TAGline

From the Treatment Action Group (TAG):
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## *Revenge of the CTLs*

# Harvard Vaccine Team Exposes Potential Dark Side of Reliance on Cellular Immune Protection

The fate of monkey #798

*January 2002 proved to be a month of mixed blessings for the AIDS vaccine field. A slew of new papers in the prestigious journal* Nature *publicly highlighted both the promise and potential pitfalls of new immunization strategies, raising the volume of scientific debates that have been quietly preoccupying researchers for some time. At the center of it all were two back-to-back articles released on January 17: one from a team of Merck researchers led by John Shiver, publicly debuting encouraging data from studies comparing multiple HIV vaccine constructs (including Merck's proprietary adenovirus-based vaccine vector) in rhesus macaques; the second from Dan Barouch and Norman Letvin's group at Harvard, presenting a cautionary tale of viral escape from vaccine-induced T-cell responses in the same animal model system. TAG's new Project Director for Basic Science, Richard Jefferys, sifted through the data and commentary to prepare this report.*

The debate sparked by these data sets revolves around the level of protection that might be afforded by

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### A Tale of Two Trials

| | Dept. of Defense | NIH/HVTN |
|---|---|---|
| Region | Thailand | Americas |
| Size | 15,800 | 11,080 |
| Immunogen | ALVAC* | ALVAC† |
| Start date | mid-2002 | ??? |
| Cost | $35-40M | $60-80M |

**canarypox 1521 (clade B) with Vaxgen gp120 (clade B/E) boost*

*†canarypox 1452 with Vaxgen gp120 (clade B) boost in one subgroup*

## *Politica Sobre Patentes*

# El Esfuerzo Hacía Acceso de los ONG Recibió Una Golpe Por El Instituto Sobre Desarrollo de Harvard

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'Arrojando la luz sin querer'

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*Un papel polémico publicado en el emisión del 17 del octubre del Diario de la Asociación Médica Americana (*JAMA*) sostuvo que, "las patentes en Africa generalmente no han sido un factor en el acceso del tratamiento." Y semejante por la Asociación de los Investigadores y Fabricantes de Fármacos (PhRMA) que catalogó la situación de las patentes en 53 naciones africanas, mostró que para las 15 drogas antiretrovirales usados para tratar la infección del VIH, el alcance patentado era acerca de 21%. Sólo en Africa del Sur era la protección de patentes extensa: con 13 de las 15 drogas patentadas protegidas. "Para estas drogas," PhRMA*

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## *Annals of Crisis*

# A Peek Back At TAG's First Year Shows How Much, And How Little, Has Changed

'Homing in on basic research'

*The beginning of this year marks TAG's tenth anniversary as the nation's only organization focused exclusively on advocating for more and better AIDS research, speeding discovery, development, approval, and distribution of better treatments, a cure and a vaccine. While the latter two goals remain elusive, the past ten years have seen significant progress—much of it instigated or accelerated by TAG. The NIH AIDS research budget has tripled in size, from $800 million to $2.4 billion per year. After TAG's pivotal 1992 report,* AIDS Research at the NIH: A Critical Review, *the AIDS research program at the National Institutes of Health was reformed and reorganized.*

*In the mid-1990s, TAG played a major part in forcing the drug companies developing protease inhibitors to study the drugs more rapidly and to provide more reliable information on how to use them. TAG also played a critical role in speeding up research on the opportunistic infections and cancers which were the leading killers of people with HIV. Since 1996, with the introduction of highly active antiretrovi-*

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*ral therapy (HAART), protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and viral load testing, antiretroviral treatment strategies have undergone a revolution.*

*Over the past seven years AIDS mortality dropped by two-thirds in the U.S. and other industrialized countries. Nonetheless, significant problems remain with anti-HIV drug adherence, cost, resistance, and toxicity. As people with HIV live longer, new problems such as lipodystrophy and liver disease now cause more problems among people with HIV living in the United States. Meanwhile, internationally, despite several years of intensified mobilization, the HIV pandemic spreads unchecked by effective prevention and existing treatment, let alone an HIV vaccine. TAG remains committed to completing our mission.*

*As we move forward in 2002, we will also look back at the work which brought us here, investigating key TAG projects and campaigns, interviewing leading researchers and activists who worked with TAG, and remembering those we have lost. Our first article focuses on TAG's formation in 1992, its dual missions of direct action and critical research analysis and oversight, our critique of the NIH AIDS research program and our call for an increased emphasis on the basic science of HIV infection—all themes which remain timely despite the progress of the past ten years. Mark Harrington transports us back to the dark days of the early 1990s.*

Nineteen ninety two was a year of crisis for people with AIDS. Twelve years into the epidemic, despite the mobilization of thousands of activists, the deployment of millions of dollars in federal and pharmaceutical research funds, and significant accomplishments in speeding development and approval of three drugs for HIV and several more for its associated opportunistic infections, AIDS research was at a low point.

AZT had been approved by the FDA in 1987 and recommended for wider use in 1991, the same year that the FDA approved ddI (*Videx*), the second antiretroviral. These drugs extended life and health by just a year or two, and failed to durably suppress the virus. In 1992 it was still unclear whether hoped-for new therapies such as inhibitors of the HIV tat or protease enzymes would prove effective. In the meantime, the AIDS and death tolls mounted relentlessly.

Despite the mobilization of thousands of activists and the deployment of millions of dollars in research funds, AIDS research was at a low point.

Activists had won entrée into the councils of the Food & Drug Administration (FDA) and the National Institutes of Health (NIH) AIDS drug development programs and oversight bodies, and had helped to broaden the research agenda to include more research on the opportunistic complications of HIV—and on women and children with HIV. Nonetheless, the prospects for treatment looked unpromising.

Scientists did not yet have a clear picture of the pathogenesis of HIV infection. It was still widely and incorrectly believed that HIV "hid" somewhere in the body in the period between acute infection and the development of AIDS ten years later. Available tests to quantify viral levels in the body were crude at best. Only a few researchers were looking for the virus in body compartments such as the lymphoid tissue, as opposed to the easier to sample bloodstream. It was not yet known how HIV destroyed the immune system and led to AIDS.

Without a better understanding of how HIV led to disease, it would be difficult to develop better treatments. Yet at NIH, despite an AIDS research budget that had steadily mounted to almost $800 million per year, the research effort was poorly coordinated. It lacked a central place where the overall research agenda could be planned, budgeted, and evaluated. Eighteen different NIH institutes each conducted their own AIDS research programs as they saw fit. Scientists in the field were depressed about the lack of progress on both the therapeutic and on the preventive vaccine fronts.

The political situation was also troubling. During twelve years of Republican presidencies, most federal action on AIDS had been instigated by—and sometimes obstructed by—Congress. The country had just emerged from a distracting war in a far-off Islamic country, and it was in recession. Health care costs were rising uncontrollably, and increasing cries were heard for the government to do something to broaden access to health care. It was difficult for AIDS and health care activists to get the attention of President George Bush.

Meanwhile, the AIDS activist movement itself was in crisis. The largest activist group, the AIDS Coalition to Unleash Power or "ACT UP," was increasingly riven by infighting, while many of its leaders and members were falling ill or dying.

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## TAG at 10: The Year 1992

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|---|---|
| Jan 22 | Treatment Action Group (TAG) splits off from the Treatment + Data (T+D) Committee of ACT UP/New York. Our media debut: Catherine Woodard's "AIDS Hit Squad Seeks More Than Attention," *Newsday*, 1.22.92. |
| Jan 27 | Eight Treatment Action Guerillas chain themselves to trucks at the entrance to Astra Pharmaceuticals (now part of AstraZeneca) in Westborough, Massachusetts, protesting excessive prices for the anti-CMV drug foscarnet. |
| | Tipped off by drug-maker Hoffmann-La Roche, which refused to provide a substantial parallel track program for ddC, FDA investigators seize batches of underground ddC from numerous PWA Buyers' Clubs nationwide. |
| Feb 4 | TAG Astra zap covered on *Sixty Minutes*, including interview with TAG co-founder Peter Staley. ACT UP and TAG member Bob Rafsky is also featured. |
| Feb 5 | FDA reports underground ddC contained between 0-200% of the putative dose. |
| Feb 19 | TAG's Mark Harrington replaces Project Inform's Martin Delaney on the ACTG's Primary Infection Committee. |
| Feb 24 | Debate in ACT UP about whether Peter Staley is colluding with drug companies by requesting money from industry for community-based clinical trials. |
| Feb 25 | TAG's Gregg Gonsalves, Mark Harrington and Derek Link meet with Deputy Director Jack Whitescarver at the NIH Office of AIDS Research (OAR), instigating the landmark TAG research critique. |
| Apr 12-15 | 14th AIDS Clinical Trials Group (ACTG) meeting, Bethesda. New drugs under discussion include FTC, d4T, tat inhibitors, protease inhibitors, hypericin and nevirapine. |
| Apr 16 | Burroughs-Wellcome sponsors "Day of Dialogue," one of the first drug-company community junkets. |
| Apr 30 | Riots in Los Angeles over Rodney King verdict. |
| May 29 | Community meeting with Syntex pharmaceuticals (now part of Roche) about oral ganciclovir for CMV retinitis. |
| Jun 19 | FDA approves ddC (*Hivid*) using its new accelerated approval regulations. |
| Jul 14 | At Madison Square Garden, the Democratic National Convention prepares to nominate Bill Clinton for president. |
| Jul 20 | 8th International AIDS Conference in Amsterdam. (Originally scheduled to take place in Boston, the meeting was moved to the Netherlands after the first Bush administration banned HIV-infected foreigners from entering the USA.) TAG's Mark Harrington debates NIAID's Anthony Fauci on *The MacNeil/Lehrer Newshour*. |
| Jul 22 | Mark Harrington gives plenary lecture on "Pathogenesis & Activism" in Amsterdam. Later he and Gregg Gonsalves present *AIDS Research at the NIH: A Critical Review* at a press conference. Media coverage: a front page story in *The New York Times* as well as "Activists home in on basic research" in *The New Scientist*, 7.18.92. |
| Sep 10 | TAG meets with NIH Director Bernadine Healy and institute directors to discuss OAR recommendations. Later we meet privately with Healy, Broder and Fauci to discuss a Manhattan Project for AIDS. |
| Sep 30 | TAG letter to ACTG principal investigator Ann Collier protests the failure of Roche to define a maximum tolerated dose for the first HIV protease inhibitor, Ro 31-8959, later known as saquinavir (*Invirase*). |
| Oct 5 | FDA approves a parallel track program for Bristol-Myers's d4T, later known as *Zerit*. |
| Oct 19 | TAG meets with Fauci and Whitescarver to discuss OAR recommendations. |
| Nov 2 | Political funeral for ACT UP's Mark Lowe Fisher. Activist funeral march to Bush NYC headquarters on 43rd Street. |
| Nov 3 | Bill Clinton defeats George H. W. Bush in national elections and becomes president-elect of the United States. |
| Nov 4 | Post-election meeting between TAG and Fauci about the OAR. |
| Nov 5 | First meeting of FDA/NIH Panel on $20 million Congressional rgp160 earmark. |
| Nov 20 | TAG meets with Tim Westmoreland from the office of Congressman Henry Waxman to discuss turning TAG's NIH recommendations into law. |
| Dec 7 | TAG meets with Michael Iskowitz in Senator Ted Kennedy's office to discuss implementing TAG's OAR recommendations in the forthcoming Senate bill 1, "the NIH Revitalization Act of 1993." |
| Dec 15 | TAG meets with Sam Broder at NCI and Fauci and Jim Hill of NIAID about the impending OAR legislation. |
| Dec 22 | FDA approves Unimed's dronabinol (*Marinol*) for the treatment of weight loss in people with AIDS. |
| Dec 23 | FDA approves Adria's rifabutin (*Mycobutin*) for prevention of disseminated mycobaterium avium complex (MAC). |

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Within ACT UP's Treatment + Data (T+D) Committee, a dozen treatment activists were determined to focus their efforts on research and treatment advocacy. Infighting was getting in the way of that focus, and so in January 1992 they split off from ACT UP and formed the Treatment Action Group. TAG's early focus included a series of direct actions targeting drug companies whose development plans were too slow: Dai-Ichi pharmaceuticals, for their glacial development of an anti-Kaposi's sarcoma (KS) angiogenesis inhibitor; whose expanded access programs were inadequate: Hoffmann-La Roche, for refusing to provide expanded access to ddC; or whose prices were too high: Astra, for the excessive price of the anti-CMV drug foscarnet. Despite widespread publicity, these civil disobedience "zaps" were becoming less effective than they had been in ACT UP's early days.

The litany of drugs which the FDA did approve over the course of 1992 showed just how slow the research progress was, and how grim the prognosis for most people with HIV. The third anti-HIV drug, Roche's ddC (*Hivid*), was approved in June—even though there was no evidence that ddC improved health or prolonged life. It was approved based on minute and transient increases in CD4 cell counts. ddC would go on to be the least widely used drug of its class. Then, in a rush of year-end drug approvals, the FDA approved two drugs for advanced AIDS—Adria's rifabutin for prevention of mycobacterium avium complex (MAC) and Unimed's dronabinol (*Marinol*), an appetite stimulant, for treatment of HIV-associated anorexia and weight loss.

An additional TAG focus was analyzing and reforming the AIDS research program of the NIH. Starting in February 1992, TAG's Gregg Gonsalves and Mark Harrington gathered information on every NIH AIDS research grant and program. By the International AIDS Conference that July in Amsterdam, they published *AIDS Research at the NIH: A Critical Review.* The report called on Congress and the Administration to strengthen the NIH Office of AIDS Research (OAR) and to provide it with the authority and ability to plan, evaluate, and budget a coordinated, streamlined, accelerated AIDS research program across all the NIH institutes and centers.

> In 1992 it was still widely believed that HIV hid somewhere in the body during the time between acute infection and the onset of AIDS.

We also called on the government to double the entire NIH budget for biomedical research. That summer and fall, TAG worked on building an alliance with AIDS researchers across the country who would be willing to support the reform efforts when legislation was introduced in Congress during early 1993. TAG also met with NIH Director Bernadine Healy and the directors of the NIH institutes—particularly Tony Fauci at NIAID and Sam Broder at the National Cancer Institute—although the institute directors generally were opposed to any plan which would subject them to evaluation or oversight. With the election of Bill Clinton as President in November 1992, the stage was set for Congress to enact sweeping reforms of the NIH AIDS program in the reauthorization legislation of early 1993.

Finally, during 1992 TAG was the first activist organization to call on researchers to refocus the AIDS research effort on fundamental basic research dedicated to elucidating the pathogenesis of HIV disease and AIDS. TAG's pathogenesis project met monthly. We began working with basic scientists as well as with clinical researchers as we had in the past. In his 1992 speech at the Amsterdam AIDS conference, TAG's Mark Harrington spoke on "Pathogenesis and Activism" and showed slides of his own HIV-infected lymph node as an example of how activists and people with HIV could contribute to and participate in basic research as well as in clinical trials.

It was clear that progress would be slow. Over the course of 1992, 79,595 Americans were diagnosed with AIDS and 41,623 of them died of the disease. At the time it seemed that those numbers would only go up for the foreseeable future.

Many of TAG's founding members were ourselves HIV-infected. Among the many activists who died of AIDS in 1992 were ACT UP/San Francisco's Michael Wright in January, TAG's Scott Slutsky in May, artist/writer David Wojnarowicz in July, and ACT UP/New York's Mark Fisher—just before the November elections. When we marched uptown on election eve, 1992, bearing Mark's body to Bush's New York City campaign headquarters in midtown, most of us felt that it would only be a matter of time—and not too long—before we too died of AIDS. But we were determined to push for changes in the research system so that later generations of the infected would have a better prognosis and a chance for a longer life. †

## A Tale of Two Trials: Vaccine Researcher Questions the Need for Two Massive ALVAC Studies

The week following the publication of the Merck studies, John Moore became the first researcher to speak up about another muffled controversy: the plans for two separate, massive phase III trials of Aventis Pasteur's canarypox-based HIV vaccine (ALVAC). Moore's commentary, also published in Nature, suggests that an excess of competitiveness between the two trial sponsors—the Department of Defense (DOD) and the National Institutes of Health (NIH)—is leading to duplicative trials that waste both human and financial resources.

The DOD's trial is to be conducted in Thailand, and plans to enroll 15,800 heterosexuals (the DOD's regulations don't allow them to work with gay men or intravenous drug users) into a trial of an ALVAC vector (vCP1521) encoding gp120 from a subtype E isolate, along with gp41 and *gag/pro* from subtype B. All volunteers will also receive two boosts with Vaxgen's bivalent subtype B/E recombinant gp120 vaccine. The estimated cost is $35-40 million and the current proposed start date is mid-2002. The NIH trial is being planned for the United States, the Caribbean and South America through the HIV Vaccine Trials Network (HVTN) and is slated to involve 11,080 volunteers comprising both gay men and high-risk heterosexuals. The protocol uses a slightly different ALVAC vector (vCP1452) encoding *env*, *gag/pro* and regions of *pol* and *nef* that are rich in CTL epitopes. One arm of the study includes a boost with Vaxgen's clade B gp120 vaccine. Estimated cost for the HVTN study is $60-80 million. (Plans for both studies are discussed in detail in the new *IAVI Report*, online at www.iavi.org.)

In addition to pointing out that the slender differences between these trials render them duplicative, John Moore also raises several scientific questions relating to the study designs. Chief among these is the notoriously poor immunogenicity of the ALVAC vector. In what must surely be a record for any experimental medical intervention, ALVAC's tortuous history has included over 40 phase I and II trials involving around 1900 volunteers. The vaccine has shown an ability to induce low-level HIV-specific CTL responses in about a third of participants at best, and these responses are rarely directed at more than one epitope. Moore also questions the scientific rationale for including a gp120 boosting component. No animal model study has shown an advantage to this approach, and recently presented data from Harriet Robinson's group at Emory reported that adding a gp120 booster to a DNA/MVA vaccine actually *reduced* efficacy rather than improving it. Moore points out that efficacy data from Vaxgen's phase III trial of gp120 will be available later this year, which will surely shed more light on this question.

To avoid duplication and wasted resources (and the potential of two huge failed trials further denting public confidence in the vaccine effort), Moore suggests that the DOD ALVAC trial go forward (perhaps with a more rational boost, for example, *gag* instead of gp120), while the HVTN concentrate on newer and more promising third-generation vaccine constructs such as Merck's adenovirus and the DNA/MVA prime-boost regimen being developed by the International AIDS Vaccine Initiative (IAVI). While a counter-argument is that these newer agents are not yet ready for phase III evaluation, it is entirely conceivable that they will reach this milestone within the next two years. And even if both proposed ALVAC trials begin as scheduled, enrollment is likely to be a lengthy process. Alternatively, Moore offers that the HVTN could assume responsibility for conducting a single ALVAC trial while DOD concentrates on bioterrorism defense. Although John Moore's advice is clearly not intended to be proscriptive, the overarching and long-overdue message of his commentary is clear: it's vital that the plans for both ALVAC trials are subjected to open public discussion before they are finalized. *RJ*

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the induction of T-cell immunity against HIV. The immunization strategies employed in both studies successfully induced virus-specific CD4+ helper and CD8+ CTL (cytotoxic T-lymphocytes) responses, but neither afforded full protection from infection. Instead, the success of the vaccines was measured by their ability to stimulate the immune system to control viral replication and thus preserve CD4+ T-cell counts and prevent clinical disease, at least in the short term.

This type of outcome contrasts with the Holy grail of vaccinology, "sterilizing immunity," wherein infection is entirely prevented or rapidly cleared, leaving no detectable trace (except for, sometimes, long-lasting immunity).

The conventional wisdom is that sterilizing immunity can only be achieved with the aid of neutralizing antibodies, and HIV has thus far proven resolutely resistant to this type of immune response (although experiments using high levels of infused lab-created antibodies, "passive immunization," have prevented infection in an SIV model). The pursuit of partial protection has thus been promoted as something of a stop-gap measure while researchers continue to try to solve the antibody challenge.

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Public dissent regarding this two-tiered approach has been muted—until now. It is the Harvard data that has finally drawn several partial protection pessimists into the open because it raises a chilling possibility: that a vaccine which offers only partial protection could end up leading to a worse outcome than no vaccination at all.

In the study, Barouch and his Harvard team found that a single viral mutation led to viral rebound, CD4 cell decline, symptomatic disease and ultimately death in one of eight vaccinated macaques. Up until that point, the monkey in question had been clinically and immunologically healthy for six months after an intravenous challenge (with the pathogenic SIV/HIV hybrid SHIV89.6P, either six or twelve weeks after the final immunization; *see footnote, end of next page*). The mutation was apparently selected for by the vaccine-induced virus-specific CTL response.

Interviewed in a Mark Schoofs *Wall Street Journal* piece, primate researcher David Watkins raises the specter of such escape mutations occurring in vaccinated humans and being transmitted onwards, potentially leading to the emergence of (yes, that media favorite): a "supervirus." While this appears to echo some of the extremely speculative arguments against global implementation of HAART, a recent modeling experiment by Andrew Read and colleagues from Edinburgh actually offers some basis for Watkins' concerns. Read modeled the potential effects of vaccines that ameliorate disease but do not prevent infection and found that under some circumstances they could potentially select for pathogens with increased virulence. Importantly, however, this result becomes less likely if the vaccine also reduces onward transmission of the infection. The potential for enhanced virulence would also be reduced if the vaccine were able to fully protect some proportion of immunized individuals.

The views of Watkins illustrate the theoretical basis for an increasing bifurcation of opinion among HIV vaccine researchers. On one side, there is a cadre displaying considerable enthusiasm and optimism about prospects for T-cell based vaccines, including Norm Letvin and the U.K.'s Andrew McMichael. On the other, an increasingly vocal group—including Watkins but perhaps most often associated with Harvard primatologist Ron Desrosiers—argues for caution, even going so far as to characterize the current mood of optimism over new vaccines as "irresponsible." Somewhere in the middle, stoic realists such as antibody expert John Moore from Cornell acknowledge that T-cell based vaccines are well worth testing, but expect that the addition of an effective antibody-based approach will be required to achieve truly protective immune responses.

## Could a vaccine that offers partial protection end up being worse than no vaccine at all?

While they have served to highlight these outstanding questions pertaining to T-cell based HIV vaccines, neither the Merck or Harvard paper claims to provide data that can resolve them. And there may be a danger of the data's being over-interpreted. The initial goal of both groups was to consistently raise CTL responses, a not-insignificant challenge as is evidenced by the decade-long travails of the ALVAC canarypox vector (*see "A Tale of Two Trials," previous page*). Also, in keeping with the preliminary nature of these experiments, only a limited number of viral antigens were employed: *env* and *gag* in the Harvard study and *gag* alone in Merck's.

The details of Barouch's work provide additional reasons for caution. The data derives from a study that was widely publicized when first published in *Science* in the fall of 2000. A DNA vaccine construct encoding SIV *gag* and HIV *env* was administered four times to rhesus macaques. Four animals received the DNA vaccine alone, while two additional groups of four animals each received a low dose of an IL-2 fusion molecule (IL-2/Ig) in either protein or DNA plasmid form at the time of the first two immunizations. Six weeks after the final booster, all macaques were intravenously challenged with SHIV89.6P. All animals became infected, but at the time of the publication of the *Science* paper, recipients of the vaccine plus IL-2 had controlled viremia and preserved their CD4 counts over 140 days of follow-up.

By contrast, four of eight controls had died and only two displayed some degree of immunologic control of the challenge virus. But subsequent to this initial report, one animal that received the vaccine plus IL-2 in protein form—monkey #798—began to lose control of viremia at around week 24 post-challenge. This was followed by a loss of CD4 T cells (week 36), symptomatic clinical disease (week 44), and death from simian AIDS (week 52).

It is the sobering tale of this macaque that forms the basis of the Harvard group's *Nature* paper. In collaboration with Northwestern University virologist Steve Wolinsky, the researchers went over the data to look for explanations for the apparent vaccine failure.

## The Importance of Letting T-Cells Take a Rest

One interesting aspect of Merck's vaccine study appears to have escaped comment. The data comprised two sets of studies, one set evaluating the vaccine vectors given singly while the second set combined the DNA vector with either Ad5 or MVA in a prime-boost regimen. In the former studies, macaques were challenged with SHIV89.6P twelve weeks after the last immunization, while in the prime-boost the challenge was administered just six weeks after the booster shot. The data clearly demonstrates that the prime-boost approach induced larger T-cell responses than either the Ad5 or MVA vector given alone, but what about the post-challenge outcomes? Looking at the graphs, it appears that control of viral load and preservation of CD4+ T-cell counts was more consistent in the animals that received Ad5 and MVA alone compared to those that received prime-boost. So what's going on here?

The explanation may relate to a fundamental tenet of T-cell immunology. CTL maven Rafi Ahmed has long noted that vaccine-induced T-cell responses need to reach a "resting memory" state in order to respond optimally to a subsequent boost or challenge. The canonical T-cell response to a vaccine involves a peak of proliferation, followed by a "death phase" and ending with a stable but lower-level population of resting memory cells. It can take several weeks for this process to play out in mice, and how long it takes in higher primates is currently unclear. It is possible that for the macaques in the Merck study that received Ad5 or MVA alone, the additional six weeks of rest between the final immunization and challenge may explain the otherwise counterintuitive results. This will be a key question to explore in future animal studies, and, according to Emilio Emini, data is forthcoming that will address the question more directly. *RJ*

Genetic sequencing of the virus revealed that between weeks 14 and 20, immediately prior to the viral breakthrough, a mutation occurred in a region of the *gag* protein targeted by the vaccine-induced CTLs. The mutation involved a single amino acid change (from threonine to isoleucine) which was absent from 8/8 viral isolates sampled at week 14, but present in 10/10 isolates sampled at week 20. Upon further analysis, CTLs targeting the original epitope were found to be 1,000-fold less efficient at recognizing the mutant virus than the original strain. Barouch concluded that it was this single point mutation which ultimately triggered the cascade of events leading to the death of monkey 798.

The data raise the question of whether such escape tactics will prove to be the Achilles heel of all T-cell based vaccine strategies. If such vaccines cannot prevent infection, will eventual immune escape and disease progression be inevitable? Could such escape variants be transmitted, and thus further diminish vaccine efficacy at the population level? The Harvard team notes that the best strategy for preventing escape may be broadening the vaccine-induced immune response (e.g., by including antigens other than just *gag* and *env*) and attempting to drive viral replication to the lowest level possible post-challenge.

In an interview with *National Public Radio* after the study was announced, Norman Letvin noted that, prior to the emergence of the CTL escape mutant, monkey 798 appeared to have slightly higher levels of viral replication than the other immunized animals. He also reported that these remaining seven macaques have continued to control viremia for more than 600 days of follow-up. Taken together, these observations suggest that while it is probably premature to conclude that all CTL-based vaccines are doomed to failure, the unavoidable implication is that increasing CTL selection pressure by vaccination could have unpredictable effects on the evolution of HIV. Careful long-term monitoring and follow-up will be critical in both animal and human studies of these approaches. †

*Footnote: SHIV89.6P is a hybrid SIV/HIV construct which contains the envelope of SIV and the core of HIV. More specifically, it was constructed by combining the genes* tat, vpu, rev *and* env *from the Dutch HIV-1 isolate 89.6 with the remaining genome of SIVmac239. The* gag *proteins of challenge virus (SIVmac239) and vaccine are therefore precisely matched, or "homologous." SHIV89.6P is noted for its ability to cause an unusually rapid and typically irreversible CD4 T-cell loss, accompanied by the swift onset of simian AIDS and death. While use of this virus allows for a rapid analysis of vaccine-mediated protection from clinical disease, many researchers raise the point that SHIV89.6P does not reproduce the more prolonged course of HIV infection observed in humans—and therefore may not be truly representative of the human* in vivo *situation. The Merck investigators themselves concede that, "the relevance of the SHIV 89.6P monkey challenge... has not been firmly established."*

*Mobilizing the Troops*

## Newly International North American Activist Alliance Gathers in Vancouver

'Gathering strength to fight'

*For the first time ever, NATAF (newly renamed from the National AIDS Treatment Activists Forum to the North American AIDS Treatment Action Forum) took place outside of the U.S., in the beautiful Canadian city of Vancouver, British Columbia. Over 450 delegates from around the U.S. and Canada joined others from Eastern Europe, Poland, Russia, Cuba, Puerto Rico, Mexico and Costa Rica in what was the first truly international NATAF. Mark Baker, editor of* Provincetown Positive*, was there to chronicle blow by blow the events of the three-day get-together. "Once again," Baker writes, "those gathered consisted of people living with HIV and their advocates—all from a multitude of diverse backgrounds, cultures and races. There were men and women; straights, gays, lesbians and people with histories of intravenous drug use; Caucasians, African-Americans, Latino/as and Asians. But for all our diversity, we had two unifying factors in common—HIV disease and our desire to become better treatment advocates and activists." An pared down version of his 2001 NATAF report follows. Thanks, Mark.*

As HIV/AIDS treatment issues were becoming more and more important in the early 1990s, a few dedicated treatment activists realized the need to create a place in which fellow treatment activists could share treatment information and further develop treatment and research advocacy. As they discussed how to do this, it became increasingly obvious that a mechanism needed to be developed to transfer the knowledge of experienced treatment advocates to members of all communities infected and affected by the AIDS epidemic. The goal was clear: create a mechanism to help educate people about treatment issues who could then take home what they learned to further educate their communities about increasing access to care and treatment. As this basis for NATAF solidified, it also became clear that the complex issues of public policy, funding and HIV prevention also had to be included due to their effects on treatment and research priorities. Out of all this, the first NATAF was born in 1995.

December 2nd was the first day of NATAF 2001. It began with a pre-conference orientation that gathered all of us together to learn how to gain the most from the next three days of plenaries and workshops. At the front of the room was a handmade timeline that began with the year 1980 and ended with 2001 entitled, "The History of HIV/AIDS." Of particular interest to me was the note at the start of the timeline indicating that 1959 was the year in which a man died in the Congo from an unidentified illness. An analysis of a saved blood sample later found him to be the first confirmed case of HIV infection—in 1959. The timeline was a graphic illustration of the events, both good and bad, that have shaped the North American HIV/AIDS epidemic. It was an apt reminder that we who call ourselves "advocates" help make history. Whether it's history in HIV/AIDS policy, treatment research and development, and/or in an individual's access to care and treatment, it's been the HIV/AIDS advocates at the center of historical landmarks.

The opening plenary that night was called, "From Where I Stand." It began with an address from a Native North American chief whose indigenous people once numbered 10,000 in this territory, yet today number a mere 360. He spoke eloquently about the parallels faced by Native Americans and people living with HIV, noting that hopelessness in our communities is caused and perpetuated by the media images which stereotype gays, PWAs, and IDUs. The fight is made easier when we come together, at places like NATAF, to work collectively to defeat the ignorance of the broader community. He ended with a moving song, traditional for his people, in tribute to all those that have died from this disease.

**Anuar Luna** of Mexico gave the first keynote speech. He stressed that the "official numbers" of people living with HIV or AIDS in Mexico—50,000—is not an accurate picture of the estimated 150,000 people in actual need of access to HIV care and treatment. The epidemic in Mexico is centered among gay men ages 15-44, but women are increasingly affected. Only roughly 75% of these—usually the ones that work—have access to treatment, but the quality of the care varies greatly. Sometimes anti-HIV drugs are available, sometimes they are not; sometimes PWAs have access to lab tests for viral load, most do not; and genotypic and phenotypic tests are still a rarity. AIDS services organizations provide limited services, mostly peer education and support. There are a limited number of "drug banks"—places that gather unused supplies of anti-HIV drugs and redistribute them to those in need. Only recently have Mexican AIDS activists started to meet with the political decision-makers to advocate for more money—$48.5 million—needed for HIV/AIDS treatment for Mexican PWAs, as well as more human resources and technical assistance to combat the disease.

**Phill Wilson** of the U.S., a 21-year AIDS survivor and a gay man of color, spoke next listing the possible repercussions of the 9/11 terrorist attacks on democratic freedoms that could affect

policies governing healthcare issues such as HIV/AIDS.

**Louise Binder** of Canada completed the opening plenary. The leading Canadian AIDS activist decided early on that treatment information would save her life. She believes that the 1996 World AIDS Conference held in Vancouver—heralded as "The Cure Conference"—was actually the birth of AIDS complacency in North America. Combination therapy—including the fabled protease inhibitors—was credited with creating the Lazarus-effect whereby PWAs who were formally on their deathbeds had tremendous initial response to HAART and rebounded to seemingly much healthier lives. Even though this effect is complicated by the toxic side effects of the drugs, most of the world breathed a collective sigh of relief, believing that the epidemic was over.

But because today's HIV treatments are a reprieve and not a cure, the need for both activism and advocacy still exists. We still need new clinical trials, new drugs, expanded access to treatments (both in North America and globally), and advocacy for improvements in the social ills that feed epidemics like HIV and AIDS—poverty, homelessness, and illiteracy. The question is—will the younger generation now being infected rise to activism to demand the cure that still eludes us? We all need to unite to create a truly global community of activists and advocates to defeat this global epidemic.

Monday, December 3rd began with a breakfast plenary entitled, "The Making of an Epidemic: The Implications of Public Policy." **Martin Schechter** of the University of British Columbia started with a presentation of statistics. As of 2001, 40 million people worldwide are infected with HIV—half of which women. In 2001 alone, there were 3 million deaths worldwide from AIDS and 5 million new infections. That translates to 14,000 new infections every day—95% of which are in developing countries, like South Africa where 1 in 3 people are infected. Against this dismal backdrop, there are new regions of the planet that hold great concern for the continued spread of HIV/AIDS. These "hot spots" include China, India, Indonesia and the states of the former Soviet Union where, globally, the epidemic is now growing the fastest.

> While there are a total of 14 proteins in the viral RNA of HIV, only 2 of them are targeted by currently approved antiviral drugs.

The afternoon workshop session IV called, "Antiretroviral Strategies: Activist Intervention and When to Start, STIs, Salvage Therapy, Long-Term Effectiveness, Adverse Events and Beyond" had the longest title of any workshop offered at NATAF. **Mark Harrington** of TAG joined **Bob Huff** of GMHC and **Ben Cheng** of Project Inform in San Francisco to present. Mark began with an overview of the evolution of the U.S. HIV treatment guidelines that were issued starting in 1997. He noted the troubling controversy that centered on the Guideline's recommendation for all people with <500 CD4 cells to begin triple-drug HIV therapy. This was recommended even though all the studies done to date at the time proved HAART's effectiveness only in people with counts <200 CD4 cells. The recommendation was based on the overwhelming belief in Dr. Ho's "Hit Early, Hit Hard" treatment theory, the possibility of HIV eradication and the goal of preventing irreversible damage to the immune system.

Due to the ensuing, almost immediate, widespread application of the new 500 CD4-based "standard-of-care" treatment guidelines, to this day the question of "When to start anti-HIV therapy?" has not been answered. Unfortunately, that key question is unlikely to be answered. Of course, today science has proven that damage to the immune system caused by HIV infection is partially reversible—CD4 cell counts can and do rebound from low nadir levels. And these new T-cells produced in the thymus do their jobs quite well.

**Ben Cheng** ended the workshop by addressing the new drugs in the HIV treatment pipeline. Besides new drugs in the existing NRTI, NNRTI and protease inhibitor classes, Ben mentioned the latest development of integrase inhibitors and entry inhibitors—the most widely known one of which is T-20. Some of the new drugs in development may be too toxic to be taken orally, but may be successfully developed as topical microbicides. On the whole, though, Ben believes that the drug pipeline is not healthy, mainly due to the fact that big pharmaceutical companies are swallowing up smaller, more HIV-specific drug companies and not necessarily increasing the size of their HIV research and development capabilities.

Kicking off another workshop which focused on effective advocacy with U.S. government agencies, AmFAR's **Jane Silver** gave a brief overview of the National Institutes of Health (NIH) and the Office of AIDS Research (OAR). She noted that the NIH is currently spending $2.4 billion annually on

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AIDS research. That accounts for 85% of the world's publicly funded AIDS research effort. Silver recommended three improvements for federal AIDS research: First is a cross-government-agency, coordinated HIV research strategy with its own dedicated budget; second is a process to influence the direction of HIV research within the NIH; and third is a watchdog capability overseeing NIH's HIV research and budget. Finally, Silver argued for the further development of coalitions with advocates for other diseases in order to reach the goals that still elude us.

**Gregg Gonsalves** spoke further on where the present system fails us. First, there is little work being done to find new targets for HIV therapy, noting that there are fourteen proteins in the viral RNA of HIV, yet we have only targeted two of them with approved drugs at present. He strongly urged advocates to push for the study of new targets. Second, there is still not enough long-term follow-up research on the HIV drugs we now prescribe. Third, and perhaps most importantly, there remains a disconnect between HIV research and HIV drug development. Whereas the NIH funds basic HIV research and clinical trials, the pharmaceutical industry still controls drug development.

Gregg noted that there are models appearing that attempt to bridge this disconnect. IAVI (the International AIDS Vaccine Initiative) is the most visible, being a public/private partnership that first identifies promising vaccine candidates from research and then provides initial support for the vaccine development. Finally, Gregg noted that we still need a system in place through the NIH to do Phase IV long-term follow-up studies in randomized clinical trials.

In the closing plenary entitled, "Infections and Inequalities: International Issues and HIV," **Dr. Julio Montaner** of Vancouver's St. Paul's Hospital noted the disconnect in many countries between areas that have the greatest number of cases of HIV infection yet the fewest antiretroviral drugs available compared to the areas with the smallest number of infections yet most drugs available. He cited the 2001 article by Hogg and colleagues in *JAMA* that found that it proved viable to start HAART at CD4 counts >200 regardless of viral loads. The article indicates that CD4 counts appeared to be a better predictor of disease progression than viral load and suggested that a count of 200 CD4 cells be the new trigger level to start HAART.

> The annual dollar figure needed to stem the tide of AIDS around the world is the same amount the U.S. spends on cosmetics each year—or the Europeans on ice cream.

Montaner reminded those gathered that after the 1996 World AIDS Conference in Vancouver, the prevailing theory in therapy was summed up by Dr. David Ho's infectious soundbyte, "Hit early, hit hard." Now in 2001, the theory is once you start HAART at CD4 counts >200 then "hit hard." He lamented that had he known back in 1996 what he knows today, 65% of HIV-infected individuals in British Columbia could have waited to start triple therapy. This would have represented a huge savings in drug expenditures, physician and lab costs, and sacrifices in quality of life.

He qualified this observation by noting that this new information is based on only 2-3 years worth of data. Therefore, there is still no definitive answer on the optimal time to start treatment. He concluded stressing that while viral load may not be as important as the CD4 count in determining when to start therapy, it is still important once treatment is started: to monitor response to treatment, viral breakthrough, the emergence of resistance and the likelihood of disease progression.

He then turned to the global front, citing the present day catastrophe of 40 million people HIV-infected worldwide and fewer than one million with access to treatment. He cited the new "hot spots" of HIV infection around the world, noting that if nothing is done soon, these places will experience an increase in HIV infection on par with that which Africa has seen in the fifteen years from 1984-99. As a result of this huge increase in poverty and a decrease in productivity, there will be financial and social ruin on a scale never before seen.

Montaner closed by noting that the idea of "human security" is increasingly based on the infrastructure needed to support people leading healthy lives. The provision of anti-HIV drugs alone will not solve the problems that face us globally. We need to promote the development of social systems that people need to be healthy, which will have a positive impact not only on AIDS, but on TB, malaria and malnutrition as well. The WHO has placed the dollar figure needed to stem the tide of HIV/AIDS by 2005 at $9.2 billion a year—the same amount that the U.S. spends annually on cosmetics and the Europeans spend on ice cream! The obvious conclusion: we either pay now or pay later, but later the bill will be much, much higher. †

*Mujeres Acertijadas*

# Los Informes del Progreso Hacia La Comprensión Sobre Cómo Algunas Personas Aparecen Luchar el VIH

'Identificando la fuente del poder'

*En los estados unidos, los estudios a plazo largo de gente infectada y de riesgo alto por VIH han implicado principalmente a hombres alegres–el grupo muy afectado en los años tempranos de la epidemia. Pero un continente lejos, en el distrito de Pumwani de Nairobi, un grupo sobre apenas de 100 mujeres ha llegado a ser muy conocido a investigadores del VIH alrededor del mundo ofreciendo la evidencia tantalizada que el sistema inmune puede, en casos raros, lucha contra el VIH. Richard Jeffreys preparó este informe. Dos reglamento relacionado, "Mantiendo el VIH a Raya: Qué Mantiene a Bebés Expuestos No Infectado?" y "Genes de HLA e Inmunidad" aparecen en el emisión del septiembre 2001 del Informe del IAVI (Iniciativo Internacional Sobre Vacunas Para Sida).*

La evidencia deriva de un cohorte de trabajadores femeninos de sexo, establecido en 1984 por Elizabeth Ngugi y colegas de la Universidad de Nairobi y la Universidad de Manitoba para el propósito de estudiar las ETS. A pesar de un estimó 60 o más exposiciones de no protegidos al VIH cada año–uno de las tasas alto documentadas de exposición en el mundo–sobre 100 de las 2000 mujeres matriculadas en el cohorte ha probado negativo para la infección del VIH para por lo menos tres años, y en algunos casos hasta 15. Los estudios de éstos "altamente expuesto persistentemente seronegativo" (HEPS, también se refirió a veces a seronegativo como expuestos o ESN) mujeres convencieron muchos escépticos esa resistencia inmunológica al VIH–y por la extensión, una vacuna del VIH–es posible.

Desde que la primera descripción de este fenómeno por investigador canadiense Plummer Franco (en la 1993 Conferencia Internacional del sida en Berlín), la Unidad de Inmunología Humana de la Universidad de Oxford en el UK y en Manitoba ha unido los equipos de Nairobi para conducir los estudios inmunológicos detallados de estas mujeres. Su meta: identificar cuáles respuestas inmunes protegen a las mujeres contra el VIH, y para usar esa información para indicar el diseño de vacunas impeditivas del VIH.

Sobre los pasados pocos años, los estudios de Nairobi–junto con ésos en otro cohortes de HEPS y en infectado del VIH, a plazo largo no progressores–ha estado sugiriendo algunos contestan. En el tarde 1990s ellos ayudaron el foco la atención de campo de vacuna del sida en la importancia de respuestas celulares inmunes en la protección, especialmente el CD8+ las células de asesino T (llamó también cytotoxic linfocitos, o CTLs). Estos días, el énfasis está identificar activado las regiones precisas del VIH (llamó epitopas) eso estimula lo que aparece ser las respuestas protectoras, y a aclarar los papeles de jugadores inmunes menos bien caracterizados, incluyendo las células CD4 y respuestas T ayuda de la mucosa, en la resistencia al VIH.

Al costado la ciencia, el proyecto fue establecido del principio para proporcionar los servicios médicos para las mujeres y frecuentar el cambio con el equipo de investigación. "El cohorte es una asociación entre los trabajadores del sexo y los investigadores," dice Joshua Kimani, la parte del equipo del Departamento de Microbiología Médico en la Universidad de Nairobi. "La asociación ha trabajado sobre los años debido a las reuniones mensuales que tenemos con los líderes de igual de trabajadores de sexo. En estas reuniones publica relacionado al continuación pobre o cualquier desdicha con los proveedores del servicio se planchan fuera." Hay también una reunión anual entre los investigadores y el cohorte entero. El equipo de investigación proporciona los servicios médicos libres, condones gratis, hospitalización de cubiertas en el Kenyatta el Hospital Nacional y puede ayudar con precios del billete de autobús y otros gastos. Los tratamientos disponibles incluyen ésos para las EST y las infecciones más fácilmente manejadas de oportunista, pero hacen no en presente incluye el nombre costoso de marca endroga tal como el antifungal Diflucan y antiretrovirales.

**El Origen del Cohorte**

Probar del VIH en el cohorte de Pumwani comenzó en 1985, cuándo especialista contagioso de enfermedad Plummer tomó lo que se pensó para ser un desvío breve de Manitoba de unir el proyecto de las EST en Pumwani. Fuera de 600 mujeres matriculadas en el tiempo, Plummer quejó encontrar que dos tercios probado positivo para el VIH. Cambiando el foco de su trabajo, él comenzó a valorar los factores asociados con ambos seroconversión y la falta de seroconversión en el uno tercero de las mujeres que probaron negativo del VIH. La observación sorprendente informada en Berlín era que mujeres que permanecen negativos dos años después de comenzar el trabajo del sexo tuvo sólo uno décimo el riesgo de seroconversión subsiguiente (sobre los siguientes dos años) comparó con a mujeres negativas del VIH nuevamente unión del cohorte. Además, esta resistencia aparente a la infección del VIH se asoció con cierta clase I genes de HLA, sugiriendo un

eslabón a respuestas CTL.

Los datos de Plummer agarraron la atención de Sarah Rowland Jones, que había visto previamente algunos casos de persistentemente mujeres de seronegativas entre trabajadores de sexo en la Gambia. (Gambia es eso protrusion que parece dedo al oeste oriental del territorio gobernado anteriormente inglés que extiende en el tercero más bajo de Senegal, cubriendo el río eponimico Gambia.) Unión arriba con el Manitoba e investigadores de Nairobi, Rowland Jones y los colegas Tao Dong y Andrew McMichael analizaron sangre prueba de las mujeres de HEPS para la evidencia de específico del VIH CD8+ la actividad de la célula T. Sus resultados, publicado en tarde 1998, mostró una asociación fuerte entre el fenómeno de HEPS y la presencia de CTLs específico del VIH dirigió contra una distancia ancha de epitopas del VIH. Esta asociación fue reforzada por estudios posteriores, mientras varias explicaciones se basaron en de factores no inmunes, tal como mutaciones en el CCR5 co gene de receptor, se excluyó.

Pero entonces vino un hallazgo que pareció inicialmente algo contra intuitivo, según Rowland Jones: el nivel de las respuestas de CTL en las mujeres de HEPS era tanto como diez vez más baja que en mujeres no infectadas. “Eso significa que no deberá contar bastante simplemente células T,” ella dice. En lugar, señaló a los investigadores hacia un análisis más cualitativo de las células que responden, por ejemplo en términos de su especificidad de epitopas, la anchura y las propiedades funcionales.

**Respuestas Mucosas**

Después que la descripción inicial de CTLs específico del VIH en la sangre, los investigadores acudieron a analizar las respuestas inmunes mucosas en las mujeres de HEPS. El primer estudio publicado, dirigido por miembro nuevo de equipo Rupert Kaul, informó la presencia de anticuerpo específico del VIH de IgA en el trecho de genital de 16 fuera de 21 mujeres de HEPS comparó con 5/19 mujeres infectadas del VIH. Opuestamente, anticuerpo específico del VIH de IgG estaba ausente de HEPS y el presente mujeres en total infectadas. Trabajar con inmunólogo italiano Mario Clerici para valorar las respuestas T ayuda en la sangre, el papel la evidencia también informada de células T específicas de Env en HEPS 11/20, pero no había la correlación con la producción de IgA en la mucosa.

Esta aparente resistencia a la infección del VIH se asoció con genes específicos del HLA clase I—sugiriendo un papel para las respuestas CTL.

El papel de IgA se exploró además en otra colaboración, este tiempo con Claudia DeVito y colegas del Instituto de Karolinska en Stockholm. Los investigadores diseñaron un sistema para modelar la transferencia del VIH a través del epithelium humano de mucosa, entonces probó la habilidad de IgA aisló del líquido de vaginal de cervico de mujeres de HEPS para bloquear el proceso de la transferencia (llamó transcitosis). Las muestras de seis mujeres se examinaron, y 3/6 redujo transcitosis de un clade B VIH primario aísla por más de dos tercios. El trabajo sugiere un mecanismo por cuál IgA podría contribuir a la protección en la superficie mucosa, aunque los autores acentúen que otros factores son probablemente también en el juego.

En la paralela a los estudios de IgA, el grupo de MRC encontró la evidencia de CTL específico del VIH en el mucosa. Las muestras de cervical y sangre que examinan, ellos encontraron las respuestas en HEPS 11/16 y 8/11 mujeres infectadas del VIH que usan un aquilatamiento del *ELISpot* para la producción de la gamma de interferon. Ellos encontraron también que las mujeres de HEPS tendieron a tener las respuestas levemente más altas en la cerviz compararon con sangre, mientras que mujeres infectadas tenidas significativamente más CTL específico del VIH en la sangre que cerviz. Este enriquecimiento aparente de mucosa CTLs en las mujeres resistentes sostiene la idea que ellos juegan un papel en la protección del VIH.

**Seroconversiónes Atrasadas**

Pero como estos estudios pasaban, los hallazgos inesperados surgían: entre 1996 y 2000, 11 de las 114 mujeres que habían reunido la definición de trabajo de la “resistencia” (trabajodores en sexo para >3 años sin seroconversión o un PCR positivo) llegó a ser infectadas del VIH y seroconvertió. Tomó a los investigadores por la sorpresa, desde que seronegatividad a plazo largo había aparecido se ser asociado de cerca con un riesgo disminuido de la infección nueva. Y provocó un esfuerzo intenso para averiguar lo que pasaba.

Pronto se aclaró que no había la correlación obvia entre esto “seroconversión tarde” y la presencia o ausencia de CTLs en pruebas previas. “La mitad de las mujeres que seroconvertó tuvo CTL [en puntos más temprano de tiempo],” dice Kaul. “Habíamos mirado una pareja de esas mujeres repetidas veces y CTLs visto muchas vez. Así que fuimos sorprendidos bastante y fuimos desilusionados para verlos seroconvertir.” Una posibilidad

obvia–que viruses que infectan tuvieron mutaciones de "escape" en el regiones fijados por las mujeres CTL–fue excluido rápidamente.

Una respuesta comenzó a desplegar cuando la búsqueda acudió a la cantidad o el tipo de la exposición reciente de mujeres al VIH. Su análisis mostró que una reducción en el trabajo del sexo–o parar para sobre dos meses o reducir el número de clientes por más de dos por día–era fuertemente, pero no absolutamente, asociado con la infección subsiguiente: 10 del 11 seroconvertidores habían reducido su exposición por estos criterios, comparó con 10 del 22 persistentemente mujeres de seronegativas. El análisis de seis mujeres en el grupo postrero encontró eso–antes que seroconvertiendo cuando ellos reasumieron el trabajo del sexo–ellos mostraron un aumentar de sus respuestas específicas del VIH de CTL. "En esas mujeres nosotros vimos una tendencia general que cuando usted toma una interrupción del trabajo del sexo, las respuestas inmunes se van," dice Kaul. "Si usted comienza el trabajo del sexo otra vez, estas respuestas a menudo regresan." Pero es poco claro por qué el regreso de respuestas en algunas mujeres mientras los otros llegan a ser infectados. Algunas posibilidades: la persistencia de CTL específico del VIH debajo de niveles perceptibles en las mujeres de HEPS, las diferencias entre respuestas de sangre y mucosa, la naturaleza precisa de la exposición del VIH después de una interrupción y respuestas inmunes no analizó en el estudio inicial, las células tal como específicas del VIH de T ayuda y/o anticuerpo IgA específico del VIH.

La implicación de estos resultados, extensamente informado en la prensa de corriente principal, era esa exposición continua al VIH puede ser importante mantener la resistencia en por lo menos algunas mujeres de HEPS. Si esto aplicaría también a vacunas es poco claro. El grupo de Oxford indica dos posibilidades. Uno es ese estímulo progresivo con antígenos del VIH se requiere, o por motores auxiliares de propulsión periódicos de vacuna o por el uso de estrategias de vacuna antígeno persistente que emplea. Alternativamente, las respuestas inducidas de vacuna establecidas antes de cualquier exposición del VIH (en comparación con la inmunidad inducida por virus vivo) quizás muestre un muy diferente dinámico.

> La evidencia de protección contra VIH en las mujeres de Pumwani ha influido fuertemente el pensamiento de los diseñadores de una vacuna para VIH.

Para mirar más de cerca para pone en correlación de seroconversión tarde contra la resistencia continuada, Kaul ahora se implica en un estudio prospectivo, que controlará una distancia ancha de parámetros inmunes. "Trataremos y obtendremos a mujeres para venir nos ve antes ellos pasan una interrupción, para que podamos buscar las respuestas específicas del VIH en aquel momento. Entonces trataremos de obtenerlos vernos en cuanto ellos vuelvan, antes ellos han comenzado el trabajo del sexo otra vez, así que podemos ver lo que es acontecido a esas respuestas inmunes." Además de controlar CTL de la sangre, los investigadores seguirán también las respuestas mucosales, mientras Keith Fowke de la Universidad de Manitoba estudiarán el CD4 las respuestas T-ayuda.

La naturaleza del virus que infecta en el seroconvertidores tarde viene también abajo el microscopio. Algunos científicos han formado una hipótesis que las mujeres resistentes tienen un latente, la infección no detectable del VIH, y que las infecciones abiertas tardes podrían representar un escape de este virus del control inmune. "Hace nada en absoluto sorpresa mí," dice Rowland Jones. Ella es reclutada la ayuda de Bette Korber del laboratorio Los Alamos y de Harold Burger de la de la Universidad de Albany para aplicar las técnicas moleculares de reloj a la fecha que el viral aísla encontró en el seroconvertidores tarde. "Ellos planean al virus de la sucesión para tratar y averiguar si es un virus viejo de Nairobi," los informes Rowland Jones. "Aunque esto no pueda contestar la pregunta definitivamente, quizás proporcione la evidencia sugestiva de una infección latente."

**La Búsqueda para Epitopas CTL "Resistentes"**

Otro foco mayor del trabajo actual deberá identificar el epitopas de CTL asociado con la resistencia. En el primer conjunto de datos para surgir de este trabajo, los investigadores informan algunas diferencias llamativas. Mirando las respuestas de CTL a un entrepaño de 54 epitopas conocido (restringido por 21 moléculas diferentes de HLA), ellos encontraron que mujeres de HEPS mostraron las respuestas fuertes a cuatro epitopas que eran muy raramente immunodominante en mujeres infectadas–dos en Pol y dos en p24-Gag. Ellos encontraron también que infectaron mujeres respondieron muy fuerte al epitopas reconocido sólo raramente, o nada en absoluto, por el grupo de HEPS. Del siete seroconvertidores tarde evaluado en el estudio, cinco mostraron un interruptor del modelo de HEPS de respuestas de epitopa hacia que de mujeres infectadas y/o la pérdida completa de respuestas al epitopa

"resistente."

Otra observación llamativa era que cuatro epitopas las diferencias que muestran entre HEPS e infectaron a mujeres son restringidas por alleles de HLA conocido para se ser asociado epidemiologicamente con la resistencia del VIH en el de Nairobi (A2 cohorte, A24, UN*6802, B14 y B18), sugerir que el efecto de estos tipos de HLA es relacionado a su probabilidad más grande de engendrar las respuestas de CTL a un repertorio de epitopas más protector.

El estudio representa un primer paso a identificar epitopas de "resistencia", pero hay más trabajo adelante–particularmente dado el "espacio de información" reveló cuando los investigadores usan las proteínas enteras del VIH, antes que epitopas conocido, para medir las respuestas de la célula T. "Vemos a varias mujeres que no responden a un entrepaño de epitopas de CTL, pero responden a Env o la Broma," dice Kaul. "Tan hay probablemente algún epitopas dentro de esos genes que no se han trazado todavía."

**Respuestas T-ayuda en Las Mujeres ESN**

No todo el alleles de HLA asociado con la protección en mujeres de HEPS pertenece a la clase I, el sistema para presentar epitopas a CD8+ las células T. Un análisis comprensivo por el grupo de MacDonald de Kelly de la Universidad de Toronto reveló un eslabón altamente significativo con la allele clase II HLA DRB*01, sugiriendo un papel importante para las respuestas CD4+ de T ayuda en la resistencia de mediatando. "Esto señala al hecho que hay un multifactorial la respuesta inmune," dice Keith Fowke, que tiene toman la tarea de analizar las respuestas de ayudan en el cohorte de Nairobi. "Ignorar la respuesta de T ayuda sería un error."

Fowke era autor recientemente dirigiendo en el primer informe publicado para mirar ambos a ayudante T y respuestas específico del VIH de CTL en las mujeres de HEPS del cohorte de Nairobi. Este estudio discernió las respuestas de ayudante T en mujeres de HEPS 7/17 que usan un aquilatamiento para IL-2 producción en la respuesta a cinco peptides de Env. El equipo de Fowke entonces se llevó a cabo tanto el ayudante como los aquilatamientos de CTL en muestras de 15 mujeres, y encontró un eslabón estadísticamente significativo entre la presencia de respuestas de ayudante T y CTL. "Los datos sugieren que son importante tener no sólo CTL pero bueno 'ayuda,'" notas Fowke. Esta observación es consistente con el trabajo básico del inmunología en modelos animales, demostrando un papel clave para células específicas de virus de ayudante T a engendrar y mantener las respuestas efectivas de CTL.

Para clarificar el papel de CD4 las células T en la protección, el grupo de Fowke usa los aquilatamientos de *ELISpot* para conducir un análisis más ancho de respuestas en las mujeres de HEPS. Aunque una cantidad significativa de datos de epitopa de CTL esté disponible, hay una escasez de la clase II definida epitopas restringido de ayudante T, uno que Fowke se propone dirigir trazando viruses del clade D de usa respuestas y clade I de virus recombinante. Otra prioridad para el equipo de Manitoba investiga la actividad específica del VIH de T ayuda en el mucosa, que nunca se ha estudiado en el cohorte (ni cualquier otros individuos expuestos de seronegativos a la fecha), debido a la dificultad de obtener las muestras con números suficientes de células.

En algunos países africanos, un cóctel triple genérico puede costar tan poco como $30 por mes. Los precios de drogas patentadas son todavía tres veces más altos.

**El Diseño de la Vacuna**

La presencia de la inmunidad aparente en las mujeres de HEPS, y en su asociación con respuestas de célula T en la ausencia de anticuerpo, ha influido fuertemente el pensando en diseñadores de vacuna del sida una influencia prontamente evidenciado por una cosecha nueva de candidatos que se proponen inducir celular las respuestas inmunes al VIH. Varias vacunas basadas en esta estrategia han mostrado la promesa en estudios recientes de mono, inclusive ésos de investigador de Universidad de Emory Harriet Robinson, Harvard Norman Letvin y Merck. Cuando más es aprendido acerca de las respuestas protectoras en las mujeres de Pumwani, ese conocimiento es probable de continuar reveladores indicadores de vacuna hacia los tipos de respuestas al blanco y el epitopas del VIH que mejor los puede inducir.

Los resultados de los estudios cooperativos del Oxford, Manitoba y los equipos de Nairobi son pasados también en a diseñadores de vacuna Tomas Hanke y Andrew McMichael en Oxford, cuyo primero generación ADN construido por MVA está actualmente en los ensayos Fase I en Oxford y Nairobi. Las generaciones posteriores de esta vacuna utilizarán información espigada del trabajo continuo con estas mujeres. †

## Tenofovir (*Viread*), Primer Agente Novedoso Antiviral Desde Seis Años, Aprobado por el FDA

El viernes, el 26 del octubre, los EE.UU. La Administración del Alimento y la Droga otorgó la aprobación acelerada al inhibidor nucleotide analógico de transcriptasa inverso de Gilead, tenofovir fumarate disoproxil (el nombre de marca, *Viread*). El marcar solicitado era para el "el tratamiento de la infección VIH-1 en la combinación con otras medicinas antiretrovirales." Tenofovir es el primer analógico nucleotido aprobado para el tratamiento de la infección por el VIH, y de tal segundo producto de Gilead. Adefovir (el nombre del comercio *Preveon*) fue rechazado por la Dirección de Alimentos y Drogas de los E.E.U.U. tarde en el año 1999 debido a la peligrosa seguridad y los resultados clínicos débiles. Inhibidores nucleotidos de transcriptasa inverso analógico son semejante a los inhibidores nucleosidos y bloque la replicación del VIH en la misma manera. La diferencia es que ese analogos nucleotidos tiene ya un grupo de fosfato conectado.

La Dirección de Alimentos y Drogas de los E.E.U.U. se basó su aprobación de tenofovir en los resultados de dos estudios clínicos, estudia 907 y estudia 902, implicando más de 700 pacientes que habían sido tratados previamente con agentes de antiretroviral pero con los signos mostrados del fracaso del tratamiento. Estudie 907 era un de 552 pacientes, de 48 semanas controlado de placebo, el estudio de intensificación del tratamiento. Los resultados veinticuatro de la semana fueron presentados a la Dirección de Alimentos y Drogas de los E.E.U.U. Estudie 902 era un estudio más pequeño, también en tratamiento los individuos experimentados, eso compara el tratamiento intensificación con tres dosis diferentes de tenofovir o placebo. El estudio se ofrece quién recibió tenofovir mostró una reducción mala de la carga de viral de 0.62 troncos comparó con los individuos que recibieron un placebo con el régimen uniforme de antiretroviral. Tenofovir está disponible como una 300 tableta de mg para ser tomada oralmente, con una comida.

Porque la aprobación de tenofovir se basó en ensayos clínicos los individuos que implican previamente tratado con antiretrovirales, la razón del beneficio del riesgo para individuos sin tratamiento tiene mas ser determinada. Además, no hay los resultados del estudio de mostrar la inhibición a plazo largo de la progresión clínica del VIH por tenofovir. Los estudios adicionales se esperan en camino para dirigir estas cuestiones: Estudia 903 matriculó casi 600 individuos no tratados y está esperado producir los resultados por medio-2002; Estudie 910, un rollo sobre el estudio de la extensión de individuos de los estudios 902 y 907, examinará los cuestiones a plazo largo de la eficacia y la seguridad. *MB*

*— viene de la primera página —*

*escribe en una liberación relacionada de la prensa, "Africa es un desierto para patentes." Mientras uno esperaría quizás que esta clase de investigación polémica del aprecia de una organización intelectual de la propiedad (el Instituto reconoce abiertamente su recibo de un $25,000 otorga de Merck sobre la terminación del manuscrito), el autor del estudio Amir Attaran que viene entre los grados del Centro Internacional sobre Desarrollo de la Escuela Kennedy de Gobierno—en Harvard.*

El motivo de Attaran parece ser una tentativa para apoyar a una llamada de su jefe, hace algún meses, para un aumento dramático en la ayuda internacional para el sida, TB y malaria en los países más golpeados. El director del Centro, Jeffrey Sachs, dijo a señor Don McNeil del *New York Times* que él sostiene el estudio (11/5 de Attaran). Pero las organizaciones no gubernamentales (NGOs, en sus siglas en inglés) tratan a gente con sida y trabajan para mejorar el acceso a medicinas dicen que las patentes bloquean fármacos baratos—y que son más fácil a tomar—de alcanzar a gente que los necesitan.

Oxfam, la Campaña de la Acción del Tratamiento, el Proyecto de Consumidor y Tecnología (CPT) y Médicos Sin Fronteras (MSF) concuerdan con el reclamo que muchas barreras estorba el acceso al cuidado de la salud en Africa, y sostienen su llamada de la ayuda internacional para financiar el tratamiento. Ellos creen, sin embargo, que los datos presentaron en el papel no sostienen las conclusiones dibujadas–y "sin querer arrojan luz sobre la extensión de barreras al tratamiento." En países africanos, la mayoría de las combinaciónes prácticas, ellos discuten, incluyen las medicinas fijas de dosis (dos drogas en una píldora) y no nucleosidos baratos. La combinación más popular de AZT/3TC está patentada en 37 fuera de 53 países. Y el único no nucleosido barato (nevirapina en la forma genérica) está patentado en 25 de 53 países.

En una declaración conjunta publicada en la respuesta al papel de *JAMA*, el cinco NGOs observan que muchas de las drogas no patentadas citadas en el estudio de Attaran, incluyendo parte del inhibidores de proteasa, no son práctico como tratamientos de primera línea en colocaciones pobres a causa de los efectos secundarios (que deben ser controlados) y los requisitos dietéticos incómodos.

Y como el equipo de Attaran/Gillespie es rápido conceder, su exposición de datos mostran que las patentes se concentran en los países donde mercados de fármacos son el más grande. En la Africa del Sur, que tiene 4.7 millones de gente viviendo con VIH/sida y representan la mitad del mercado de los fármacos en Africa, 13 fuera de 15 fármacos son protegidos. Todo tocado, completamente la mitad de la gente con el VIH/sida en Africa viven en países con barreras de patentes significativas sobre fármacos antiretrovirales.

Los autores concluyen que aunque los precios de fármacos patentados se bajen, los países africanos no serán

*— sigue en la próxima página —*

capaces de proporcionarlos. Pero desde que las terapias triples genéricas ahora pueden costar tan poco como $30 un mes, los números significativos de individuos–y sus empleadores–puede proporcionar el tratamiento. Los precios patentados, por el contraste, son todavía tres veces más altos que los precios genéricos. Esto significa que para una cantidad de ayuda internacional que ellos llaman entendiblemente, tres veces más personas pueden ser tratadas si se permite la producción genérica.

Una declaración que llamó para una interpretación "pro" la salud pública en el TRIPS (en sus siglas en inglés; un acuerdo sobre protección de patentes para la propiedad intelectual) fue puesto por 60 países en vía del desarrollo en una sesión del concilio el septiembre de 2001 sobre TRIPS en el acceso a medicinas. La declaración, firmado por 41 naciones africanas, expresa que, "Nada en el acuerdo TRIPS prevendrá a miembros de tomar las medidas para proteger la salud pública." La declaración, que se considera en esta Organización Mundial del Comercio (OMC) de mes la conferencia ministerial en Doha (Qatar), ha sido opuesta por Estados Unidos, Suiza, Japón y Canadá. Si nada cambia, comenzando en 2006, todos países de la OMC se obligarán otorgar las patentes de medicinas para un mínimo de 20 años.

Más recientemente, los gobiernos de la Union europea han prometido a sostener la clarificación de las órdenes bajo que los países en vía de desarrollo pueden romper las patentes durante tiempo de emergencias nacionales de salud. Los ministros extranjeros de la Unión europea han apoyado el uso de TRIPS para permitir a los gobiernos otorgar las licencias especiales para fabricar las drogas para luchar las epidemias como el sida y el tuberculosis. El representante especial de la Casa Blanca para asuntos comerciales, Robert Zoellick, ha tomado la misma posición y dijo que él ha mostrado a los EE.UU. "Bueno hace" ofreciendo para extender la fecha tope para la conformidad repleta con TRIPS para países en vía del desarrollo a 2016–con una moratoria de 5 años en desafíos de la OMC a cualquiera nación de Africa subsaharano que rompe las patentes para tratar crises nacionales de salud.

Brasil, India y la Africa del Sur, sin embargo, quieren la linguaje más fuerte y encabezan la campaña de los países en vía de desarrollo para apoyar una propuesta que dice que, "Nada en el acuerdo TRIPS prevendrá a miembros de tomar las medidas para proteger la salud pública." Cuando *TAGline* entra en prensa, el progreso pequeño se informa de la OMC que reúne en Qatar–aunque el cuestión de patentes en presencia de crises públicas de salud se dice para haber dominado las discusiones allí. Mientras tanto, el cuidado de NGOs eso, "Es crítico que las conclusiones falsas dibujadas [en el informe de Attaran/Gillespie] no dirigen a gente a creer que patentes no son una barrera al acceso a los tratamientos." †

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