

Keystone Symposium: Industry Vaccine Candidates in the Spotlight

For six intense days, scientists gathered in the Canadian Rockies for the annual Keystone conference on HIV Vaccine Development (28 March-4 April 2003, Banff, Alberta). This year's agenda offered a typically broad range of themes, from new findings on viral escape in monkeys to studies grappling with the question of just which T-cell subsets are most important for fighting HIV and evaluating vaccine candidates. Here we present headline stories from three corporate players: VaxGen, which discussed results from its recently completed Phase III trial; Merck, with updates on its Phase I clinical trials and announcing a new partnership with Aventis Pasteur; and Wyeth-Aherst, describing a strategy that may improve the usefulness of DNA-based vaccines. Other conference topics will be covered in our next issue.

Philip Berman, developer of VaxGen's gp120-based AIDSVAX[®] vaccine, gave a much-anticipated talk on the outcome of the company's North America/Europe Phase III trial. It was the first presentation of the trial's efficacy results to a scientific audience, following a 24 February webcast describing the initial analysis. At that time, VaxGen made the startling and highly controversial claim that, although the vaccine showed no efficacy across the whole cohort, it protected about two-thirds of African-American, Asian and mixed-race volunteers.

But outside researchers quickly discovered a key flaw in the statistical analysis, greatly weakening the company's claim that the protection data showed high statistical significance. Nevertheless, VaxGen stood by its statement that the vaccine holds promise for this mélange of non-white racial subgroups, a conclusion they said was supported by unreleased data correlating protection in these subgroups with higher antibody levels.

Against this backdrop, Berman's talk in Banff provided a first glimpse of these (and other) studies aimed at building a biologically plausible case for race-based efficacy. "Our hypothesis is still that protection depends on the amount of antibody and the strain of virus," he said. He also discussed

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VAXGEN TRIAL YIELDS TROVE OF BEHAVIORAL AND SOCIAL SCIENCE FINDINGS

BY EMILY BASS

When data from VaxGen's completed AIDSVAX trial were released in February, the media flurry focused on the efficacy results, which were disappointing. Nearly lost in the shuffle were the trial's unqualified successes with recruitment and retention. Here, data refuted pre-trial concerns about the feasibility of following thousands of high-risk vol-

unteers over three years and seven immunizations. Similarly, early fears about major changes in risk behavior during the trial also proved to be unfounded. As the efficacy data continue to be analyzed and debated (see article above), examination of how the trial cohort was managed, and of participants' motivations and experiences, offers some encouraging

lessons—and clear prescriptions—for future Phase III studies.

Incidence rates were higher than anticipated

One concern facing the VaxGen team at the outset was whether they could establish a North American and European cohort with high enough HIV incidence rates for an efficacy trial.

VaxGen: Are There Hints of Race-Based Effects?

BY PATRICIA KAHN

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possible gender-based differences in protection. Slides from the talk are available on VaxGen's website (see www.vaxgen.com/invest/index.html).

But to HIV sequence expert Bette Korber (Los Alamos National Laboratory), the data showed no more than “a hint of a hint of an effect.” Further dimming the vaccine's prospects, Berman said there is no evidence of reduced viral load or slower CD4 T-cell decline in vaccinees who became infected.

Trial Results and Racial Subgroups

He began by reviewing the study's main results, which are summarized in the figure on page 3. Overall there was no difference in infection rates between the vaccine and placebo arms during the trial. But in the 314 African-American volunteers, 9 of 111 placebo recipients (8.1%) became infected, compared with 4 of 203 (2%) vaccinees. From these numbers, VaxGen initially reported 78.3% efficacy in this subgroup, with a confidence interval (CI) of 29-93% and a “p-value” <0.02—meaning that there is less than a 2% probability that these results are due purely to chance. Neither the Asian or mixed race subgroups (73 and 111 volunteers, respectively) gave statistically significant results, but when all 3 groups were combined, VaxGen calculated an efficacy of 66.8% (CI 30-84%; p<0.01).

It was these confidence intervals and p-values, plus the pooling of disparate racial groups, that were challenged after the webcast. That's because the more subgroups analyzed in any study, the more likely it becomes that a seemingly significant result can arise by pure chance. To correct for this, the analysis must include a statistical penalty based on the total number of subgroups examined—which VaxGen, despite initial statements to the contrary, apparently did not do.

According to statistician Steve Self (University of Washington, Seattle and HIV Vaccine Trials Network), even conservative assumptions about the number of subgroups they analyzed drop the lower CI boundaries below zero and increase the p-values, greatly reducing the significance of the race-based efficacy claim. But he doesn't dismiss the findings entirely, saying that the data raise “interesting, intriguing hypotheses that are worth pursuing.”

Does Gender Matter?

Berman also presented a breakdown of infection rates by gender, showing a trend towards more favorable results in women. Although vaccines are traditionally seen as gender-neutral, recent evidence that a candidate vaccine against HSV-2 may work only in women have challenged this notion, especially for sexually-transmitted diseases (see article, page 5). For AIDS-VAX®, while there were 4 infections among 93 women given placebo (4.3%), only 1/175 female vaccinees (0.6%) became infected; for men, the figures were 94/1586 and 190/3155 (5.9 versus 6%). However, the results were not statistically significant, given the small number of women (about 5% of the cohort).

While the low numbers of women and minority

volunteers (and infections) make it difficult to nail down the significance of these trends, gender may play a role in what VaxGen has viewed as race-based. Although Berman did not show gender data on the African-American subgroup (which was nearly 50% women), working back from VaxGen's numbers indicates that 4/53, or 7.7% of black women given placebo became infected, compared with 0/93 vaccinees; for black men, it was 5/58 (8.6%) and 4/110 (3.6%). Adding to the uncertainty, the male-female differences could also reflect anal versus vaginal routes of transmission. In one clear lesson from the trial, this dilemma highlights the need to ensure that future cohorts are broadly representative of the wider population.

Antibody Levels, HIV Strain and Protection

Searching for a possible biological explanation of race- (or gender)-based efficacy, Berman presented data on antibody titers in a small subset of the cohort. The studies measured both binding and neutralizing antibodies (NAb) to the vaccine's lab-adapted HIV-MN strain, but not to GNE8, the second strain. GNE8 was isolated from an infected vaccinee in an earlier trial of AIDS-VAX® (made only with the MN strain) and was later incorporated into the vaccine so as to broaden its range.

Overall, these data show modest trends in the “right” direction, but without answers yet on their statistical significance. NAb titers in uninfected white males given vaccine (124-139 men) were up to 30% lower than in vaccinated African-Americans (49-53 men); women had about 2-2.5-fold higher titers than men (comparing 67-82 women to 200 men).

Turning to studies of HIV strains in infected volunteers, Berman discussed whether AIDS-VAX® may have blocked infection by viruses with gp120 identical to the vaccine, while allowing transmission of more divergent isolates. This “sieve analysis,” done by Peter Gilbert (University of Washington), was based on a 6 amino acid sequence in the V3 loop of both MN and GNE8 (although the sequences flanking this region differ between the two strains, according to Berman). Looking at volunteers from minority racial groups, the data showed that fewer vaccinees than placebo recipients were infected with strains matching the vaccine in this region (about 55 versus 30%, with p=0.0016). In contrast, white volunteers showed no differences in viral strains between vaccine and placebo groups.

These early data sets—which Berman says will take 6-12 months to complete—leave several issues unresolved. For example, since lab-adapted strains are far more neutralization-sensitive than primary ones, the MN neutralization data say little about whether AIDS-VAX®-induced NABs can block primary strains. Berman's response is that conventional neutralization assays “do not reflect physiological conditions for antibodies directed against gp120,” and he rejects the notion that these data would shed light on whether AIDS-VAX® is protective. However, results of passive antibody experiments in the monkey SIV

Trial Basics

Vaccine: gp120 from two clade B strains (MN, GNE8)

Participants included in final data set: 4,741 MSM (94.6%), 268 high-risk women (5.4%).
83.5% white, 6.5% Hispanic, 6.3% black, 1.5% Asian

Randomization:
2:1 (vaccine:placebo)

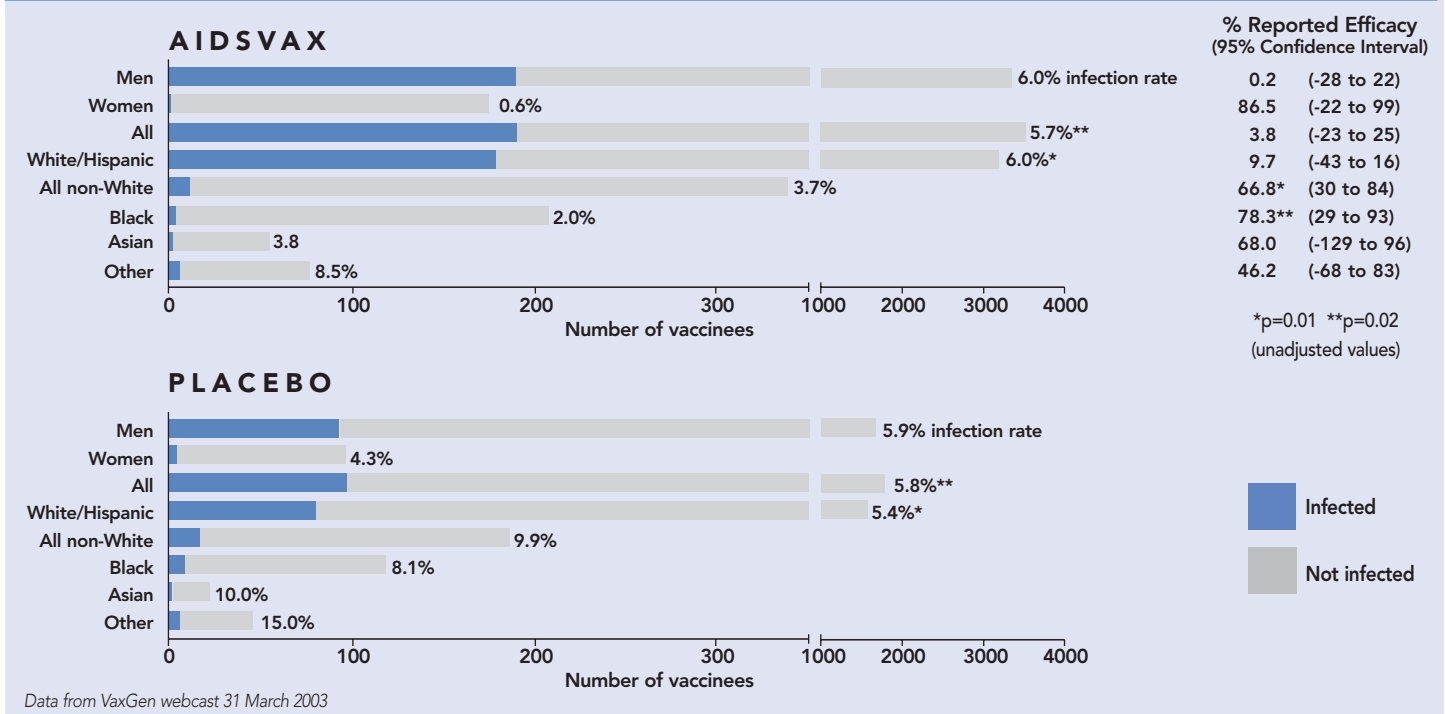
Conducted at 58 sites in North America, 1 in The Netherlands

7 vaccine doses (months 0, 1, 6, 12, 18, 24, 30) over three years

Primary endpoint: prevention of HIV infection

Secondary endpoints: lower viral load; slower CD4 T-cell count decline in breakthrough infections

AIDSVAX TRIAL RESULTS



model lend strong support to the predictive value of such assays (see *IAVI Report*, Dec 2002-Jan 2003, p.2).

A related question is the relevance of the region used for sieving, which is usually hidden from NABs in primary isolates and therefore “an unlikely target for neutralization” of these strains, says antibody expert David Montefiori (Duke University). And, while the observed sieving is consistent with immune pressure from the vaccine, Montefiori asks whether there might be other explanations. For example, he speculates, “since the V3 loop is important in tropism, could strains with different V3 loops be more or less likely to transmit in different racial groups?”

After Banff: What's Next for AIDSVAX?

While at this point the data yield no solid evidence for protection in any subgroup, the question facing the vaccine community is whether they clearly ex-

clude it—and, if not, whether further trials in humans may be warranted. But with VaxGen unable to fund such studies, says spokesman Lance Ignon, the onus has now shifted to NIH. On 23 April, the National Institute for Allergy and Infectious Diseases (NIAID) convened a meeting of outside HIV experts and key stakeholders with VaxGen scientists and collaborators to review the trial data. In a brief statement issued afterwards, NIAID said it would proceed with an independent analysis, leading to a decision on whether government funding for further development of the vaccine is justified. This process, say insiders speaking off the record, reflects a sense that the data on hand do not definitively refute VaxGen's claim.

Additional analyses could also prove useful. One informative direction would be a sieve analysis over a longer region, ideally the full gp120—for which sequence data is available from 336 of 368 in-

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Since launching its first HIV vaccine clinical trials in 1999, Merck has emerged as a major player in the field, with over 600 people now enrolled in its preventive vaccine studies. So far the company has focused on two candidates—one based on naked DNA, the other on a vector made by modifying adenovirus-5 (Ad5), a common virus that causes colds in humans. Both vaccines exclusively target the cellular immune system.

In a data-packed presentation, Emilio Emini, who heads Merck's vaccine research, reviewed results from ongoing preventive trials and described work in some new areas—including improved vectors, multi-gene vaccines and novel prime-boost

combinations. Primate studies with Ad5-based vaccines will be covered in the next *IAVI Report*.

As the company evaluates data from its trials and weighs candidates and strategies for the next wave, several questions are at the forefront. One is whether its DNA vaccine is performing well enough to be kept on the A-list of candidates. Another is how to best overcome pre-existing immunity to Ad5 (seen in about 70% of people in most populations, due to the widespread distribution of wildtype virus) and to develop more immunogenic vaccine regimens. Some approaches being studied: Using either higher doses of Ad5 vaccine or different adenovirus serotypes, combining Ad5 with a DNA prime or

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Update on Merck's AIDS Vaccine Program

BY PATRICIA KAHN

pairing it with a different type of vaccine.

Ongoing Trials

Clinical studies so far have focused on testing the DNA and Ad5 vaccines individually and in a prime-boost combination. Both of these initial constructs were developed as “proof-of-concept” candidates carrying the HIV-*gag* gene, with additional genes to be added at a later stage.

Emini emphasized that the trials are still ongoing, so any conclusions remain provisional. The data shown were mostly evaluations of immune responses to Gag using Elispot assays for interferon-gamma producing cells, with results expressed as the number of responding cells (spot-forming cells, or SFC) per million white blood cells.

DNA-*gag*: On its own, DNA-*gag* has shown low immunogenicity in volunteers vaccinated four times (at weeks 0, 4, 8 and 26). Both 1mg and 5mg doses elicited weak responses in 21/130 (16%) volunteers at 12 weeks and in 36/117 (31%) at the 30-week timepoint (with geometric means of 64-140 SFC and a range of 36-431 across all groups). Neither alum nor the CRL-1005 adjuvant improved responses substantially over those seen with DNA in saline.

Ad5-*gag* and pre-existing immunity: The Ad5-*gag* constructs are proving to be more immunogenic, with about 60% of all volunteers responding at both 8 and 30 weeks. But the data also show a clear blunting of responses in people with pre-existing immunity (PEI) to Ad5.

These preliminary conclusions come from an ongoing study in four groups of 18-29 volunteers, with each group receiving an escalating dose of Ad5-*gag* (ranging from 10^8 to 10^{11} viral particles) at weeks 0, 4 and 26. In presenting the results, Emini subdivided the data according to volunteers' level of PEI: High (defined as neutralizing antibody titers over 200); mid-range (18-200) and none, with roughly equal numbers of participants in each group.

Combining the low- and mid-range PEI groups, at week 30 there were 24/35 (69%) responders across all dosage groups; surprisingly, the lowest dose worked about as well as the highest. The mean number of SFC ranged from 224 to 412, while individual responses varied from 25 to 1381.

The group with high PEI responded less well, showing only 5/18 (28%) responders and in most cases requiring a higher vaccine dose (4 of the 5 responders were in the two highest dosage groups). Stated another way, while high PEI blunted responses at the lower doses, it appears that higher doses can at least partially overcome this immunity.

DNA-*gag* and Ad5-*gag* prime-boost: Emini also reported on immunogenicity of the DNA/Ad5 combination, comparing it with an Ad5-only regimen. Besides its possible effect on improving overall immune responses, DNA priming is seen as a potential strategy for reducing the Ad5 dose (and/or number of doses) and thereby helping to overcome

PEI. The study was done by priming twice (in the Ad5 group) or three times (for DNA), then boosting at week 26 with a low dose of Ad5 (10^7 particles).

Disappointingly, DNA does not look substantially better than Ad5 as a prime for an Ad5 boost, based on 30-week data. The high PEI group had 7/20 (35%) responders to DNA/Ad5, compared with 5/18 (28%) for Ad5/Ad5. Mean SFC counts were 187 versus 125, with overlapping ranges of 10-485. The trend was similar for the low- and mid-range PEI volunteers, although DNA/Ad5 induced higher responses in some individuals (reaching 2,300-2,800 SFC, compared with 1,400 for Ad5/Ad5). Emini says that final decisions about the fate of the DNA vaccines will be made once the complete data are in.

But these data—with their implication that DNA may not add significant value to an Ad5 vaccine—have led Merck to change plans for its upcoming international Phase I trial. Instead of testing DNA/Ad5, as originally anticipated, the 435-person study will use Ad5 alone. The study will be done through the US HIV Vaccine Trials Network (HVTN) at sites in the US, Brazil, Thailand, Malawi, South Africa, Haiti and Peru, and should start within the next few months.

New Combinations, New Vector Strains

In the meantime, Merck is evaluating other possible candidates to combine with Ad5.

Boosting with canarypox: Just days before the Banff meeting, Merck announced a partnership with Aventis Pasteur to test that company's canarypox-based HIV vaccine (ALVAC vCP205). In his talk Emini summarized the monkey data behind this decision, with more complete results shown in a poster by Danilo Casimiro and colleagues. Another factor favoring ALVAC is its well-established safety record, with more than 2,000 volunteers immunized in clinical trials over the past decade.

The crucial study looked at animals primed with a low dose of Ad5 (10^7 - 10^9 particles) at weeks 0, 4 and 26, followed at 56 weeks by a boost with either ALVAC vCP1606 or MVA carrying HIV-*gag*. Canarypox boosting gave the highest responses, which ranged from 1,200 to 2,300 SFC at two weeks post-boost and dropped off by about two-thirds at 8 weeks. An MVA boost induced 800-1,354 SFC at week 2, down to 100-300 at week 8. Interestingly, the synergy between Ad5 and canarypox disappeared when the vaccines were used in the reverse order, with canarypox as a prime and Ad5 as a boost. Challenge data are not yet available.

But the decision to move an Ad5/ALVAC combination into Phase I trial is firm, with Merck due to start a trial imminently. The study will recruit volunteers who were previously vaccinated with Ad5 and then boost them with ALVAC.

Other adenovirus serotypes: Given the dampening effect of PEI on responses to Ad5-based vaccines, Merck is also investigating less common strains of adenoviruses as potential as vaccine vec-

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Does Gender Matter for HIV Vaccines?

New Approaches to an Open Question

BY EMILY BASS

Do vaccines work differently in men and women? Over the past few years, this question has been transformed from a far-flung supposition to a serious query for HIV vaccine researchers, even cropping up in the recent analyses of VaxGen data (see Keystone article, page 1).

This type of discussion marks a fairly radical shift. Globally, millions of men, women, boys and girls receive immunizations each year, and there is little evidence of gender-specific effects in any of these products.

The first hint of the new paradigm came in September 2000, with a brief but startling announcement from GlaxoSmithKline (GSK): Data from the company's two Phase III trials appeared to show that a candidate vaccine against herpes simplex virus-2 (HSV-2) was about 74% efficacious in preventing HSV-2 disease in women who did not have HSV-1, a related virus that causes cold sores and confers some natural protection from HSV-2. In contrast, the vaccine showed no significant protection in men. However, the trials were not statistically powered to measure efficacy separately in men and women, so the results—while striking—were not definitive evidence of a gender gap (*IAVI Report* Jul-Sep 2001).

Since that announcement, the vaccine research field has moved from skepticism about the influence of gender on vaccines to more active investigation, particularly in the context of vaccines against sexually transmitted infections (STIs).

In November 2002, GSK and the US National Institutes of Health (NIH) launched a new 16-center Phase III study of the HSV-2 vaccine, which aims to enroll 7,550 female volunteers—enough to determine efficacy in women only. And if the earlier findings are confirmed, then the world will have the first gender-specific vaccine on its hands, along with a host of questions about the potential for similar effects in other vaccines.

“The herpes trial is at the back of everyone's minds” in HIV vaccine development, says IAVI's scientific director, Wayne Koff. “If it turns out that [the findings] are real, it's going to open a whole new field.”

In fact, the field already exists. November 2002 saw the launch of a second women-only Phase III trial of an STI vaccine, in this case against four sexually-transmitted strains of human papillomavirus (HPV). HPV is a family of more than 100 viral strains, a few of which are linked to genital warts, cervical and anal cancer. Since cervical cancer is the most common malignancy associated with HPV

infection, Merck, which is sponsoring these studies, has so far conducted its trials almost exclusively in women. (A small number of men were included in early Phase I safety trials.)

To date, Merck has conducted two proof-of-principle studies of separate HPV vaccines in women—one against the two main strains that cause genital warts, and another against two strains linked to cervical cancer. Both candidates appeared to show strong protective efficacy in women, as measured by the absence of HPV DNA matching the vaccine strain in cervical specimens, or of cervical intraepithelial neoplasia (*N Engl J Med* 347:1645;2002; see *IAVI Report*, Jul-Sep 2002). The ongoing women-only Phase III trial, which is taking place at sites in North and South America, Southeast Asia, Africa, Europe and the Middle East, tests a combination vaccine against all four strains. This study will follow subjects for at least two years—longer than previous studies—to allow researchers to monitor the key endpoint: Whether the vaccines reduce the risk of cervical cancer, which may develop many years after HPV infection.

Will the same candidate vaccine also protect men from infection with the HPV strains that cause genital warts and anal cancer? To answer this question, Merck may conduct separate trials in men, says Eliav Barr, a lead investigator on the Merck team. “We will not rely on efficacy data in women to make statements [about efficacy] in men.”

Barr's dogma-defying statement is characteristic of the new—though by no means universal—perspective on STI vaccine research. It's an approach that is informed by an ever-expanding knowledge of mucosal immunology and hormonal influences on health and disease, fields which provide potential explanations for observed gender differences in susceptibility and prognosis for many STIs. In the AIDS field, researchers are paying attention to differences in rates of transmission from women to men and men to women, and gender gaps in viral set point and viral load following infection. “People are starting to say, ‘Follow the women,’” says IAVI's Koff.

Pieces of the Gender Puzzle

Beyond the HSV-2 vaccine studies, the only other data bearing on adult gender differences and vaccines address side effects and levels of immune responses, not protection itself. A primary source of these data is the US Army. At a November 2002 meeting* on gender and HIV/AIDS, Philip Pittman (US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland), reviewed these studies, starting with the most recent findings on anthrax vaccines. During Operation Desert Storm,

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**Sex and Gender Differences in HIV (4-5 November 2002)* sponsored by the Forum for Collaborative HIV Research

there were numerous reports of severe local reactions in women military personnel. At first, Pittman said, it was assumed that women were “just complaining” more than men.

However, a post-9/11 prospective study of different immunization routes and dose schedules of anthrax vaccine confirmed the initial reports: In women, the traditional, subcutaneous regimen led to more frequent, severe and long-lasting local reactions (including lesions and subcutaneous nodules) than in men. Pittman also reported that women in this group had significantly higher antibody titers than their male counterparts. Moving back in time, Pittman surveyed studies from the mid-90s which showed gender-specific differences in antibody responses to vaccines against Venezuelan Equine Encephalitis virus, yellow fever and botulin toxin. In several of these instances, women had lower antibody titers than men, in contrast to the data from the anthrax study.

VaxGen has added another piece of data to the puzzle: Compared to men, women had higher titers of antibodies against gp120 (in ELISA tests and in neutralization of the HIV-B(MN) strain, one of two strains upon which the vaccine was based). This finding is the latest reports of differences in antibody titers in men and women (or boys and girls). Similar results have been reported in response to other vaccines, including measles and hepatitis B. And mouse and human studies have shown that women have higher levels of serum immunoglobulins than men when exposed to the same pathogen, suggesting an increased propensity for antibody production in women—which could translate into higher vaccine-induced antibody titers. There are also well-documented gender differences in the risk for certain autoimmune diseases. However, none of these gaps has ever been directly linked to a male-female split in vaccine-induced protection, making the data little more than an interesting footnote in vaccine research.

Which Matters Most, Bugs or Bodies?

The GSK findings have moved gender from footnote to foreground, and raised the question of where the differences come from. At this point, answers are purely speculative. David Bernstein (Cincinnati Children’s Hospital, Ohio), a herpes researcher and investigator on the GSK trials, wryly sums up the two prevailing hypotheses. “One is that women are the stronger sex, and make more T-cells or more antibodies, or more of whatever is protective,” he says. “The second is that men and women respond to vaccines equally well, but that the infection begins in different ways.”

Bernstein and Moncef Slaoui, a senior vice-president at GSK and head of the HSV-2 vaccine development effort, favor the latter explanation. In this model, men and women have essentially the same amount and type of immune responses in their blood, but these defenses do not translate into equal

protection at the local site of infection. This could be due to gender differences in how well vaccine-induced responses penetrate the genital tract, or to enhancement of vaccine effects by naturally-occurring defenses. Women’s genital tracts are bathed in antibodies, including IgG and IgA, mucins and other innate host factors such as defensins. In contrast, men’s genital tracts are protected by a keratinized outer layer of skin with far fewer immune defenses at the surface. A viral infection that starts at a break in the penile epithelium is therefore less likely to encounter protective defenses than one occurring at the surface of an intact vaginal membrane.

The basic immunologic data that GSK collected in its first two studies have so far not revealed any gender differences. As reported in the *New England Journal of Medicine* (*N Engl J Med* 347:1652;2002), there were no statistically significant differences between immunized men and women in blood levels of binding and neutralization antibodies to HSV-2 and glycoprotein-D (a component of the adjuvant). GSK also looked at cell-mediated immune responses in a small subset of vaccinees. Slaoui says that these data, which were not included in the NEJM article, showed no evidence of gender differences.

To get a better picture of what immune responses are protective in women, the HSV-2 vaccine trial team is planning substudies, scheduled to start in late 2003, that will take place at Phase III sites. These studies will look at possible correlates of protection, including mucosal CD4 and CD8 T-cell responses and HSV-2 antibodies in the blood and genital tracts. They will also measure HSV-2 shedding in the genital tract.

Even if these substudies yield insight into how and why women are protected, the broader implications of HSV-2 protection in women only—assuming that this result is confirmed in the Phase III trial—still remain to be seen. “It is hard to really know whether the data are generalizable or whether they are specific to the antigen and disease in question,” says HVTN head Larry Corey (University of Washington, Seattle), who heads the US HIV Vaccine Trials Network and has also studied herpes vaccines.

The Glaxo team agrees that the finding might be related to unique characteristics of HSV-2. Except for episodic outbreaks in the genital mucosa, HSV-2 is contained in the neural tissue, a relatively immune-free zone. This means that the burden of protection and immune control falls almost entirely on mucosal immune defenses, where there are significant differences between men and women. Following this line of argument, vaccines against STIs that remain confined primarily to the genital tract or sequestered compartments—i.e., HSV-2 and HPV—might be more likely to show gender-specific differences than vaccines targeting STIs such as HIV or Hepatitis B, which spread to the blood, where immune defenses in men and women are more similar. Indeed, the hep-

“We will not rely on efficacy data in women to make statements about efficacy in men.”

—ELIAV BARR
on Merck's papilloma virus vaccine

IS HORMONAL CONTRACEPTIVE USE A FACTOR IN HIV VACCINE TRIALS?

BY EMILY BASS

The choice to use—or not use—condoms impacts enormously on women's risk of acquiring HIV. But it is possible that other methods of contraception could also impact women's susceptibility to HIV—for better or for worse. For example, new studies are looking at whether the diaphragm reduces HIV acquisition risk by covering the cervix, a site that is particularly vulnerable to infection. And there is a large body of data, much of it contradictory, on how hormonal contraceptives (HCs) might affect acquisition of HIV.

All of this work has implications for vaccine trials. In addition to providing ongoing condom promotion, vaccine trials also ask women participants to use an effective form of birth control to prevent pregnancy during the study. If these methods do impact on vulnerability to HIV, they could also affect analyses of vaccine efficacy, a possibility that was raised at a recent NIH-sponsored meeting on fertility regulation and HIV.*

The meeting began with an overview of HC-HIV research by Christine Mauck of CONRAD (Arlington, Virginia), a reproductive health research organization. Mauck traced the topic back to a 1991 study led by Frank Plummer (University of Manitoba), which found a link between longer duration of oral contraceptive (OC) use and HIV infection in a cohort of Kenyan sex workers. Follow-up research in sex workers, including studies by Julie Overbaugh (University of Washington, Seattle), confirmed this finding and extended it to injectable contraceptives (ICs) such as Depo-Provera. But other studies, including new data from

serodiscordant couples cohorts in Rwanda and Zambia, and from the Rakai district community cohort in Uganda, did not find this association. Overall, Mauck said that the HC-HIV link was seen in studies of sex workers and women with multiple partners but not in studies of women recruited from family planning and antenatal clinics.

Fine-tuning Messages and Protecting Options

In the face of this contradictory data, most researchers agree that including information about potential HC-HIV interactions in family planning education could do more harm than good, by scaring women away from a birth control method that affords great privacy and autonomy.

The current popularity of HC was dramatically illustrated in a talk by Iqbal Shah (World Health Organization), who reported that in the six countries at the heart of the African AIDS epidemic—Botswana, Swaziland, Zimbabwe, Lesotho, Zambia and South Africa—66% of women who practice family planning use hormonal pills or injectables, while only 4% rely on condoms. Shah and others pointed out that this figure shows the failure to position condoms as tools for preventing pregnancy as well as STDs.

Researchers like Julie Overbaugh and Susan Allen (University of Alabama, Birmingham), a lead investigator on serodiscordant couples studies, suggest that AIDS research projects, including vaccine trials, can help develop more nuanced messages. Trial sites can work with local family planning clinics, to include IUDs, diaphragms, and other methods, and can tailor their messages depending on the study population. For instance, Overbaugh suggests that in sex

worker populations, trial planners “would have to think twice about intervening to promote any kind of hormonal contraceptive use.”

A Potential Trial Variable

When a vaccine is eventually licensed, it will have to work in populations that include HC users. As Overbaugh suggests, vaccine trials can help gather data on whether and how these methods impact vaccine efficacy in preventing HIV infection or slowing disease.

The most compelling data relating to this question come from Overbaugh and her colleagues, including the Mombasa Research Team. Speaking at the recent Keystone HIV Vaccine Conference in Banff, Overbaugh reviewed data gathered from a group of female sex workers who have been followed for ten years so far. In this group, OC or IC use increases the risk of becoming HIV infected—and appears to be linked to faster rates of disease progression. In 2000, her group published data showing that many of these women were infected with more diverse viral populations than men (*Nat Med* 6:71;2000). Since then, she's presented as-yet unpublished data which show a link between diversity and more rapid disease progression. This diversity is more likely to be seen in women who use hormonal contraceptives than matched peers who used other methods of birth control. Overbaugh also mentioned an earlier study showing that women who use OCs shed more virus, and that shedding increases with OC dosage.

Some of these unpublished data were presented by Overbaugh's colleague Jared Baeten (University of Washington, Seattle) at the February 2003 Retrovirus meeting. In this study, women who used the injectable contra-

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Fertility Regulation and Systemic Hormones in HIV-infected and At-Risk Women (13-14 January, 2003, sponsored by the National Institutes of Health, McLean, VA)

ceptive DMPA (the generic name for Depo-Provera) at the time of HIV infection had a persistently higher viral set point (by 0.3 log) and faster CD4 cell count decline than those who did not use ICs. Both of these trends are associated with more rapid disease progression. Reflecting on the implications for vaccines, Overbaugh says, “Trial designers will have to include hormonal contraceptive use as a variable,” and monitor potential effects on transmission and progression.

Probing for Mechanisms

Why might hormonal contraceptives affect risk? Animal and basic science studies have provided some intriguing clues.

One early theory suggested that progesterone decreases the thickness of the vaginal membrane, which in turn facilitates HIV infection. This hypothesis has been tested in at least three primate studies, including a widely-discussed experiment by Preston Marx (Tulane University, New Orleans) in which female macaques were given implants that elevated progesterone to levels seen in the second half of the menstrual cycle. These macaques and a control group, which received placebo implants, both received a low-dose vaginal challenge. Monkeys with implants were nearly eight times more likely to become infected than the control group

(which was challenged during the first half of the menstrual cycle, when progesterone levels are at their lowest.) Vaginal biopsies on a parallel set of animals showed that progesterone-treated monkeys had significantly thinner vaginal membranes.

But the explanation may not be so simple. Subsequent studies linked progesterone treatment to vaginal thinning in monkeys, but also found that monkeys, who have thinner vaginal mucosae than women, metabolize progesterone more slowly than humans. Monkeys also exhibit different tissue changes across the menstrual cycle.

Another point is that hormonal contraceptives might alter the genital tract immune milieu. Many components of this environment, including cell populations, activation markers and cytokine-secretion patterns vary across the menstrual cycle under natural hormonal regulation. Mucosal immunologist Charles Wira (Dartmouth University, New Hampshire) has found fluctuations in expression of CCR5 and CXCR4 (receptors that HIV uses to enter cells) in uterine epithelial cells across the menstrual cycle (samples obtained from patients undergoing hysterectomies).

A recent study from Manu Prakash at Imperial College, London (*J Reprod Immunol* 54:117;2002) showed differences in activation markers and cell pop-

ulations in cervical samples from HIV- and STI-negative women (sampled at the same time in their menstrual cycles) using hormonal contraceptives, compared with those who did not. HC users had a higher level of CCR5 expression on cervical CD4 and CD8 T-cells compared to non-HC users, and a higher proportion of dendritic cells—targets for HIV infection—in the cervical epithelium.

While intriguing, these studies do not explain why HCs would be associated with HIV acquisition in some women and not in others. One theory is that sex workers have a different level of immune activation in the genital tract—perhaps due to exposure to STIs and semen from many partners—and that HCs may have a more pronounced impact in this context.

New answers could come from a 6,000-women study in Uganda, Thailand, and Zimbabwe, that will compare rates of HIV infection, pregnancy and contraceptive method-switching in women using both HCs and condoms and those using condoms alone.

As these population-based data are being gathered, Wira advocates a complementary focus on hormones and local immune responses in vaccine trials. “If you’re trying to interfere with infection in a setting where the immunologic parameters vary, then of course these variations need to be considered.” ♦

THE FEMALE GENITAL TRACT: A GLOSSARY

Ectocervix: a zone of tissue on the outer cervix; thicker than the endocervix and with a squamous epithelial layer contiguous to the vaginal mucosae.

Endocervix: a zone of tissue characterized by a thin columnar epithelial layer containing target cells for HIV, including macrophages and dendritic cells. Endocervical secretions are sampled using “SnoStrips” or swabs; cell samples are obtained using cytobrush, which dislodges cells within the cervical canal.

Lower reproductive tract: vaginal canal and cervix (uterine opening).

Upper reproductive tract: uterus, ovaries and fallopian tubes.

Vaginal Mucosae: highly heterogeneous tissue of the lower reproductive tract; top layer (vaginal epithelium) containing squamous cells (see ectocervix) and a range of immune cells, such as dendritic cells and macrophages, although at lower proportions than in the endocervix. The epithelial surface is covered in mucins, IgA, IgG (components of the adaptive immune system) and innate defense components.

EUROPEAN UNION LAUNCHES AFRICAN CLINICAL TRIALS PROGRAM

BY MARK BOAZ

On 27 March 2003, the European Parliament endorsed the creation of an Africa-based clinical trials program to test new medical products targeting AIDS, malaria and tuberculosis. The endorsement came with €200 million in direct funding from the "Sixth Framework Programme," the European Union's (EU) research strategic plan for 2002-2006, and an expectation that another €400 million will be contributed over this timeframe through in-kind support from national programs and additional donations from industry, member state governments, multilateral agencies and other sources.

Pending final approval by the European Council on 12-13 May, the program will be launched as an entity independent of the European Commission (EC), with its own scientific planning board plus a fundraising and administrative body.

The European and Developing Countries Clinical Trials Partnership (EDCTP) will support Phase II/III clinical studies of both therapeutic and preventive interventions (including drugs, vaccines and microbicides), according to Arnd Hoeveler, Head of the EC's Poverty-Related Diseases Unit that coordinated the program's planning. The research agenda will be set once a Partnership Board is established, and will be organized around several core objectives: Building laboratory and human capacity in developing countries; fostering both North-South collaborations and South-South networking; facilitating better integration of European national programs; and development of locally relevant and affordable interventions for the developing countries. Much of the EDCTP's activity will build on sites and projects already supported through bilateral programs between single European and African countries, although the current plan states that groups from any country can participate. While the Sixth Framework Programme's activities on poverty-related diseases require at least two European and two African partners, it remains to be decided whether the Partnership Board will extend this requirement to the EDCTP.

The Partnership Board will consist of 12 researchers—four selected by an African strategy committee (see box) that is already at work, four by the European states, and four more by the initial eight members, according to Dagmar Baroke of Germany's Ministry for Research and Technology, who is involved in planning the EDCTP. Two representatives of the EC will also sit on the Board but will not have voting rights. Spending and administrative authority will rest with a separate group consisting of members from the member states' national research agencies, and which will establish one Secretariat in the Hague and another at an African location still to be decided.

Recruitment for an Executive Director of the EDCTP is underway, with advertisements for this position and also those for Board members placed in the press. Planners anticipate a call for research proposals by September, and expect the first projects to be chosen in late 2003. Although no official numbers are yet available, sources say that about €30 million will be committed by year's end.

The EDCTP's organization, and its independence from the EC, is based on a legal structure called a European Economic Interest Group (EEIG)—a structure that has been used for a broad range of other scientific and cultural activities supported by the EC, such as the Arte cultural channel on cable television. For the EDCTP it was adopted in order to circumvent the fact that EU research activities are funded in five-year blocks (within Framework Programmes, which set the scientific priorities), but that a mechanism was needed to allow EDCTP projects and funds to continue beyond this limited period. EEIGs can continue as long as they receive support—whether from subsequent EU Framework Programmes or from other sources.

So if the EDCTP receives new funding for the post-2006 period, it will be able to initiate new projects beyond that date, says Baroke. But a more immediate challenge, she adds, will be for the program's administrative arm to nail down contributions beyond the EU's direct €200 million allocation and the in-kind support from member nations. ♦

The EDCTP's Developing Country Coordinating Committee

Members of this group were chosen to represent four regions of Africa (sub-Saharan, East, Central and West) and the three diseases that fall under the EDCTP. The members are:

For HIV/AIDS: Simon Agwale (Nigeria), Kobus Herbst (South Africa), Anatoli Kamali (Uganda) and Lynn Zijenah (Zimbabwe)

For tuberculosis: Kashongwe Munugolo (DRC), Joseph Odhiambo (Kenya), Voahangy Rasolofo (Madagascar) and Oumou Sow (Guinea)

For malaria: Dicky Akanmori (Ghana; committee chair), Francine Ntoumi (Gabon; committee co-chair), Akin Sowunmi (Nigeria) and John Waitumbi (Kenya)

Taking a Rights-Based Approach to AIDS Research

AN INTERVIEW WITH

At the last two International AIDS Conferences, the Canadian HIV/AIDS Legal Network has co-sponsored workshops (“Putting Third First”) that have been widely recognized for bringing together AIDS advocates from diverse fields, including microbicides, vaccines and treatment. The common ground is a human rights-based approach, which argues that international statutes are important tools for advancing treatment and prevention agendas. Australian-born David Patterson was a

founding member of the Network in 1992 and is now its director of International Programs and Capacity Building. Trained in law and public policy, Patterson has helped the Network develop its comprehensive approach, to promoting AIDS vaccine research and access to treatment in Canada and around the world. Recently, he spoke with IAVI Report Senior Writer Emily Bass about why scientific research on AIDS vaccines and other interventions is a human right.

David Patterson



How can a human rights-based approach be used to further HIV vaccine research—or any scientific research?

The rights-based approach draws on a strong, developing body of international law that proclaims and secures the rights of individuals with respect to their governments. In the area of HIV/AIDS, we’re looking particularly at the right to health. Governments have to assure the conditions under which people can be healthy.

We argue that if there’s research which needs to be done—for example, on new treatments or prevention technologies, like vaccines and microbicides—then governments have the obligation either to do that research or to make sure it gets done.

What are some of the international agreements you invoke in making these arguments?

The source document for all our work is the Universal Declaration of Human Rights, which proclaims that every human being should be guaranteed the right to education, freedom from persecution, and a standard of living adequate for their health and well-being. Most governments have entered into legally-binding treaties whereby they promise to assure the rights set out in the Universal Declaration. For civil and political rights, governments have committed to immediate action; for other areas, like health, they have committed to acting to the best of their ability according to their national resources.

The right to health and other obligations are also set out clearly in the International Covenant on Economic, Social, and Cultural Rights (ICESCR), which has been ratified by over 140 countries. The ICESCR is one of the treaties which guarantees the rights set out in the Universal Declaration.

How effective are these treaties, especially when countries like the US do not sign them?
[The US has never ratified the ICESCR,

although it signed in 1977.]

International law is being tested at the moment, and in some areas it’s been strengthened and extended. For example, we’re seeing the introduction of an international criminal court, and the further development of mechanisms for handling individual complaints under human rights treaties.

Even countries that are uncomfortable with the idea of a universal human rights framework are beginning to acknowledge that these laws exist. When North Korea tried to withdraw from the nuclear nonproliferation treaty, the fact that they announced they were going to withdraw, in the way that the treaty proclaims, actually meant that they saw themselves as being bound by it.

Human rights lawyers also argue that these declarations are customary international law, meaning that countries can be held to their principles even if they have not signed a specific treaty.

Where are examples of international covenants being applied in the field of HIV/AIDS?

One example is the case that South African activists brought against the government to gain national access to antiretrovirals which reduce mother-to-child transmission. The arguments put before the court addressed not only South Africa’s constitutional obligations, but also its obligations under international law.

There was also a case of a foreign national in the UK who was facing deportation to his home country, but was so sick with AIDS that he surely would have died if he had been deported. The European Court of Human Rights held that it would have been a breach of his human rights to send him back, given his condition. It’s a rather limited decision because it applied to someone who was very ill. But at the same time, it was a decision that put access to treatment in a human rights framework.

It doesn’t take much to go a bit further and argue that if you have an epidemic but no cure or affordable treatment, then governments are obliged to explore vaccines as an option.

How have can these covenants be linked

to AIDS research?

Vaccines are starting to be included in a growing body of work on the right to health. For example, in August 2002, the UN Commission on Human Rights appointed Paul Hunt, a law professor from New Zealand, to serve a three-year term as a special rapporteur on the right to health, focusing on neglected diseases and HIV/AIDS in developing countries. We're going to provide him with the materials that have been developed on obligations of governments around AIDS vaccines and research, so they can be factored into his work.

AIDS vaccines were also being incorporated into the latest version of the UN guidelines on how international law applies to AIDS. The original version was prepared in 1996, a time when vaccines and treatments weren't high on the agenda in the context of the developing world. Last year the guidelines were revised, and they now make direct reference to legal and other measures to assure access to treatments and vaccines.

The UN General Assembly Declaration of Commitment on HIV/AIDS is not binding on states, but it's another advocacy tool we can use.

How can governments start to get involved in vaccine research?

National vaccine plans are a great entry point. They are evidence of governments taking up their responsibilities to address the right to health in the domain of epidemic diseases, which are specifically mentioned in the ICESCR.

A national vaccine plan can lay out the ways that governments will fulfill some of the obligations related to assuring this right, including investing in the research directly, or assuring private sector conditions such as tax incentives, that encourage investment. A plan can also lay out commitment to investment in basic science; support for public-private research partnerships; creation of laws to limit liability claims; and government-backed compensation funds for vaccine manufacturers. National vaccine plans can also be explicit about the ways that governments will ensure the right of access to the benefits of scientific research, which is also proclaimed in the ICESCR.

So far, Canada is the only industrialized country which is developing a national plan. How did this happen?

Community advocacy around HIV vaccines actually started in Canada in 1999 on legal and ethical issues. Together with the Center for Bioethics of the Clinical Research Institute in Montreal, we developed a background paper. The next step was a national workshop, funded by the government agency Health Canada, that brought together many groups—including men who have sex with men, injection drug users, and aboriginal

peoples and AIDS researchers. Out of that came recognition of the need for a much more coherent strategy in Canada.

We released a set of recommendations in a report (www.aidslaw.ca/Maincontent/issues/vaccines.htm) and at the Network's satellite meeting in Barcelona, (www.aidslaw.ca/barcelona_2002/e-barcelona2002.htm). And in Barcelona, the Canadian government representative announced that Canada would actually develop a vaccine plan.

What will the plan include?

As it stands now, the plan will involve a research strategy and an access strategy, which will look at complicated issues around a vaccine's degree of efficacy, costs, and the use of partially protective vaccines. We're also committed to including a component on Canada's international response around the development of HIV vaccines.

Another suggested element is a communications plan. Before release of the VaxGen data, the Network worked closely with the Canadian AIDS Society to distribute materials and brief the press. Once the data came out, David Thompson, who works on national vaccine issues at the Network, did extensive media interviews. So the NGO community was prepared in a way that showed coordination and leadership. We hope the national vaccine plan in Canada will include government planning for similar activities.

As other countries go through this process of making national plans, differences will surely emerge. Is there a point where we get some consensus?

I would be delighted if five or six countries came up with vaccine plans within the next year or so. Especially if they addressed research obligations and so on, because this would give advocates another tool for holding governments to their commitments.

But we're a long way from the situation where we've got a problem with too many conflicting vaccine plans. The first few may be quite different from one another. But the more they're shared, the more people will draw on the experience of the groundbreakers, and the plans will become more homogeneous over time.

The challenge is to recognize that there is commonality. My sense is that countries often think their situation is so specific that they have little to learn from other countries. Yet from a global and historical perspective, we can see this is not true.

Getting back to the topic of treaties and agreements, does international law also apply to corporations?

We're not seeking to apply international human rights law directly to corporations at this

continued on 12 ►

stage. I think it could undermine the credibility of the tools we have. If we say that international law assures everyone the right to everything, and that everyone has a commitment to assure this right, then it just becomes meaningless.

So we have to recognize the limitations of international law, while at the same time asserting the responsibility of governments to regulate corporations within their respective and collective jurisdictions.

Are there other ways to apply some of these principles to companies?

There is a whole area of exploration into this—it's very cutting edge. The United Nations has created a Global Compact with businesses to assure human rights and environmental awareness in the context of globalization (see www.unglobalcompact.org/Portal). There have been other efforts, too. The International Labor Organization (Geneva) worked with businesses, government and labor to develop a code of practice on HIV/AIDS in the workplace, addressing stigma and discrimination, treatment and care for workers. There's an expectation that once a process like this has taken place, then the three sectors will move it forward, and the ILO made a call for that in February, 2002.

But these initiatives are not legally binding. As advocates, we call this area "soft law." The hard law is the treaties—the ink on the paper. Soft law is this expanding area of a sense of obligation that other actors should respect international law, even when they are not directly bound by it.

In the AIDS vaccine field, we can develop memoranda of understanding with transnational corporations involved in research and, eventually, distribution of vaccines—similar to the commitments which have been made to reduce the prices of antiretroviral medications in the developing world.

Is there a tension between the kinds of intellectual property [IP] issues in developing vaccines—where companies need assurances that IP will be protected—and treatment, where the move is towards generic manufacturing?

We have to acknowledge that the private sector isn't going to invest unless there is a predictable international IP environment. At the same time, we recognize the overwhelming imperative to provide affordable treatment as soon as possible to people living with HIV in developing countries.

I think the answer lies in recognizing that intellectual property must be respected in order for research to continue, and, simultaneously, that the poorest countries should be allowed to utilize existing protections and mechanisms to assure access to treatments. This means that we in the West will continue to pay high prices for our medications, and that we will carry the burden of the research agenda so that people in developing countries can

benefit from this research.

Governments also have an obligation here, which is to guarantee purchase in both developed and developing world contexts. If we can do this—for example, through long-term commitments of governments and institutions like UNICEF and the World Bank to purchase vaccines—then it will also strengthen companies' willingness to develop vaccines based on the most common clades in developing countries, if clade turns out to be important for vaccine efficacy.

Can the research community draw on international law to protect or improve the rights of people in certain potential trial populations, like commercial sex workers and IV drug users?

Governments want this research, and they don't want to be seen to be obstructing it. So trials are another advocacy opportunity. We can say to governments, "Look, we have a concern here." We need to ask for a clear statement from host and partner countries on issues such as confidentiality [around serostatus or trial participation] and protection of human rights, so the research can proceed.

So it's an incremental process.

Absolutely. I think when people look at laws, they see things in black-and-white. But people who work in the law know that there are many factors which influence a decision to prosecute, and that a lot can be done without actually achieving law reform. In fact, law reform may be the last thing to come about, once communities and authorities realize what is necessary.

The Durban and Barcelona "Putting Third First" satellite meetings brought together treatment, vaccine and microbicide advocates. Based on that experience, where are the opportunities for collaboration among these fields?

There are many areas. Treatment access is a key issue for vaccine research because of the need to assure the best treatment for participants who become infected during the course of trials.

Increasing the health care budget at country level is another area for joint collaboration. So is assuring mechanisms for distributing health commodities, whether they're treatments, HIV vaccines or other vaccines. Medical literacy amongst practitioners and the communities is another common agenda point.

How do you respond to cost-benefit analyses which pit treatment against prevention, or funding for existing interventions against research into new ones?

The difficult decisions about budget allocations can best be made by the countries that are directly affected. We hope they will do that with full community consultation. I don't think that we

“Countries often think their situation is so specific that they have little to learn from others. The challenge is to recognize commonality.”

Best- and Worst-case AIDS Epidemic Scenarios Discussed at Davos

BY EMILY BASS

This January's World Economic Forum (WEF) meeting in Davos, Switzerland featured a three-hour workshop on "The Economic Impact of HIV/AIDS." Led by IAVI CEO Seth Berkley, participants considered best- and worst-case scenarios for government and industry responses to HIV/AIDS in the next decade. (The full text of both scenarios is available at www.weforum.org/pdf/Initiatives/GHI_2003_HIVAIDS_S_Scenario.pdf) The workshop was a continuation of a series of discussions about multisectoral involvement in AIDS and vaccine development held over the past year at regional WEF meetings in New York, Cape Town and New Delhi (see *IAVI Report* March/April and May/June, 2002).

In the best-case scenario, entitled "Fighting Back, Saving Lives," rich countries donated 0.7% of their GDP to development, poor countries received debt relief, and global mobilization resulted in greatly expanded access to treatment and prevention, and more research on new vaccines and drugs. As a result, African countries saw infection rates drop from peaks of 30-40% in 2002 to 5% in 2020, while India and China kept national prevalence below 1%. In contrast, the worst case scenario, "A World in Crisis," considered the impact of global denial of the HIV/AIDS

threat, and of "time and effort wasted arguing over numbers of infected people." Participants were told that this scenario could result in 60-70 million deaths in Africa, a workforce in which 15-30% of workers were HIV-positive, and a GDP that was 30% lower than predicted by the year 2010 in the absence of AIDS.

Key recommendations were presented to all participants in a report-back session where panelists included Gordon Conway (President, Rockefeller Foundation), former US President Bill Clinton, Richard Feachem (Executive Director, Global Fund to Fight AIDS, Tuberculosis and Malaria), and Indra Nooyi (President and CFO, PepsiCo, USA). These recommendations included the development of measurement systems and performance indices of how well countries, companies and other sectors are responding to the epidemic; and analysis of positive advances in countries and communities—so that, for example, the Global Fund might learn from a company's approach to providing care for its workers.

A dominant theme in the discussions was that "the world does not have a sense of crisis," says Berkley, and that a chronic gap remains between talk and action on the need for about a truly comprehensive response.

Also at the Davos meeting, Bill Gates announced a US\$200 million Foundation grant to establish the "Grand Challenges in Health Initiative," a public-private partnership with the US National Institutes of Health (NIH) that will seek to advance research on interventions for AIDS, TB, malaria and other global health threats. Harold Varmus, President of the Memorial Sloan-Kettering Cancer Center in New York and former NIH director, heads the Initiative, which will issue a Request for Proposals (RFP) for grants up to \$20 million in Q3 2003. Gates highlighted some of the key challenges the Initiative intends to tackle, including new strategies to treat and prevent HIV; improved diagnostics for resource-poor settings; drugs to prevent reactivation of tuberculosis, interventions to prevent mosquitoes from transmitting malaria; and effective treatments for childhood diarrheal diseases.

The workshop, report-back session and Bill Gates' announcement continued a trend towards giving more attention to global health concerns at the annual WEF meeting. Speaking of this year's session, Berkley said, "There was a general agreement that corporations have to go beyond social responsibility to assume a role as advocates with governments, NGOs and other stakeholders." ♦

IAVI Report Errata

- The December 2002-January 2003 *IAVI Report* ("Physician-Turned-Senator Bill Frist to Lead US Senate") incorrectly reported that Senate majority leader Bill Frist is the only physician in the US Congress. Congressman Bill McDermott (Washington State, D), co-founder of the Congressional Task Force on International HIV/AIDS, is also a physician.
- The October-November 2002 *IAVI Report* ("Immunogenicity Assay Standardization Efforts Underway") omitted the following members of the ICC multi-lab comparison: US Vaccine Research Center, Merck & Co., BD Biosciences, and UCSF. The program is being coordinated by Aline Rinfret, (Associate Scientific Director of CANVAC), Jill Gilmour (IAVI) and Skip Maino from BD Biosciences, which is donating reagents to the project.

can easily say from the outside that a different proportion should be going in one direction or the other. The way we can assist is by advocating for full community consultation, sharing information and models, and by assuring governments the best possible deal on the medications they want to purchase—for example, through bulk purchase agreements, regional purchase strategies, generics.

What are your goals for the next year?

Our short-term plan is to have a follow-up meeting between vaccine, microbicide and treatment activists to advance our common agendas.

With IAVI, we're also looking at national legislative frameworks that can advance vaccine research and access, and at what experience has been gathered so far. For example, India's Lawyers Collective HIV/AIDS Unit, which co-hosted the Barcelona satellite along with the Legal Network and South Africa's AIDS Law Project, has been invited to submit proposals for an HIV/AIDS bill that we expect will contain some vaccine-related proposals. So we are very interested in the Indian experience, particularly because it is being done in a consultative fashion.

We are also developing a community action

kit, which will take many of the issues we've discussed here and set them out in ways that advocates can easily use. We'd like to pilot test it in different languages and countries.

How has the field changed over the past few years?

Jonathan Mann used to talk about the legal and ethical imperative to undertake vaccine research. At the first satellite meeting we had in Durban—I think there were about three vaccines in the pipeline at that time—we were saying, listen, governments actually have legal obligations to invest much more heavily in this area.

Since then the climate has changed a lot, and we've seen a much greater interest and investment in HIV vaccines from both our private sector foundations and from governments—although I wish we had more Phase III trials.

But I think the principle is there: That governments are not only obliged to assure the right to health for HIV-positive people, but also to assure the best possible prevention technologies for people who are HIV-negative. Besides being a moral and ethical obligation, we also have to look at this as an international legal obligation. ♦

IAVI Seeking New Editor for IAVI Report

It is with deep regret that IAVI announces the upcoming departure of Patricia Kahn as editor of the *IAVI Report*. The organization wishes her well in her next endeavors and is grateful for her contribution in making the *IAVI Report* an important source of information on AIDS vaccines for the global community.

We are currently seeking a new editor, who will be charged with maintaining and developing the *IAVI Report* as a news service for the field, catering to a diverse readership. S/he will supervise a current staff of three, along with freelance writers and external consultants (layout, graphics, etc.). S/he will also contribute to IAVI's overall materials, information and publication strategy, and to the organization's presence at major international meetings. The position is based at IAVI's New York headquarters.

Qualifications include graduate degree (or equivalent experience) in a relevant field; at least seven years' experience in science journalism, at least half in an editorial role; very strong editing, writing and managerial skills; proven leadership and networking skills; and in-depth scientific knowledge of AIDS vaccines. Experience in online content development is desirable. Must be willing to travel extensively in industrialized as well as developing countries.

IAVI also anticipates hiring additional writing and editorial staff at a later date, and welcomes preliminary inquiries for the future.

Applicants should send a cover letter, CV, and three recent writing/editing samples by 10 June 2003 to:

Global Recruiting Consultant
mhowden@iavi.org

◀ **KEYSTONE: VAXGEN TRIAL** *continued from 3*

fections in the trial. (This collection—the largest set of sequences on newly-transmitted isolates—is “invaluable,” says Bette Korber.) Other studies might probe the biological activity of NAb, for instance asking whether NAb from vaccinees neutralize strains from infected placebo recipients (i.e., “un-sieved” strains) better than those from other infected vaccinees.

Another important issue is infection clusters—especially the 4 infections among placebo recipients at a single site in Chicago, on which the race and gender trends hinge. (This site enrolled one-third of all the trial's women, and most were African-American; see article, p.1). The key question is whether these infections represent a statistical blip or non-vaccine factor, such as a social network among these volunteers—an idea made more plausible by the finding that 3 (and possibly all 4) women were infected by the same man, says site coordinator Parrie Graham. But she adds that these women are extreme loners leading marginalized lives, and that the transmitting male (involved in the local drug scene) is equally likely to have had sexual partners among the vaccinated volunteers. Continued monitoring of new infections in these and other volunteers in the subgroups of interest—even without the biannual vaccine boosts—might be one way to get more concrete answers.

Final data from a 2,500-person IDU study of AIDS-VAX® in Thailand is expected late this year. ♦

With reporting by Mark Boaz

NEW MEMBERS FOR IAVI SAC, BOARD

In January 2003, Ian Gust took over from Jaap Goudsmit as chair of IAVI's Scientific Advisory Committee (SAC), which helps guides ongoing projects and future initiatives. The SAC is composed of 12 experts in AIDS vaccine development and related fields, and has three sub-committees: Vaccine science, project management and clinical trials.

Gust has been on IAVI's SAC since it began in 1997. An MD and medical virologist, he directed the WHO Collaborating Centre for Virus Reference and Research for 18 years, and presently sits on the WHO Expert Panel on Virus Diseases. Gust is a professorial fellow in Microbiology and Immunology at the University of Melbourne and non-executive director of an Australian biotech company, Biota.

There have also been changes to IAVI's Board of Directors. Geoffrey Lamb, Vice President of Resource Mobilization and Cofinancing at the World Bank, has taken over from Lee Smith as chair. Lamb is also a board member of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Other new Board members, replacing those whose three-year terms have finished, are: Awa Coll-Seck (Minister of Health and Prevention, Senegal), Chrispus Kiyonga (Chairperson, Global Fund to Fight AIDS, Tuberculosis, and Malaria), Kapil Sibal (Member of Parliament, India), Paul Klingenstein (general partner and founder of Aberdare Ventures, a venture capital company) and Ian Gust, representing IAVI's SAC. A complete list of SAC and Board members is available at www.iavi.org/about/

IAVI CORE IMMUNOLOGY LAB UP AND RUNNING

IAVI's Core Immunology lab, based at the Chelsea and Westminster Hospital in London and run by Frances Gotch, is now fully functional. Its present activities are centered around analyzing samples from ongoing IAVI vaccine trials and providing training for African and European laboratory staff.

In November, the lab sponsored a three-day course in good clinical laboratory practice (GCLP) for staff of current and future trials. Participants included researchers from the core lab, the Oxford UK trial site, the Kenyan AIDS Vaccine Initiative and the Uganda Virus Research Institute—all of whom are involved with ongoing trials—along with others from Rwanda, South Africa and Sweden, where trials are planned. The course covered issues pertaining specifically to vaccine studies, including regulatory requirements, personnel organization in the lab, writing and adhering to standard operating procedures, sample handling, data management and accountability. The British Association of Research Quality Assurance led the course. A similar course is planned for April 2003, to include research teams from India and China.

The Core lab analyzes samples from the London trial site, in addition to selected samples previously analyzed in the field labs of all IAVI-sponsored vaccine trials. This head-to-head comparison of data provides quality control for the field labs and confirms that the data are valid and reproducible.

INDIA WORKSHOP LOOKS AT CHALLENGES AROUND WOMEN AND VACCINE TRIALS

On 22-23 November 2002, the IAVI India Team hosted a consultation on gender issues and HIV vaccine trials. The meeting's 25 participants included women's health advocates, representatives of NGOs, PLWHAs, public health policymakers, lawyers, ethicists, vaccine scientists, trial administrators, and researchers with experience in conducting other types of vaccine trials, particularly contraceptive trials.

In India, as in many other parts of the world, there may be special challenges to women's participation in vaccine trials. The discussion mapped out issues that could arise at all phases of vaccine development. In the past, community concerns have stopped, or severely delayed, problematic biomedical research in India. Participants agreed to continue working with IAVI to identify and address issues that could arise through vaccine testing.

The meeting generated several action steps, which will be pursued through the work of small advisory groups. Key issues include development and review of informed consent protocols; gender sensitization for all stakeholders involved in vaccine preparedness and testing; and community mobilization. The report-back from the meeting concluded that, "While the gender lens has to be focused on the needs of entire communities, families, and men, the realities of women and socially and economically vulnerable groups are to be kept in the foreground."



IAVI APPOINTS NEW POLICY ADVISORY COMMITTEE

In February 2003, IAVI announced the establishment of a Policy Advisory Committee that will provide guidance to the organization as it expands its activities in both global advocacy and policy research.

Committee members have been drawn from academia, non-profit organizations and the private sector, and bring expertise in areas such as delivery systems for vaccines, introduction of new health care technologies, economics of vaccines, international financial mechanisms, regulatory issues and international development.

The committee members are:

- David Apuuli**, Director-General, Uganda AIDS Commission
- Amie Batson**, Health Specialist, World Bank and Co-chair, Global Alliance for Vaccines and Immunization Financing Task Force
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- Ciro de Quadros**, Director, Division of Vaccines and Immunization, Pan American Health Organization
- R. Gordon Douglas, Jr.**, Director, Strategic Planning, Dale & Betty Bumpers Vaccine Research Center, US National Institutes of Health
- Christopher J. Elias**, President, Program for Appropriate Technology in Health
- Lieve Franssen**, Head, Unit B/3 (Social & Human Development), Directorate General Development, European Commission
- David Heymann**, Director, Communicable Diseases, World Health Organization
- Purnima Mane**, Chief Fund Portfolio Director & Director for Asia, The Global Fund to Fight AIDS, Tuberculosis & Malaria
- Jean-Marie Okwo-Bele**, Senior Advisor & Team Leader, Immunization Plus, UNICEF
- Bernard Pecoul**, Director, Access to Medicines Campaign, Médecins Sans Frontières
- Seung-il Shin**, Senior Advisor for International Development, VaxGen Inc.
- Jean Stéphenne**, President and General Manager, GlaxoSmithKline Biologicals
- Joseph Stiglitz**, Professor of Economics, Columbia University
- Mark Wainberg**, Director, McGill University AIDS Centre

Working with two study populations—men who have sex with men (MSM) and high-risk women—the trial’s planners established inclusion criteria intended to select for volunteers at high risk for sexual infection. In the MSM group, this meant using a detailed questionnaire to gather data about sexual behaviors and other risk factors, and selecting individuals who reported anal sex with a male partner within the past year. Men in monogamous relationships with HIV-negative partners for at least 12 months were excluded. For women, enrollment criteria were smoking crack, exchanging sex for money or drugs, having five or more male sex partners within the past year, or having sex with an HIV-positive man within the past month.

Using these criteria, the study population was found at the trial’s end to have an annual incidence rate of 2.7% (2.8% in men; 1.5% in women)—higher than the 1.5% rate used for designing the study protocol. This is not unusual: trial designs generally use conservative incidence estimates, so that the study will retain its statistical power to measure efficacy even if infection rates decrease, for example due to ongoing risk-reduction counseling.

In an effort to recruit a high-incidence cohort, at least one site applied more than one risk criteria to its cohort. “We knew from prior experience that, to recruit high-risk women, trials have to require at least two risk factors,” said Rick Novak, principal investigator at a Chicago site that enrolled about one-third of the female participants, and who helped VaxGen develop the screening protocol for women.

It is possible to recruit and retain cohorts of high-risk women

“Small but mighty” could be the rallying cry for the 308 high-risk women recruited for the trial. Despite their being only about 6% of the cohort, studies of this group yielded a wealth of information about recruitment and retention of a population traditionally considered difficult to retain in long-term studies.

Sites in Chicago, the South Bronx and Boston proved that, with the right strategies, it can be done. “You need a full time person from the community working on retention,” says Pamela Brown-Peterside, principal investigator at the New York Blood Center’s South Bronx site. Extensive contact information is also critical: The Bronx group developed a six-page locator form, while in Chicago, the volunteers—who moved roughly once every six months—provided contact information for a female relative most likely to know their whereabouts. Tracking women also meant dealing frequently with the police and prison systems. “The police gave us a back telephone number, which we used on many occasions,” says Parrie Graham, the Chicago women site’s study coordinator. Since Illinois Institutional Review Board regulations prohibited visits to incarcerated women, the team stayed in contact by mail, sending magazines, Christmas cards and trial updates, until the women were released.

Retention success also lay in going beyond the study requirements. In the South Bronx, the

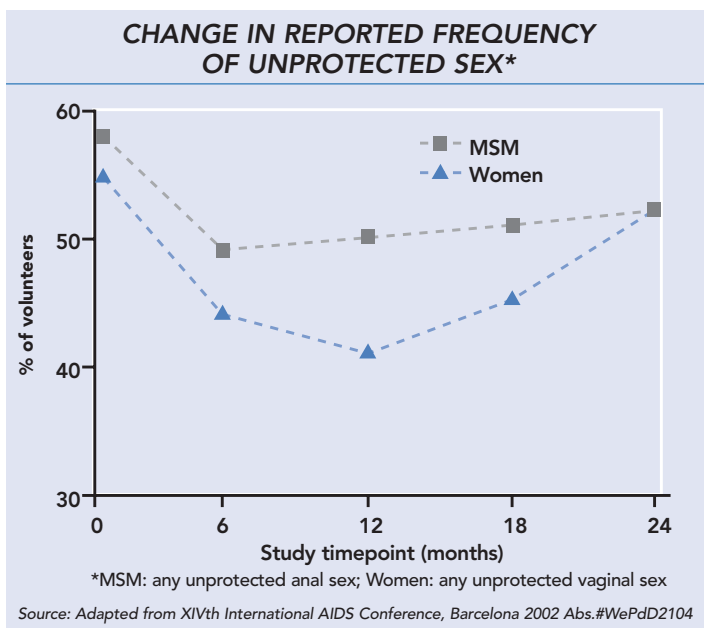
site made contact with participants every three months, rather than the required six; the Chicago team photographed participants to help its outreach workers locate them for follow-up visits. The results: Follow-up rates comparable to those for the MSM group. Looking beyond trials, Novak points out that women like those involved in the study will also be important groups to reach with a licensed vaccine.

The trial did not eliminate—or encourage—risk behaviors

Alongside VaxGen’s clinical monitoring of the volunteers, researchers from the US Centers for Disease Control and Prevention (CDC) studied participants’ perceptions and behaviors over the course of the trial. Their data—which only include individuals who received all scheduled immunizations—contradict worries that high-risk acts would skyrocket in the context of an efficacy trial. As reported by Brad Bartholow at the Barcelona AIDS conference (abs. #WePdD2104; see figure), participants’ reported risk behavior remained at or below baseline levels 24 months after the trial began.

But looking more closely, there are subtleties within these findings. Rates of *any* high-risk behavior in both men and women dipped below baseline at intermediate trial visits and then began to climb again, remaining below baseline in men. But in women, the drop-off ended by 12 months, at which point reported risk behaviors began to climb again until they were back to baseline at 24 months. A different pattern emerged for reports of unprotected sex with an HIV-positive partner. Here, rates decreased slightly from baseline and then remained stable out to 24 months in both genders. (Three year findings from the CDC have not yet been made public.) VaxGen’s newly-released behavioral data, which has a 36-month timepoint, is based on *all* study participants, including those who dropped out or missed visits.

The CDC’s study was designed



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tors. Emini briefly described early studies with Ad24, 34 and 35—three strains that do not cross-react immunologically with Ad5 (or one another) and show less than 10% seroprevalence in populations that have been studied, which should largely eliminate the problem of PEI. More detailed data were shown in a poster by Andrew Betts and colleagues.

Initially, a key obstacle was that these new strains did not grow in the laboratory cell lines used for producing Ad5. But the Merck researchers were able to engineer the crucial gene from Ad5 into the other strains, enabling all three strains to grow efficiently. Next, the *gag* gene was added to vectors made from each strain and used to immunize six macaques (10^{11} viral particles) at 0 and 4 weeks.

All three constructs were somewhat less immunogenic than Ad5 alone, but Ad24 and Ad34 both seem to work well in prime-boost combinations with Ad5, according to Emini. As more data on these and other serotypes is collected, the company will decide whether to move any of them forward into human trials.

More antigens in an improved Ad5 vector:

Another trial due to launch soon will add the HIV *pol* and *nef* genes into the *gag*-containing vaccine. These genes have been built into an improved (more genetically stable) version of the Ad5 vector called MRK5Ad5, which an ongoing clinical study shows to be at least as good as the original vector in eliciting antigen-specific responses. ♦

Although DNA-based vaccines are being developed against many diseases, results in humans have not lived up to the initial promise shown in animal models. By themselves they are usually poor inducers of antigen-specific immunity; as the first of two vaccines in a prime-boost combination—the most common way to use DNA vaccines—the jury is still out, although Merck's data on DNA/Adenovirus5-based vaccines in humans so far are disappointing (see article on page 3).

Several studies presented in Banff set out to address this problem by combining DNA vaccines with “molecular adjuvants”—molecules such as cytokines that may enhance immune responses.

One such approach was described in back-to-back talks by collaborators John Eldridge (Wyeth-Aherst) and David Weiner (University of Pennsylvania), who are analyzing the effects of cytokines IL-12 and IL-15 on the immunogenicity of a DNA vaccine against SIV. Their data in macaques show that these cytokines enhance not only cellular immune responses but also the level of antibodies, which are not usually induced by DNA vaccines. Challenge data are not yet available, but will provide crucial information on whether this enhanced immunogenicity leads to better protection, as it did in earlier studies of this approach (using IL-2) by Dan Barouch and Norman Letvin of Harvard Medical School.

IL-12 and DNA: Proof of Principle

Eldridge began by presenting a study in macaques comparing responses to an SIV-*gag* DNA vaccine given with and without a plasmid encoding IL-12. This cytokine is thought to be one of the most potent adjuvants for inducing cellular immune responses, and has been shown to improve vaccine protection in flu, malaria and other disease models in animals. In the Wyeth study, five groups of five macaques were immunized at weeks 0, 4 and 8 with SIV-*gag* (1.5 or 5mg of DNA) with or without IL-12. Immunogenicity was determined by measuring IFN-gamma-producing cells using Elispot assays.

Looking at the 10-week timepoint, the data

show clear enhancement of immune responses in animals vaccinated with IL-12 plus SIV-*gag*, compared to those given DNA vaccine alone. The increase was seen in both the number of responders (10/10 versus 5/10 with DNA only) and the magnitude of the T-cell response, with peak responses about 5-fold higher when IL-12 is present. (Mean numbers of spot-forming cells [SFC] with vaccine plus IL-12 were 1,344 and 1,433, for low and high DNA doses, respectively, compared to 256 and 338 with DNA alone.) IL-12 also led to more persistent responses, with roughly two-thirds of peak response levels retained at week 20 (about 1,000 SFC), but only 30-50% (about 100 SFC) with DNA vaccine alone.

Next, Eldridge described findings on IL-12 in a prime-boost regimen with SIV-*gag* DNA and a second vaccine based on Vesicular Stomatitis Virus (VSV), made by John Rose's group at Yale University together with Wyeth. After priming with SIV-*gag* and IL-12 DNA, animals boosted twice with VSV vaccine (containing SIV-*gag* and HIV-*env*) showed an 8-fold increase in Elispot responses to Gag, peaking at a mean of 3,772 SFC. Anti-Gag binding antibodies were also boosted by half a log (to a mean titer of 32,768, compared to 4,096 after DNA priming). The observed response levels are comparable to those obtained with other prime-boost regimens that protect monkeys from disease (such as Harriet Robinson's DNA/MVA and Merck's DNA/Adenovirus).

IL-15: Boosting Memory

Following Eldridge's talk, David Weiner described studies showing enhancement by IL-15, an important cytokine for the induction and maintenance of CD8 memory.

Macaques were divided into three groups of six animals, with one group receiving DNA vaccine alone, the second given DNA vaccine plus IL-15 plasmid, and the third, placebo. Data after two of three planned vaccinations (the study is still ongoing) showed the highest responses in the DNA/IL-15 group (averaging 447 SFC), with all 6 animals responding. Only 3/6 animals in the DNA-only

Can DNA Vaccines Get a Boost from Cytokines?

BY MARK BOAZ AND RICHARD JEFFERYS*

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atitis B vaccine—the only licensed vaccine against a sexually transmitted disease—appears to protect men and women equally well.

But neither HBV nor HSV-2 exactly mirror HIV infection, where there is already evidence of gender-specificity from the point of infection onwards. Julie Overbaugh (University of Washington, Seattle) has found that women are initially infected with a greater number of HIV

variants than men (see article, page 7), and that this diversity is linked to more rapid disease progression. Other studies have shown that HIV-infected women also have lower viral loads and higher T-cell counts than matched male counterparts, a finding which is already affecting thinking about HIV vaccine trial design. “Gender is an important issue in evaluating T-cell-based vaccines,” says Corey. “[HIV-positive] women have lower viral loads than men, so using viral load as a surrogate [for vaccine efficacy] requires stratification” by gender in the analysis of results.

With its women-only efficacy trial now underway, Merck is also starting to lay the groundwork for baseline studies of HPV infection in men. Before the company decides whether or not to test its vaccine in men, it will analyze the types of cells and tissues the virus infects, the natural history of disease, dynamics of viral clearance, and outbreaks of warts in heterosexual men, and men who have sex with men. Besides their usefulness for vaccine studies, these data (which already exist for women) will also help guide recommendations for use, marketing and public health messages around HPV immunization. Even if HPV turns out not to be a health problem for heterosexual men, says Barr, “there is the notion of immunizing them to protect the women who will be their partners.”

Practical Implications for the HIV Field

Several general lessons for HIV vaccine trials can be drawn from these studies. One is the importance of gender-related enrollment targets. While it will rarely be feasible to conduct trials with sufficient power to measure efficacy separately in each gender, it should be possible to enroll enough volunteers of each gender to detect trends towards gender-specific effects, which can then be further investigated in single-sex studies like the current HSV-2 trial. The recent Phase III VaxGen study enrolled very few women, and so was unable to either assess protection in women, or detect a trend towards protection in one gender (see VaxGen results article, page 1.)

Another critical lesson is that it is feasible to enroll young women in trials of vaccines against sexually-transmitted diseases. The lower limit of age in Merck’s Phase III trial is 16, and both Merck and GSK have already begun additional bridging studies to show safety and immunogenicity in younger adolescents and children; both companies also report that many parents are willing to enroll their daughters in these trials. In the case of the HPV vaccine, the fact that the vaccine is designed to prevent cancer—which has a very different stigma from STIs—may have also played a role in parents’ openness to adolescent enrollment.

These studies may also lead to new regulatory precedents. If its candidate proves efficacious, GSK will seek a female-only indication for its HSV-2 vaccine. If efficacy is shown in both genders, then

Gender and Vaccines: A Bibliography

DIFFERENCES IN VACCINE-INDUCED RESPONSES

Monath, T. *et al.* **Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III, multicenter, double-blind clinical trial.** *Am J Trop Med Hyg* 66:533;2002

Vaccines: live attenuated yellow fever vaccines from two different manufacturers
Key findings: Male gender, Caucasian race and smoking associated with higher antibody titers

Pittman, Phillip. **Aluminum-containing vaccine associated adverse events: role of route of administration and gender** *Vaccine* 20:S48;2002

Vaccine: Anthrax vaccine adsorbed (containing aluminum hydroxide)
Key Findings: The frequency and severity of local reactions was statistically higher in women than in men following first subcutaneous immunization. Women receiving SQ immunization also had higher antibody titers than men receiving the same course (unpublished data presented at Sex and Gender Issues in HIV, Washington DC, November 2002, sponsored by the Forum for Collaborative Research. Available at: www.hivforum.org/publications/PhillipPittman.pdf)

Pittman, Phillip **“Effect of Gender on Antibody Response and Adverse Events Associated with Immunization,”** Sex and Gender Issues in HIV, Washington DC, November 2002, sponsored by the Forum for Collaborative HIV Research. Available at: www.hivforum.org/publications/PhillipPittman.pdf

Vaccine: live attenuated yellow fever vaccine
Key findings: Women statistically less likely to respond than men (15% versus 9% nonresponders).

Pittman, *et al.* **Long-term duration of detectable neutralizing antibodies after administration of VEE vaccine and following booster with inactivated VEE vaccine,** *Vaccine* 14:337;1996

Vaccines: live attenuated Venezuelan Equine Encephalitis (VEE) vaccine with whole-killed boost (formalin-inactivated virus, in adjuvant C-84).
Key findings: Age and gender influence level of antibody responses. Males were 2.2 times more likely to respond to live-attenuated VEE (defined as antibody titers above a specific threshold) than matched female counterparts. 18-39 year olds were 2.1 times more likely to respond than volunteers over age 40.

DIFFERENCES IN PROTECTION/OUTCOME

Holt, EA *et al.* **Differential mortality by measles vaccine titer and sex** *J Infect Dis* 168:1087;1993.

Vaccines: live attenuated measles vaccines at 10-fold (medium titer) and 100-fold greater titers than standard measles vaccine
Key findings: Increased mortality was associated with high-titer vaccine for girls but not for boys. Similar mortality patterns have been noted in two other populations.

Stanberry, L *et al.* **Glycoprotein-D-adjuvant vaccine to prevent genital herpes** *N Engl J Med* 347:1652;2002

Vaccine: herpes simplex virus type 2 (HSV-2) glycoprotein-D-subunit vaccine with alum and 3-O-deacylated-monophosphoryl lipid A
Key findings: Vaccine showed 73-74% efficacy in preventing disease (38-42% in completely preventing infection); 0% efficacy in men.

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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: Accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.

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Merck plans to license its vaccine for men and women. However, there will be a lag between trials in women and men. This is also true for microbicides, which are being tested largely in women, although they could also be used by men who have sex with men.

Ultimately, AIDS vaccines will have to advance to Phase III efficacy trials to determine whether and

how gender influences vaccine-induced protection. GSK's Slaoui speculates that the gender differences seen in the HSV-2 vaccine trials will emerge again in the confirmatory Phase III study, and in the context of other sexually-transmitted diseases. "My gut feeling is that it's going to be a general effect with significant implications for vaccine development for diseases such as HPV—but more importantly, for HIV." ♦

▶ VAXGEN TRIAL BEHAVIORAL STUDIES *continued from 4*

to answer questions on whether rates of risk behavior were influenced by volunteers' assumptions about whether they received the vaccine or placebo. Statistical analysis showed that male participants who believed they had received the vaccine reported significantly more frequent unprotected anal intercourse (UA) than those who thought they received a placebo or were unsure; they also showed an upward trend in UA between 12 and 24 months.

These data provide a clear take-home message: Ongoing assessment of beliefs about vaccines, plus appropriate counseling, is crucial during efficacy trials. They also reveal some perplexing trends. For example, women who assumed they received the placebo had higher rates of risky behavior

at 24 months than those who thought they were given vaccine, although these trends disappeared at 36 months. The findings also raise thought-provoking questions about whether similar (or more severe) trends might be seen in the context of a partially effective, licensed vaccine—when vaccinees will not be receiving continuous counseling to counteract a false sense of protection.

Could vaccine trial participation actually increase risk behavior? To tackle this question, the CDC is now comparing a group of VaxGen volunteers with a comparable cohort of about 800 people (not in a vaccine trial) meeting similar risk criteria and given the same counseling messages, minus vaccine information.

The trial data also underscore

the need for tailored messages. Women were significantly more likely than men to believe that the vaccine was highly effective (defined as 76-100% effective), and to cite protection from HIV infection as a motivation for their participation. Volunteer assumptions or motivations were not analyzed by demographics; however, the women had significantly lower income, education and literacy levels than the male volunteers, factors that may have contributed to specific beliefs. (Men and women volunteers used the same tools for informed consent and knowledge assessment.)

As the *IAVI Report* went to press, the CDC was preparing an article summarizing the full 36-month data on behavior change and reported rates of risk behavior. ♦

▶ KEYSTONE: DNA VACCINES *continued from 17*

group responded, with one "outlier" showing a robust response (557 SFC) and the remaining ones averaging 50 SFC.

Weiner also presented data from mice showing that IL-15 can partially replace CD4 T-cells as helpers for CD8 responses in animals depleted of CD4 cells and vaccinated with DNA/IL-15. He speculates that this might suggest an important use for IL-15 in therapeutic vaccination, since most HIV-infected people have reduced CD4 cell numbers and/or impaired function.

Summarizing the overall approach, Weiner concluded that the use of IL-12 or IL-15 might enable DNA vaccines to achieve levels of immunogenicity comparable to those reported for viral vectors. He also emphasized that humoral as well as cellular responses appear achievable—raising the possibility that DNA might be a feasible vector to deliver future immunogens that induce neutralizing antibodies.

Clinical Development Pathway

To move the approach into clinical trials, plans call for two preventive vaccine studies with

the US HIV Vaccine Trials Network, plus a therapeutic trial at the University of Pennsylvania. The preventive trials will use an HIV-*gag* DNA vaccine and either IL-12 or IL-15, and should start within a year; both studies may expand later to include a boost with the HIV-VSV vaccine. Discussions are also underway with the Walter Reed Army Institute of Research (WRAIR) on combining its multi-clade DNA vaccine candidate with cytokines.

In the meantime, studies are underway to investigate some regulatory questions arising from the use of cytokines as vaccine adjuvants. In a poster by Sangeeta Bhargava Periwal and the Wyeth/U. Penn. team, the researchers showed that expression of IL-12 after immunization with plasmid is relatively short-lived, peaking at six days and showing only trace levels at 30 days. Weiner says that ongoing discussions with the FDA are defining other potential issues and the studies needed to address them. ♦

**Richard Jefferys is Basic Science Project Director at the Treatment Action Group, an AIDS advocacy organization based in New York.*

vaccine BRIEFS

GLOBAL FUND UPDATE: NEW CHAIR, NEW CALL FOR PROPOSALS

On 29-31 January, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) held its fourth Board meeting in Geneva, Switzerland. At the meeting, US Secretary of Health Tommy Thompson was approved as the new GFATM Chair, replacing Ugandan health minister Chrispus Kiyonga. Suwit Wibulpolprasert, Deputy Permanent Secretary for the Thailand Ministry of Health, was elected as Vice Chair.

At the January meeting, NGO and community delegations joined the Fund's Technical Review Panel in voicing concern about the modest targets for provision of ARVs in proposals approved to date. Collectively, these proposals from the first two funding rounds will offer ARVs to approximately 491,000 individuals at the end of five years, less than 10% of the estimated 5-6 million HIV-infected individuals who require treatment worldwide.

To accelerate a scale-up, the NGO and community delegations proposed that countries whose proposals included ARVs have a higher ceiling for the amount of funds that can be requested in a single proposal. They also called for clearer guidelines on participation of people living with HIV/AIDS, NGOs and community groups in the Country Coordinating Mechanisms mandated by the Fund. These suggestions have yet to be adopted and may be considered at the next Board meeting in October.

The next deadline for proposals is 31 May 2003. But as the Fund moves forward, it faces a financial shortfall, which could prove calamitous to its credibility and ability to make good on existing commitments. As of October 2002, US\$2.1 billion had been pledged to the Fund through 2006—with only \$483 million actually paid into the Fund's coffers. Richard Feachem, GFATM executive director, has said that the Fund needs \$6.3 billion in 2003 and 2004 alone.

(For complete application guidelines visit www.globalfundatm.org; for a list of successful applications, visit www.aidsplan.org)

TWO NEW PHASE I TRIALS LAUNCHED IN AFRICA

Screening of volunteers for two studies of a DNA/MVA vaccine strategy began in Kenya and Uganda on 13 January and 19 February 2003, respectively, following an ongoing Phase I/II prime-boost trial of these candidates in the UK (IAVI 006). The vaccines contain most of the *gag* gene from HIV subtype A, in addition to 25 CTL epitopes from conserved regions across the HIV genome. They were designed by Tomas Hanke and Andrew McMichael at the University of Oxford, based on collaborative studies with researchers at the University of Nairobi.

The Kenya trial (IAVI 010)—the country's third, after two Phase I studies that assessed the DNA and MVA vaccines separately—is a collaboration between the Kenyan AIDS Vaccine Initiative (headed by Job Bwayo) at the University of Nairobi and IAVI. The 111-volunteer trial will compare immune responses induced using different immunization sites for the MVA boost, following DNA primes at months 0 and 1.

The Uganda study (IAVI 009) is the country's second HIV vaccine trial, and is a collaboration between the Uganda Virus Research Institute in Entebbe and IAVI. Pontiano Kaleebu is principal investigator of the trial, which will enroll 50 HIV-negative volunteers and aims to compare immune responses induced by either one or two DNA immunizations prior to an MVA boost.

Further details on these and other preventive vaccine trials are available at www.iavi.org/trialsdb

NEW DIRECTOR GENERAL FOR THE WORLD HEALTH ORGANIZATION

On 28 January 2003, Jong Wook Lee was announced as the new Director General of the World Health Organization. Lee narrowly edged out Peter Piot of UNAIDS to win the nomination, which is decided through a complex, confidential voting procedure. Lee will begin his five-year term in July 2003, following formal approval at the World Health Assembly meeting in May. A Korean physician, Lee directed the Stop TB program, a global alliance led by WHO to eliminate tuberculosis, and served as head of the WHO Global Program for Vaccines and Immunizations. He will replace outgoing Director General Gro Harlem Brundtland.

US\$15 BILLION AIDS BILL CLEARS FIRST BIG HURDLE

On 1 May 2003, the US House of Representatives approved the US Leadership Against HIV/AIDS, Tuberculosis and Malaria Act of 2003 (HR1298), which sets specific targets for expanding HIV treatment in developing countries with severe epidemics—up to 2 million people in 2006. It also prioritizes the use of generic medications, which can cost as little as US\$250 a year. The bill is the legislative embodiment of a proposal first made by President Bush on 28 January in his annual State of the Union address to the US Congress and represents a major increase in funding to battle AIDS in the world's hardest-hit regions.

The legislation authorizes spending up to \$3 billion per year for five years, which includes \$10 billion in new money. It also reserves up to \$1 billion in the 2004 budget year for the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)—well above the \$200 million that the President requested in earlier calls for AIDS funding. In response to concerns among some Republicans that the Fund is "inefficient," the bill calls for establishment of a federal task force to monitor spending by the GFATM.

Although widely hailed as a significant step forward, the bill contains controversial provisions on family planning and HIV prevention that have been heavily criticized by many AIDS and health organizations. While it endorses the "ABC" model (abstain, be faithful, use condoms) that helped lower infection rates in Uganda, a last-minute amendment earmarks one-third of the \$600 million in prevention funds to abstinence-until-marriage programs. "By diverting AIDS money to ineffective programs, money will be wasted, and more importantly, lives will be lost," says Holly Burkhalter of Physicians for Human Rights, an organization that shared the 1997 Nobel Peace Prize. On another hotly-debated issue, groups providing abortion counseling can receive these US funds only if abortion and family planning services are financed and run separately from AIDS prevention activities—a requirement that could create significant hurdles for poor, rural clinics.

The debate now shifts to the Senate, which must pass similar legislation before the program can be enacted. Any differences in the Senate and House versions must then be reconciled, after which Congressional appropriations committees allocate the actual dollars for these programs. President Bush is pressing the Senate to pass legislation by the end of May.