2016. Scientifically, complete success would require that immune correlates of the protection be determined to inform further improvements in vaccine design. It would also be necessary to identify pharmaceutical collaborators or licensees for large-scale manufacture, and to develop the infrastructure required to administer the vaccine to those at high risk throughout the world.

In an outcome Nabel called “success with limitations” he said a 2016 licensure would be ambitious and it would be necessary to refine the existing candidate for a licensure trial. This would entail, among other things; engineering improved T-cell immunogens to elicit better coverage against circulating isolates; optimizing DNA immunogenicity through adjuvants, electroporation delivery, and stimulatory cytokines; and developing second generation recombinant adenovirus (rAd) vectors like rAd35 (see below), hexon chimeric rAd5, and rAd26. In preparation the VRC has engineered a rAd35 prototype candidate that contains a single clade A Env insert, and an Investigational New Drug (IND) submission has been filed with the Food and Drug Administration (FDA). Contingent on its approval, Phase I studies are scheduled for May this year that will test rAd35 alone and in combination with the Ad5 and/or DNA.

In the event that PAVE 100 shows no efficacy then Nabel said it would be necessary to develop next generation vaccines, particularly candidates that elicit broadly neutralizing antibodies, mucosal and/or innate immunity, and consider the use of persistent vectors. Nabel said it may also be time to seriously consider radical new concepts like inducing responses to self molecules like CD4 or CCR5 to try to interfere with HIV infection.

Nabel finished up by describing research that the VRC is undertaking to look at the neutralizing antibody problem, such as the mutagenic stabilization of the CD4-bound conformation of gp120 to produce immunogens (see below, Wyatt).

Persistent vector

Louis Picker of Oregon Health and Science University presented data in the rhesus macaque model on T-cell populations, particularly the elicitation of effector memory T (T_{EM}) cells that he suspects may be in the best position, both spatially and temporally, to exploit the window of opportunity that precedes the massive replication and mutation in SIV infection. He is hoping that SIV-specific cells with T_{EM} differentiation

can be elicited with non-lentiviral vectors, specifically the novel rhesus cytomegalovirus (RhCMV) vectors that he and colleagues are developing. Picker called CMV the “quintessential” inducer of T_{EM} responses, and other potential advantages of CMV as a vector include: efficient re-infection; low pathogenicity; lifetime persistence of both vector and response; and a large genome with potential for manipulation.

After showing that the RhCMV vectors express the SIV gene inserts at high levels, the team assessed the immunogenicity of vaccine candidates with different inserts. Picker showed data that repeated re-immunization with RhCMV containing different inserts elicited robust

step-wise increases of SIV-specific CD4⁺ and CD8⁺ T-cell responses both in peripheral blood and lung lavage, a representative mucosal site, even at very low doses. He described CMV as the “Energizer Bunny” of vaccine vectors that keep going and going, resulting in responses that “rival or exceed” those elicited by any other viral vector to date. All vectors persisted at secretory sites (mouth and bladder).


Picker concluded by saying that definitive challenge studies in immunized macaques will happen later this year, and thinks that RhCMV vectors will provide the opportunity to see if “ T_{EM} flavored” T-cell responses offer enhanced efficacy against pathogenic SIV challenge. He and colleagues also plan to investigate how genomic modification might increase immunogenicity and decrease pathogenicity through deletion of non-essential genes involved in immune evasion or modulation, and the application to human CMV.

Heterologous control


One of the most exciting new findings presented at Keystone came from David Watkins of the University of Wisconsin-Madison. As part of IAVI’s LAC his research group has been looking at live attenuated SIVmac239 Δnef protection of rhesus macaques. There are several published studies where macaques have been homologously protected from pathogenic SIVmac239 challenge, reducing set-point viral load by about 1.5 logs at most.

However, rather surprisingly, very recently his group have found that animals vaccinated with SIVmac239 Δnef and challenged six months later with pathogenic SIVsmE660 are robustly protected from this heterologous challenge—the geometric mean viral load four weeks after challenge was lowered by an impressive 3 logs. Macaques with Mamu-B*08 and -B*17 MHC alleles showed the most impressive control, and Watkins alluded to data that show these alleles bind similar peptides to the HIV-ameliorating human HLA-B*57 and -B*27 alleles.

Watkins cautioned that it was still early days but such a reduction in viral load is the most impressive described to date with a het-



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erologous challenge, and he is hopeful that the system will provide immunogenetic clues to further understanding heterologous control.

Lessons on cellular immunity

While cellular immune responses are unlikely to be sufficient to protect people from HIV infection, they do clearly play a role in the control of HIV in infected individuals. Walker has been studying different categories of people who spontaneously control HIV infection without ARV therapy. In his cohort of elite controllers—HIV-infected individuals who maintain a viral load below 50 HIV RNA copies/ml of blood—more than 25% of the individuals do not have any genetic characteristic, such as an HLA allele like B*57 or a particular chemokine receptor, that has been previously shown to correlate with protection against HIV. The level of neutralizing antibody responses in Walker's elite controllers are also very low and the CD8⁺ T-cell responses are both of lower breadth and magnitude than those seen in progressive infection, targeting primarily Gag. John Mascola of NIAID reported also seeing a greater breadth of T-cell responses in progressors than in long-term nonprogressors, in his cohort of 32 HIV-infected individuals.

Yet something permits these individuals to still keep HIV in check. "We don't really have a clue as to why this is, but we're trying to recreate this phenotype with a vaccine," said Walker. "We sure hope it's the immune system that's doing something because that's good news for vaccine development." His group is now studying the antiviral effects of cytotoxic T-lymphocyte (CTL) responses in elite controllers.

It's not magic

To further expand the body of knowledge on how cellular immunity functions in HIV, researchers are also studying the role of CD4⁺ and CD8⁺ T-cell responses in controlling or clearing other viral infections. "The way T cells behave isn't magic," said Picker, "there are rules and we're beginning to understand those rules."

Rick Koup and colleagues at the VRC are investigating how CD8⁺ T-cell responses are involved in vaccine-induced protection where cellular immunity is known to play an important role and also how these cells function in response to other pathogens, including vaccinia, CMV, and HIV-2 infections. His group has observed an association between polyfunctional CD8⁺ T cells that secrete multiple cytokines/chemokines—including CD107a, IFN- γ , TNF- α , MIP-1 β , and interleukin (IL)-2—and control of HIV replication. Polyfunctional CD8⁺ T cells secrete even more IFN- γ , on a per cell basis, than a monofunctional cell that is only secreting this single cytokine, said Koup. But he also points out that while such polyfunctional CD8⁺ T-cell responses are capable of providing life-long protection against vaccinia virus, they aren't even able to protect against superinfection with a different strain of HIV.

In CMV infection, CD4⁺ T cells produce higher levels of MIP-1 β than in HIV infection. Koup said studies have shown that cells that secrete

MIP-1 β and are CD57⁺ contain 20-fold lower levels of HIV, indicating this cytokine may actually play a protective role against HIV infection.

The adaptive immune system, especially the T-cell response, controls CMV for the lifetime of the host. There is evidence that this immune control is mediated, at least in part by CD4⁺ T cells, which can perform both their traditional helper function and antiviral effector functions, according to a presentation by David Price of Oxford University in the UK.

He is studying, in collaboration with colleagues at the VRC and Oregon Health Sciences Center, the role of CMV-specific CD4⁺ T cells in persistent infection of rhesus macaques. After sorting CMV-specific CD4⁺ T cells expressing both CD25 and CD69—markers of T-cell activation—in both acute and chronic CMV infection in macaques, Price observed that the CD4⁺ T-cell repertoire is polyclonal during acute infection and evolves substantially over time, becoming much less polyclonal during the period of chronic infection.

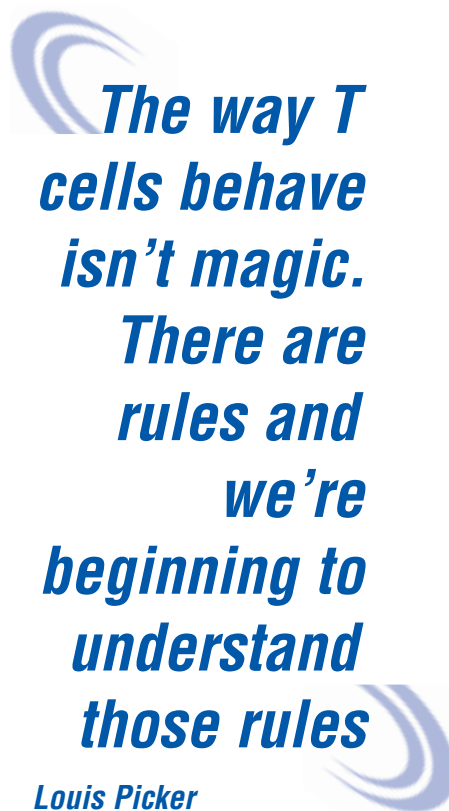
When macaques that were already infected with RhCMV were re-challenged 224 days later, there were transient breakthroughs of virus, but overall the animals controlled the virus more effectively than in primary infection. Their CD4⁺ T-cell responses were also more diverse and polyclonal during secondary infection. Furthermore, the dominant CD4⁺ T-cell clonotypes in these repertoires were a repeat of those observed in primary infection. These data indicate that the CMV-specific CD4⁺ T-cell clonotypes induced after primary infection persisted in the memory pool and contributed to the immune response after reinfection.

Bigger isn't always better

Charles Bangham of Imperial College London is studying the antiviral CTL response in human T-lymphotropic virus type 1 (HTLV-1), which preferentially infects both CD4⁺ and CD8⁺ T cells. This virus infects from 10 to 20 million people worldwide and can cause chronic inflammatory diseases and a rapidly progressing and fatal leukemia, but 95% of those infected are able to effectively control the virus and remain healthy, leading Bangham to ask why most people infected with HTLV-1 don't develop disease.

Individuals infected with HTLV-1 have strong virus-specific immune responses, involving both antibodies and T-cell responses. The HTLV-1-specific CTLs are extremely abundant, chronically activated, and directed primarily against the Tax protein of the virus (*Curr. Opin. Immunol.* **12**, 397, 2000), and according to Bangham these cellular immune responses play a dominant role in controlling HTLV-1 infection.

The HTLV-1 viral load varies greatly between individuals and the main determinant of this variation *in vivo* is the lytic efficiency of virus-specific CD8⁺ T cells (CTLs). Bangham said that in a typical HTLV-1-infected individual, each CD8⁺ T cell kills approximately five virus-infected cells per day, leading to the destruction



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of almost two billion HTLV-1-infected CD4⁺ T cells each day.

The efficiency of these CTL responses is determined partly by HLA class 1 genotype. However Bangham said there is not an observed correlation between the frequency of virus-specific CTLs and their efficacy—many infected individuals who mount the most effective cellular immune responses also have the lowest quantity of virus-specific T cells. Rather, their lytic capacity is associated with high granzyme expression and, according to yet unpublished data from Bangham's group, Tax-negative CD4⁺ FoxP3⁺ T regulatory cells seem to control the rate of CTL killing capacity in HTLV-1-infected individuals.

This analysis predicted that CD4⁺ T memory cells—the main cell type infected by HTLV-1—turn over abnormally fast in HTLV-1 infection. Recently, Bangham's group verified this by tagging lymphocytes *in vivo* with deuterium-labeled glucose.

Bangham contends that studying the cell-mediated immune response to other viral infections, especially persistent viral infections such as HTLV-1 or CMV, will help to improve the understanding of HIV infection and can be useful to AIDS vaccine development. "It will enable us to identify and quantify the factors that determine the efficacy of the antiviral cellular immune response and to understand the dynamics of persistent viral infections," he says. The finding that the frequency of virus-specific cellular immune responses is not necessarily a reliable guide to their efficacy in HTLV-1 infection also seems to hold true for HIV infection, based on some of Walker's data from HIV controllers. In these individuals immune responses directed towards less variable regions of the virus, like Gag, are correlated with immune control even if they exist at much lower levels than CD8⁺ T cells that target the highly variable Env. Walker said it's not yet time to start tossing out vaccine candidates that include *env*, but he does suggest caution. "We need to look at this data closely and see if there is competition between Gag- and Env-focused responses," added Walker.

Picturing the Holy Grail

While researchers sort out the functions and meaning of cellular immune responses, structural biologists are painstakingly trying to figure out how and where the already-identified broadly-neutralizing antibodies bind to HIV. Several presentations focused on how structural biology can be used to identify sites of vulnerability on the virus, as was done recently by the work of Peter Kwong and colleagues at the VRC (see *An Interview with Dennis Burton: Structure-func-*

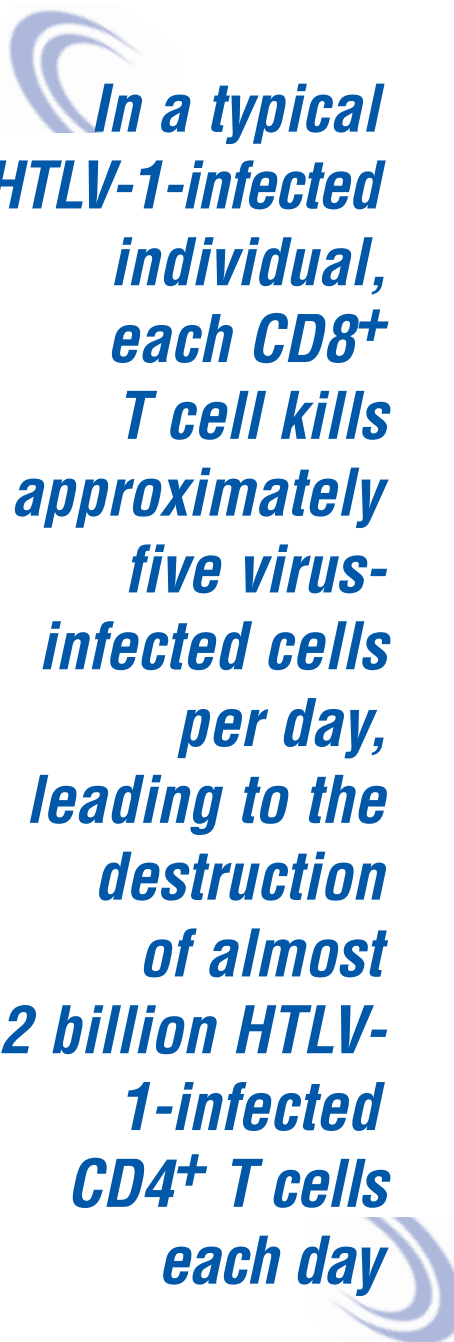
tion in HIV research, LAVI Report 11, 1, 2007). Information like this should eventually lead to the structural-based design of immunogens that can be used in AIDS vaccine candidates. But as Rich Wyatt of the VRC pointed out, this has been a remarkably difficult task and in the 9 years following the elucidation of the structure of HIV gp120 bound to CD4 and the CD4-induced antibody 17b, there has been only incremental progress.

Part of the reason for this difficulty is the extreme flexibility of the gp120 molecule, which hides the functionally-conserved regions from neutralizing antibodies and diverts the immune response to irrelevant conformations; it also employs other diversionary tactics, like immunodominant variable loops and a mask of glycan residues. Ideally, researchers would like to lock the gp120 protein into a particular conformation related to that of the functional spike to see if they can induce different antibodies or increase the neutralization potency of antibodies against the virus. Wyatt and his colleagues have been trying to do just this by stabilizing the CD4-bound conformation of gp120 with various space-filling mutations and internal added cysteine pairs within gp120, with the aim of eliciting antibodies to the CD4 binding site.

To try to lock the gp120 trimer into place, Wyatt's group started out by making YU2 gp120 trimers that incorporated space-filling mutations. They then measured the entropy readout of the molecule to determine the effect of these mutations on its stability. The space-filling mutations resulted in a trimer that was 30-40% stabilized, but it only minimally increased the antibody neutralization potency as compared with other pseudotypes and offered no increase in breadth of antibodies directed towards the CD4 binding site. Next they tried also adding cysteine pairs into the core of gp120 to further stabilize the trimer relative to CD4 interaction; as a by-product, 17b affinity also increases with these changes. With these additional changes, core gp120 interaction with CD4 was stabilized by 55% as measured by calorimetry, but the recombinant Env molecules would no longer fold into a trimer.

Testing immunogenicity of the stabilized core proteins in rabbits revealed that 17b-like antibodies were elicited at high titer but neutralization capacity was not enhanced.

Wyatt's group will now assess the percentage of antibodies directed towards the stabilized gp120 core that are CD4-like and will also attempt to stabilize the CD4-binding region by alternative strategies. They see the large increase in 17b-affinity as establishing proof of principle and now hope to be able to do the same with the CD4 binding site. ■



In a typical HTLV-1-infected individual, each CD8⁺ T cell kills approximately five virus-infected cells per day, leading to the destruction of almost 2 billion HTLV-1-infected CD4⁺ T cells each day

paings still have much to do in many cultures around the world. According to UNAIDS, the number of people living with HIV continues to climb in every region in the world. Young people between the ages of 15 to 24 accounted for 40% of new HIV infections in 2006. Shockingly, in India, where more HIV-infected people live than anywhere else on the planet, 43% of women have never even heard of HIV. Even in the media-saturated US, misconceptions abound—one study showed that roughly 47% of African Americans believe an AIDS vaccine is available but is being withheld (*J. Acquir. Immune Defic. Syndr.* 40, 617, 2005). One in five Americans say they would be “very” or “somewhat” uncomfortable working with someone who has HIV or AIDS.

The nature of any behavior-change campaign is to challenge the status quo, and this alone is often sufficient to cause unease and controversy. But campaigns have managed to change behavior in other health areas, like increasing the number of seatbelt users, reducing the number of smokers, and mass immunizations of children. When HIV and sexual practices are the topic, it is even more difficult to balance the message between educating and offending. “It is tempting to think that behavior change is just an impossible goal,” says Tony Barnett, an HIV/AIDS researcher at the London School of Economics. “That is not true. People’s cultures are very variable and changeable. However, they are more changeable from within than from without.”

Change from within

All successful public health campaigns follow certain principles. These include conducting formative research to identify the target population, identifying stakeholders, pre-testing messages and media, and conducting follow-up research to analyze the impact and benefit. A truly effective campaign, however, requires local involvement, national leadership, use of the right sort of media to reach people, and a sense that the campaign originates within the culture rather than being imposed by outsiders.

A Zimbabwean campaign to reduce stigma illustrates how involving local people can make a difference in how the message of the campaign is received, says Devora Joseph, acting director of AIDSMark, a program engaged in the social marketing of HIV prevention products and services and run by the nonprofit organization Population Services International (PSI). PSI and its local partners identified HIV-infected people willing to talk about their experience

and featured them in radio and television ads and on posters as part of the campaign, “Don’t Be Negative About Being Positive.” PSI’s research indicated that people who had heard the campaign’s messages were more accepting of people living with HIV/AIDS, and that overall they had a greater awareness of HIV/AIDS.

Strong national leadership can also pay off. Many credit Uganda’s president, Yoweri Museveni, for his role in the success of his country’s campaigns to reduce HIV transmission—prevalence fell from about 15% in the early 1990s to roughly 6.7% in 2005. While debate has simmered over which prevention methods (whether abstinence, being faithful, or condoms) were responsible for this decline, Museveni’s leadership and participation is widely praised. For example, Museveni urged men and women to become more sexually responsible through an ongoing series of AIDS radio messages. Each radio message began with the beating of a drum, the traditional instrument used to transmit urgent warnings among villages, a cultural reminder that helped people accept Museveni’s message as genuine and urgent.

Another important factor in a campaign’s acceptance is the knowledge that the campaign originated from within the country rather than from outsiders. In Thailand the 100% condom campaign, which required that all sex workers use a condom in every sex act, was strongly endorsed by the national government and identified in the public consciousness with health minister Mechai Viravaidya, who became affectionately known as “Mr Condom.” The program involved distributing condoms, educating sex workers and clients, and shutting down venues that did not comply with the law. The policy is credited by the United Nations Development Programme with reducing new infections from 140,000 in 1991 to 19,000 in 2003. In total more than one million Thais have been infected since the start of the epidemic there, but last year the World Bank estimated that if the country had not implemented such an effective prevention campaign then a further 7.7 million people would have been infected by now (see Figure 1).

With a subject as complex as human behavior, billboards, posters, and other mass media cannot be the only outlets for delivering the message. In rural areas people often live miles from the nearest television, radio, or even billboard. Instead educators combine media campaigns with other interventions such as counseling, support groups, peer



A truly effective campaign... requires local involvement, national leadership, use of the right sort of media to reach people, and a sense that the campaign originates within the culture rather than being imposed by outsiders



educators, and traveling-theatre groups. Campaigns have been forced to become creative. In many parts of Africa, health educators stage local soccer matches in the villages. These competitions draw people from the surrounding area, and the health educators use the event as an opportunity to convey messages about HIV/AIDS.

Conveying these messages is especially effective via interpersonal communication, where a trained educator engages members of a target population. One such program in India sponsored by PSI and the United States Agency for International Development is called "Operation Lighthouse." About 3600 educators give out condoms and information to truckers, port workers, fisherman, and sex workers in 12 port cities across the country. The goal is to reach every person in the target group several times during a three-month period with a single, consistent message, such as how to use a condom. After the first

three months the educators change the educational message to a related topic such as sexually transmitted diseases. The program has demonstrated behavior changes, but it is very resource intensive. "Thinking that one can just put up a billboard and say 'use a condom' is oftentimes not adequate," says Joseph, "especially with a high-risk, vulnerable population like the sex workers and truckers we work with in India."

One size does not fit all

Without the sense of ownership and strong local leadership, campaigns can be worse than ineffectual; they may be counterproductive. For the 2002-2003 World AIDS Campaign, UNAIDS commissioned a series of posters designed to illustrate AIDS-related stigma and appeal to people in places as diverse as Africa and India. The slogan "Live and Let Live" was featured on posters of headshots of people thinking about family members who had

AIDS. An analysis by researchers at McGill University, Canada found that many people were confused and thought that the posters were condoning stigma rather than discouraging it (*J. Health Communication* **11**, 755, 2006). "The 'one size fits all' approach may not be appropriately suited to health-related campaigns," says Leanne Johnny, who conducted the study with colleague Claudia Mitchell.

One-size-fits-all does not apply even within a country's borders, says Kwaku Yeboah, director of prevention and mitigation at the nonprofit health organization Family Health International. Most developing countries do not have homogenous populations—city-dwellers often embrace modern lifestyles while others in rural villages get much of their information and care from elders and traditional healers. "It is absolutely important to have that local participation to guide you in understanding people's thinking processes," says Yeboah, "because perception is sometimes reality."



Figure 1. Thai condom campaign poster. Posters such as this have been highly effective in raising awareness about the importance of condoms.

In Botswana in 1988, the government initiated a campaign to educate people about HIV/AIDS and promote condom use that was highly influenced by Western ideas. At the time many people did not yet know anyone who had contracted or died of AIDS. In rural areas the campaign was met with disbelief and condoms became associated with promiscuity and a breakdown of traditional values. As a result many Tswana people (the southern African people who inhabit Botswana) began to believe that AIDS was a disease brought on by immoral behavior. "Modernity, and indeed the modern state, was increasingly associated with sexual laxity and disease, an affront to Tswana morality," writes Suzette Heald, an anthropologist at Brunel University (*J. Biosoc. Sci.* **38**, 29, 2006). People considered the disease as something that couldn't happen to them and so saw no reason to change their behavior.

Of course these attitudes are not unique, and are often all too apparent in developed countries. To Tony Barnett at the London School of Economics, it is not surprising that such measures are ineffective. "We don't know much about human sexual behavior in general," says Barnett, "let alone cross-culturally." Given that we don't know the reasons that people have sex, said Barnett, we have no reason to believe that it is easy for people to start using condoms, nor should we believe that abstinence is an easy choice.

Finding out why people engage in the sexual practices that they do is essential for designing campaigns that can deliver on the promise of reducing HIV transmission rates, as Barnett and colleague Justin Parkhurst point out in a 2005 article in the *Lancet* (*Lancet* **5**, 590, 2005). The cultural meaning of sex can vary not only between countries but between social groups in that country. Sexual choices are determined not only by culture but by the social and economic context in which people live. This is especially true among women. "Whether or not people have sex with each other may be less to do with culture and much more to do with decisions that people make in order to survive, particularly where women are concerned," says Barnett.

In many regions of the world, women are economically dependent on men, lack the power to demand fidelity or condom use, and live under threat of violence from an intimate partner. As a result the HIV/AIDS epidemic is becoming increasingly female. In Swaziland, one of the most heavily affected countries, HIV prevalence among pregnant women

attending antenatal clinics was 43% in 2004. Similarly high prevalence figures are found throughout southern Africa. In China, women comprised 39% of reported HIV cases in 2004, up from 25% two years earlier.

For many women, particularly those in resource-poor settings, transactional sex is a necessary means of survival. Since the onset of the AIDS pandemic an age old concept has been redefined and poses new threats to young women who see cross-generational sex with 'sugar daddies' as a way to empower their status. These young women are at greater risk of acquiring HIV since, on average, older men are more likely to have had the chance to become HIV infected and to have multiple partners.

To combat the trend, PSI has developed campaigns in Uganda, Cameroon, Kenya, and Mozambique that appeal to parents, young women, and their male partners. The campaigns carry the message that cross-generational sex can increase the risk of HIV infection (see Figure 2). In Uganda, PSI is collaborating with political leaders and community organizations to create stigma against these relationships. The campaign includes posters of a leering older man with the caption, "Would you let this man be with your teenage daughter? So why are you with his?" In Cameroon, the "No to Sugar Daddies, No to AIDS" campaign via television, radio, and print is raising awareness and changing societal views about the practice.

Some programs encourage men to treat women more respectfully, as does a campaign aimed at seasonal farm workers in South Africa. During harvesting season, male supervisors often have sex with female workers in exchange for better working conditions, extra money, or to secure employment in the first place. Women often have less knowledge of HIV/AIDS than men and are unlikely to request that their partner wear a condom. Sonke Gender Justice, a Cape Town-based non-governmental organization (NGO), runs weeklong workshops that teach supervisors not to abuse their position of authority to sexually harass or exploit female workers.

Future campaigns may be modeled on interventions like a recent one in South Africa. The Intervention with Microfinance for AIDS and Gender Equity (IMAGE) study assessed a structural intervention that combined loans to poor households for income generation, such as retail businesses selling fruit and vegetables, new or second-hand clothes, or tailoring businesses. The women also received a gender and HIV training curriculum. The blinded random-



Finding out why people engage in the sexual practices that they do is essential for designing campaigns that can deliver on the promise of reducing HIV transmission rates



ized study looked at outcomes such as interpersonal violence, an independent risk factor for HIV infection, and rate of unprotected sex with a non-spousal partner. The intervention led to a 50% reduction in levels of intimate-partner violence although it did not reduce episodes of unprotected sex (*Lancet* 368, 1973, 2006).

The strength of this type of intervention, says Barnett, is that it doesn't try to alter people's

behavior by telling them what they should or should not do, but rather it gives women economic opportunity that they wouldn't otherwise have and with it the potential to change their decision making around sex.

Campaigns that empower women and provide economic opportunities can reduce HIV-related risks. In Uganda, Museveni recognized the benefits of empowering women

Campaigns that empower women and provide economic opportunities can reduce HIV-related risks

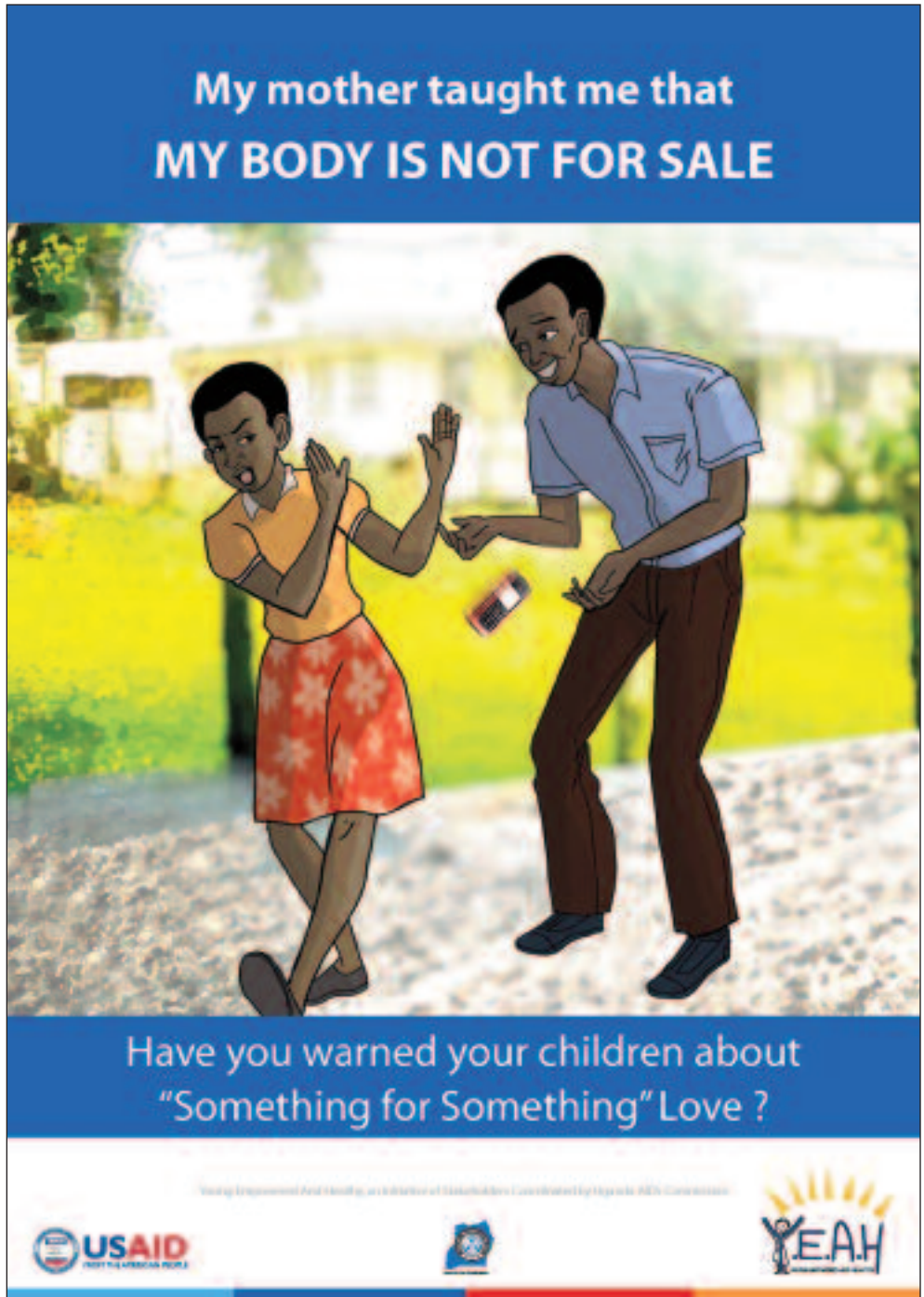


Figure 2. Ugandan campaign poster. Population Services International (PSI) distributes campaign posters such as this to raise awareness about cross-generational sex and the increased risk of HIV infection.

and created a Ministry of Women's Affairs, charged with enforcing laws against sex with minors. Gender-equity messages became a part of general education in the schools, and the government started up programs to offer loans to women for small businesses.

Major international organizations are also now embracing the need for cultural and structural interventions to assist women. Campaigns in many developing countries aim to alter the structural reasons that contribute to HIV transmission by changing male attitudes towards women and empowering women economically. "To stop the feminisation of the epidemic, as well as the epidemic itself, we have to initiate legal but also social, cultural and economic changes to challenge some of the most pervasive social patterns and gender norms that continue to fuel the AIDS epidemic," wrote Peter Piot, head of UNAIDS, in a March 9, 2007 editorial in the *Bangkok Post*.

AIDS vaccine campaigns

The developing world has no monopoly on misunderstandings about HIV and AIDS. In the US misconceptions are common among the very populations in which the epidemic is growing fastest—AIDS diagnoses among African Americans have grown from 25% of cases diagnosed in 1985 to 50% in 2005. Lack of accurate knowledge about HIV/AIDS among African Americans and Latinos is hurting not only transmission rates but also recruitment of participants in vaccine trials.

Only about 17% of people enrolling in AIDS vaccine trials in the US are African American or Latino, according to Cornelius Baker at the Academy for Educational Development (AED), an organization that designs public health campaigns. AED is the recipient of a five-year contract worth \$2.7 million per year from the National Institute of Allergy and Infectious Diseases (NIAID), and the goal of the campaign is to create an environment where people are willing to participate in those trials.


One of the first steps will be to educate target populations about the facts. The long history of medical injustice towards African Americans in the US has left a legacy of distrust. The belief that a vaccine against AIDS is available but is being withheld is not fantastical when one considers that poor African Americans are on long waiting lists in states like South Carolina to receive antiretroviral therapy. "There are deeper belief systems operating that standard social marketing is not going to be able to eliminate," says Baker.

AED is currently studying how to penetrate groups that are resistant to the facts about HIV despite being exposed to mass media. In keeping with the need for locally-grown campaigns, Baker says AED will parcel the money out to local organizations to create campaigns or work within existing outreach groups, rather than design a national campaign. One strategy is to identify local or community leaders or role models, rather than looking to national leaders, says Katharine Kripke, assistant director of research at NIAID. "We are asking, 'Who do people look up to? Who do they get their information from?'"

Think locally, act globally

Bringing expertise from affected communities is just one way in which public health officials plan to refine and sharpen public health campaigns. Increasingly, international agencies are moving away from top-down approaches and instead are funding local or community planners. These agencies are recognizing that structural efforts to improve the economic and social power of women could go a long way toward rolling back infection rates.

Yet women are not the only target. While the Thai sex-worker campaign was a success, that success came at the expense of rising transmission rates among ignored populations, namely men who have sex with men (MSM) and intravenous drug users. HIV prevalence among MSM increased from 17% in 2003 to 28% in 2005. In February the Thai government began its first public health campaign to target these populations. The five-month-long Sex-Alert campaign, run by Family Health International, NGOs, and the country's Ministry of Public Health, will deliver safe sex messages through magazine and radio advertisements, cell phone and text messages, the internet, and posters. Condoms and lubricants will also be distributed.

The future of public health campaigns will undoubtedly become more complex with the availability of new HIV interventions—male circumcision, vaccines, microbicides, diaphragms, pre-exposure prophylaxis, and other measures—that could all one day require new messages that must be crafted and disseminated to a wide range of people. This time, consideration of the underlying reasons for people's sexual behavior could inform a more effective set of public health campaigns. 

Catherine Zandonella, MPH, is a freelance writer whose work has appeared in Nature and New Scientist.



Lack of accurate knowledge about HIV/AIDS among African Americans and Latinos is hurting not only transmission rates but also recruitment of participants in vaccine trials



Optimizing HIV prevention research

IOM panel bears from second batch of experts on the pitfalls and promise of conducting HIV prevention research

by **Kristen Jill Kresge**

The field of HIV prevention research is shifting into a new era. The recently completed trials indicating that male circumcision is about 60% effective at preventing heterosexual HIV transmission in men spurred the World Health Organization to prepare guidelines on implementing this into the comprehensive prevention of HIV/AIDS. Meanwhile, many other HIV prevention strategies, including microbicides, vaccines, the female diaphragm, treatment of herpes simplex virus (HSV-2), and the prophylactic use of anti-retrovirals (ARVs), are currently undergoing testing in multiple clinical trials around the world.

But these trials face many potential snags. Among these is a lower-than-expected HIV incidence in many populations, which makes it more difficult to determine the efficacy of these interventions. Higher-than-expected pregnancy rates among women who participate in these prevention studies also impedes data collection and slows the pace of research. These were two of the main subjects addressed when the esteemed Institute of Medicine (IOM), part of the US National Academy of Sciences, convened its first meeting on the methodological challenges in HIV prevention trials in the US this past winter (see *Advisory panel considers complexities of HIV prevention trials, LAVI Report 11, 1, 2007*).

At the second in a pair of meetings on this subject, held on April 19 in London, the independent panel selected by IOM gathered more information about the challenges and successes in conducting HIV prevention trials involving microbicides, HSV-2 suppressive therapy, the female diaphragm, and male circumcision, while very little, if any, of the discussion centered on AIDS vaccine trials in particular. Some of the overarching concepts discussed at this meeting included measuring adherence to the intervention being tested, selecting the best candidates to advance into clinical trials, and strategies for optimizing trial design.

These meetings, as well as the final report from the IOM that will be released this coming fall, were prompted by a request from the Bill & Melinda Gates Foundation, which is currently funding trials of several new prevention technologies. According to Robin Shattock

of St. George's Hospital Medical School in London, funding organizations are increasingly interested in the potential complications of conducting prevention trials and how funds are spent. "Donors are getting much wiser to the costs of these trials and their likelihood of success," he told the panel.



Incidence

One theme that emerged during the first IOM meeting was the overwhelming need for research groups to have accurate HIV incidence estimates when designing a trial. There are different methods for estimating incidence in a particular community, including the use of previously published data, the BED capture enzyme immunoassay that uses the ratio of anti-HIV immunoglobulin G (IgG) to total IgG to determine early HIV infection, or traditional epidemiological studies that document new infections (see *Advisory panel considers complexities of HIV prevention trials, LAVI Report 11, 1, 2007*). Obviously, the last of these is the most expensive option, but as Kenneth Mayer, professor of medicine and community health at Brown University in Rhode Island, told the panel: "The most costly and time-consuming methods for determining incidence are the most reliable."

Several examples of how imprecise incidence estimates can negatively affect prevention trials were discussed in the first meeting. During the second session, Gita Ramjee, director of the HIV prevention unit at the South African Medical Research Council, extolled the benefits of conducting preliminary studies to estimate HIV incidence in the communities where a future trial will occur. Before selecting sites to conduct several microbicide trials currently being conducted in

South Africa, Ramjee and her colleagues conducted two, 14-month-long feasibility studies at four sites and found that the HIV incidence ranged from 5.0% to 8.5% per year.

"Preparedness studies are extremely valuable," said Ramjee. "You don't want to select a trial site and then find the incidence is too low," she added. One possible fix for the problem is designing clin-


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Kenneth Mayer

ical trials on a set number of events or end points, in this case HIV infections, rather than on an expected incidence of infection. The idea of end-point-driven trials was mentioned by several of the IOM panelists as a way to eliminate the potential of a trial closing prematurely and inconclusively because it was based upon an inaccurate HIV incidence.

Retaining female volunteers

HIV prevention researchers have observed much higher-than-anticipated pregnancy rates among female volunteers in many trials and since pregnant women must interrupt their use of the experimental intervention due to potential safety concerns, this has become an important issue. These interruptions, which in many cases last nearly the length of the trial, often confound data collection and consequently some trial sponsors are now requiring women to take hormonal contraceptives to be eligible for enrollment. This point was re-emphasized at the second meeting by Helen Rees, executive director of the reproductive health and HIV research unit at the University of the Witwatersrand in South Africa.

Rees proposed that free hormonal contraception should be offered to all women participating in HIV prevention trials, but she did not suggest that it be compulsory. She also raised concern that offering free contraception to women who couldn't otherwise afford it might serve as an unfair inducement for them to participate in the trial.

Rees also noted that pregnancy may actually increase a woman's risk of becoming HIV infected biologically, as well as behaviorally, since pregnant women are even less likely to use condoms. Both of these factors argue for allowing women to continue using the experimental intervention during pregnancy. This is probably most feasible for the PrEP trials and some of the microbicide candidates that incorporate already-licensed ARVs that are currently approved for use by pregnant women. A recommendation on whether or not contraception should be a requirement for participation in HIV prevention research and how trial sponsors should deal with product use during pregnancy will likely come in the IOM's final report.

Determining adherence

The need for researchers to accurately assess a volunteer's adherence to the product/device is another complication shared by

most new prevention technologies because they are self-initiated and require consistent and correct use to be effective. Despite extensive volunteer education during trials, adherence is rarely perfect and this can profoundly affect the interpretation of trial results.


Several invited speakers at both meetings addressed different methods researchers use to determine self-reported adherence and sexual behaviors. Coital diaries, where volunteers record their sexual activities as well as use of condoms or the intervention being studied, are one method. Another is coating the applicators used to deliver microbicides with a compound that changes color when it comes in contact with vaginal fluids. Inspection of used applicators can then be tallied with coital diaries.

A further complication related to adherence was encountered in the trials testing the ability of the female diaphragm to prevent HIV infection. Researchers observed an adherence rate of about 70% to both condoms and the diaphragm amongst all volunteers, and although this impressive adherence rate is encouraging, if women who are most likely to use the diaphragm also have the highest adherence to condoms, it could potentially mask the diaphragm's effect. This concern was shared with the IOM panel by Nancy Padian, executive director of the Women's Global Health Imperative at the University of California, San Francisco, who conducted this study.


Andrew Nunn, associate director of the clinical trials unit at the Medical Research Council in the UK, said evidence also suggests that adherence to interventions like microbicides or the diaphragm may decline with time. To avoid this affecting data interpretation, Nunn suggested only following volunteers for one year to determine efficacy of the intervention and then subsequently for longer periods to determine adherence.

New trial design



Nunn also emphasized the importance of smaller Phase IIb trials—which have recently become *de rigueur* in the AIDS vaccine field—to rank microbicide candidates according to their efficacy before initiating larger and much more costly Phase III trials. He emphasized the importance of collecting efficacy data as soon as possible for the microbicide field in particular, which has been dogged lately by the closure of some Phase III trials



Preparedness studies are extremely valuable. You don't want to select a trial site and then find the incidence is too low



Gita Ramjee


Funding agencies are ultimately the ones who make the decision about which candidates are worth moving forward


that indicated the candidate at best offered no protection, or at worst actually increased a woman's risk of contracting HIV (see *Advisory panel considers complexities of HIV prevention trials, IAVI Report 11, 1, 2007*).

"To be able to show it works at all would be an achievement," said Nunn, who emphasized that preliminary efficacy data will be vital to secure funding for large-scale trials. Shattock shared this concern and said funding agencies are ultimately the ones who make the decision about which candidates are worth moving forward.

Monkey see, monkey do

Shattock also proposed that the microbicide field start using a rational development strategy, including more rigorous preclinical testing using the rhesus macaque model to determine pre-clinical efficacy. "I don't think this is setting the bar too high," he said.

Many of the microbicide candidates that are currently in Phase III efficacy trials have never been tested in non-human primates or against HIV strains that are circulating in Africa. And critically, most have not been evaluated against CCR5-tropic HIV, which is by far the most commonly transmitted virus.

Several of the early-stage microbicides have more specific activity and are based on existing ARVs, including non-nucleoside reverse transcriptase inhibitors like tenofovir and CCR5-inhibitors, and Shattock said these appear to be much more potent. "We can start to look at picking the best drug in a category and taking it into clinical trials," he said.


But Nunn also presented several of the drawbacks to relying too heavily on the limited data that Phase IIb trials provide because it could lead researchers to abandon potentially useful products that only have a modest

efficacy, which is all most experts expect from a first-generation microbicide.

Anticipating IOM recommendations

When the final report is issued it is likely to contain recommendations that will be useful for funding organizations, trial sponsors, and the groups conducting clinical trials of new prevention technologies—especially when evaluating new candidates—and is intended to improve trial design and encouraging more efficient use of research funds. It may also help create more consensus within the somewhat disparate field of HIV prevention.

By the time the IOM's report is released, results from the diaphragm trials and perhaps the HSV-2 suppression trials will already be available. If either or both of these interventions show promise, the task—as with male circumcision—will be implementing educational programs and making these prevention technologies available to those who are at highest risk of contracting HIV.

Over the course of the two meetings a few of the IOM panelists kept returning to the notion that different HIV prevention strategies should be tested in combination, rather than in parallel. One panelist remarked that if HIV treatment trials were done similarly to those in the prevention field, "we never would have gotten anywhere." Trials to test combinations of modestly effective, behaviorally-dependent interventions—like microbicides, the diaphragm, and PrEP—together with already-tested methods like male circumcision, may be more complicated to design and more expensive to conduct. But they may also be the best way to determine what is necessary to finally roll back the number of new HIV infections and make headway in curtailing the pandemic's spread until an effective preventive AIDS vaccine is available. 



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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust, The Rockefeller Foundation, The Starr Foundation, The William and Flora Hewlett Foundation; the Governments of Canada, Denmark, Ireland, The Netherlands, Norway, Sweden, the United Kingdom, and the United States, the Basque Autonomous Government as well as the European Union; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, Google Inc., Merck & Co., Inc. and Pfizer Inc; leading AIDS charities such as Broadway Cares/Equity Fights AIDS and Until There's A Cure Foundation; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

Pharmexa-Epimmune and Bavarian Nordic begin AIDS vaccine trial

The biotechnology companies Pharmexa-Epimmune and Bavarian Nordic initiated a Phase I AIDS vaccine trial, funded by the US National Institutes of Health (NIH), at the end of April to evaluate the safety and immunogenicity of two vaccine candidates administered in a prime-boost combination. The first candidate, EP1233, is an epitope-based DNA vaccine candidate developed at Pharmexa-

Epimmune with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The second candidate uses a modified vaccinia Ankara (MVA) viral vector to deliver HIV proteins matching those in the DNA candidate.

This trial is being conducted by the HIV Vaccine Trials Network (HVTN) and is known as HVTN 067. Investigators plan to enroll 108 volunteers at sites in three US cities—Nashville, Rochester, and San Francisco—and preliminary results are expected by the end of the year.

Guidelines for male circumcision issued

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recently issued recommendations on the practice of male circumcision for HIV prevention (www.who.int/hiv/mediacentre/MCrecommendations_en.pdf). They suggest the procedure should be recognized internationally as an important intervention to reduce the transmission of HIV and advised countries with high HIV prevalence and low rates of male circumcision to consider rapidly and dramatically increasing access to this surgical procedure for men at risk of heterosexual transmission of HIV. The guidelines also recommended that circumcision be included broadly as part of a comprehensive strategy to prevent HIV transmission, along with the use of condoms, voluntary counseling and testing services, and the treatment of other sexually transmitted diseases.

The release of these guidelines follows an international consultation with various governments, researchers, human rights advocates, funding agencies, and civil society members that was held from March 6-8 in Geneva, Switzerland. Many individual countries are also in the process of establishing national guidelines on the introduction of male circumcision programs.

UNAIDS chose to issue these recommendations after the results from three randomized, controlled clinical trials showing the procedure can reduce the risk of heterosexual transmission of HIV infection in men by as much as 60%. These trials were conducted in Kisumu, Kenya; Rakai District, Uganda; and Orange Farm, South

Africa. Studies to predict the impact of different prevention technologies on the course of the epidemic suggest that implementation of circumcision programs in sub-Saharan Africa could prevent 5.7 million new HIV infections over the next 20 years.

The WHO/UNAIDS guidelines recommend more research on how male circumcision will affect HIV transmission to women, as well as the risks and benefits of performing circumcision in men who are already HIV infected. An ongoing study sponsored by the Bill & Melinda Gates Foundation is looking at how male circumcision affects HIV transmission to female partners. Unpublished data from an already conducted study in Uganda, which was presented at an Institute of Medicine Meeting on HIV prevention trials (see *Optimizing prevention research*, page 12), suggests that HIV transmission between recently circumcised HIV-infected men and their female partners may be increased if they engage in sexual activity before their surgical wound is completely healed, and this process may take longer in HIV-infected men.

Another concern for developing countries is ensuring access to safe services, which requires training providers to conduct the procedure under sterile conditions and then monitoring compliance. The recommendations also suggest that men seeking circumcision be offered counseling services to help prevent behavioral disinhibition.

Researchers are planning to establish a limited number of sites to serve as centers of excellence for adult male circumcision. The site in Rakai, Uganda where the US NIH-sponsored trial was conducted has now received funding from PEPFAR to serve as a center of excellence in the region.

Institute of Medicine releases report on US AIDS plan

The prestigious US-based Institute of Medicine (IOM), a division of the National Academy of Sciences, recently released a report on the US President's Emergency Plan for AIDS Relief (PEPFAR), satisfying a requirement set by Congress for a three-year review of the initiative. PEPFAR is a five-year, US\$15 billion program and represents the largest commitment made by any nation to fighting HIV/AIDS. It currently provides HIV education, treatment, and prevention services in 15 countries, including Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. After conducting a comprehensive evaluation of PEPFAR's progress, including visits to many of the countries targeted by the initiative, the IOM praised the program's efforts to provide medical care to millions of people, particularly in severely resource-strained settings. Since its inception in 2003, PEPFAR has provided antiretroviral therapy to more than 800,000 individuals, voluntary counseling and testing services for HIV to almost 19 million people, and services to prevent mother-to-child transmission of HIV to more than 6 million pregnant women.

The report also made several recommendations on how PEPFAR could improve their approach, including removing provisions that set aside \$3 billion—far more than is spent on condom distribution or preventing mother-to-child transmission—to focus on abstinence-only education, which has been one of the most controversial aspects of the program. Critics say this restriction has taken funding away from evidence-based strategies and pushed abstinence instead of the more comprehensive ABC approach (abstinence, be faithful, use condoms). Jaime

Sepulveda of the University of California, San Francisco who chaired the IOM committee said a one-size-fits all approach to HIV prevention is not helping and that PEPFAR should promote evidence-based prevention strategies, including promotion of clean needle and syringe exchange programs in countries where the epidemic is fueled primarily by injection-drug users (*Lancet* 369, 1155, 2007).

The IOM also recommended that PEPFAR no longer require all generically produced versions of antiretrovirals (ARVs) be licensed by the US Food and Drug Administration before they can be purchased and used in PEPFAR's programs. Instead the independent panel recommended that PEPFAR support the already-established generic drug approval system at the World Health Organization. The advantage of using these so-called generic ARVs is that they can be purchased at much lower costs than those produced by the pharmaceutical companies that brought them to market.

Other recommendations included transitioning from an emergency-based approach to a longer-term strategic plan, addressing the long-standing issues that contribute to the spread of HIV in each of the target countries, and expanding and improving care and treatment services for orphans.

The goals of PEPFAR are to provide ARVs to 2 million HIV-infected people, prevent 7 million new HIV infections, and provide care services to 10 million individuals either infected with or affected by HIV/AIDS, including orphans. The legislation supporting this initiative must be reauthorized by Congress this fall before entering its final two years. Sepulveda said in the report that the lessons from PEPFAR should be used to motivate other nations to make even larger investments in HIV/AIDS programs in the countries hardest hit by the pandemic.

South Africa launches new AIDS plan

At the end of April the South African government released a new national AIDS plan, outlining the country's strategy to combat the epidemic. At the end of last year, there were 5.5 million South Africans living with HIV/AIDS, according to estimates from UNAIDS, and the number of HIV-infected people continues to rise. In response to these grim statistics, the 160-page plan includes a proposal for halving the number of new HIV infections by 2011. It also proposes improving diagnosis of HIV/AIDS, providing life-saving antiretroviral treatment to 80% of the estimated one million South Africans that are in need, and reducing the rate of mother-to-child transmission of HIV to below 5% over the next

five years. Implementation of the report's proposals will cost an estimated \$6 billion.

The "HIV and AIDS and STI Strategic Plan for South Africa, 2007-2011" was prepared after consultation with government officials, UNAIDS, research institutions in the country, and several representatives of civil society. The release of this comprehensive plan was lauded by many organizations, including the Treatment Action Campaign and AIDS Law Project, and civil society representatives who have been critical of the government's sluggish response to the AIDS epidemic. It was also endorsed by the recently restructured South African National AIDS Council (SANAC).