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tagline

TAG
Treatment Action Group

NEWS ON THE FIGHT FOR BETTER TREATMENT, A VACCINE, AND A CURE FOR AIDS

Toward a Credible National AIDS Strategy in the U.S.

Comments by Mark Harrington, executive director of the Treatment Action Group, for the Ford Foundation–hosted meeting on developing a national AIDS strategy for the United States.

BY MARK HARRINGTON

In April 2008 the Ford Foundation hosted a meeting of over 40 national AIDS leaders to discuss the elements of a national AIDS strategy for the United States. Amazingly, despite the fact that the United States insists that the foreign countries who receive U.S. international AIDS assistance develop and implement a national AIDS strategy, American leaders have never insisted that they develop one for the nation itself. Below are the suggestions TAG's Mark Harrington—with input from Richard Jefferys, Sue Perez, and Tracy Swan—provided prior to the Ford Foundation meeting.

What Should a National AIDS Strategy Look Like?

A national AIDS strategy for the United States would include a serious effort to reverse and reduce the spread of HIV; provide high-quality treatment and care services to all HIV-infected people while preserving their rights and dignity; and intensify research to combat the epidemic, ultimately leading to a cure and a vaccine for HIV that can be disseminated to all who need them in the United States and around the world.

To be credible, a national AIDS strategy would need to have firm targets for reduction of transmission and for universal access and uptake of prevention, care, and treatment services.

To provide a clear picture of the epidemic a national AIDS strategy would need accurate and complete reporting of HIV transmission. Currently there are both structural and cultural barriers to such complete reporting, ranging from the patchwork of testing and counseling laws and regulations (structural barriers) to deep-seated and often well-justified mistrust of both government and the health system (cultural barriers) by many of the communities most affected by the pandemic.

Without new leadership, new resources, and new solidarity among those at risk, the HIV positive, and society as a whole, a national AIDS strategy is unlikely to succeed.

To reverse this mistrust will require enormous changes, including a strong political commitment to reversing the spread of HIV using all scientifically proven and ethical methods of prevention; consultation and involvement of affected communities at all levels; significant efforts to overcome the patchwork and inefficient health care system in the United States; and intensified research efforts. Without new leadership, new resources, and new solidarity among those at risk, those who are HIV-positive, and society as a whole, a national AIDS strategy is unlikely to succeed.

There are also significant uncertainties that would need to be resolved through research and by monitoring and evaluating the progress of a national AIDS strategy as it unfolds. Among these uncertainties are:

- We lack a clear, detailed picture of the current state of the HIV pandemic, including current HIV prevalence and current incidence. Without this more

Continued on page 2

WHAT'S INSIDE

National AIDS Strategy 1
Measure the epidemic; get serious about prevention; reform health care; increase the research budget.

CROI Webcast Reviews 3
A look inside the most important HIV conference of the year.

The Future Is Generic 5
Activists gather in Delhi to meet with Indian generic drug makers.

What's in the ARV Pipeline? 7
Unfortunately, not much.

View from the Mountaintop 10
NIAID convenes vaccine summit.

Treatment Complacency 12
Contentment with current drugs risks limiting future options.

detailed picture of the current epidemic and where it is going it will be harder to develop an effective strategy.
• We lack a clear picture of what the best strategies are for optimizing uptake of testing and counseling while protecting people's rights, dignity, and privacy. Targeting only health care providers, who are often overworked and underresourced, or targeting only "prevention for positives," leaves out many who are at risk as well as most of the recently infected—and up to (according to possibly inaccurate CDC estimates) one-third of the chronically infected.
• We lack a clear quantitative understanding of how to maximize the effectiveness of the scientifically validated prevention tools we already have, such as sexual and reproductive health education including HIV, STI, and condom education; harm reduction, safe needle use, syringe exchange, and drug-substitution therapy; and use of antiretroviral therapy for prevention as well as for treatment (among, for example, pregnant and nursing mothers, discordant couples, or people episodically exposed to HIV). Therefore, how much prevention programming needs to be undertaken to radically reverse the epidemic—it would be reasonable at first to set a goal of reducing HIV transmission by 50%—is not clear. Nonetheless, it would clearly require a major expansion of resources and a reinvigoration of community-based, peer-led prevention approaches that target the communities where transmission is most frequent, as well as general approaches involving universal HIV education and routine access to voluntary, opt-out HIV testing in health care and other institutional settings.
• Without systemic health care reform the implementation of any strategy will be incomplete.
• Without systemic reform of the nation's failed "war on drugs" the implementation of any strategy will be incomplete.
• Without reform of HIV prevention, care, and treatment programs in the nation's correctional systems the implementation of any strategy will be incomplete.
• To achieve universal access to care and treatment, all individuals at risk for or living with HIV need this to be guaranteed as a public good (similar to TB prevention and treatment, but better funded and ongoing).
• Ultimately the solutions to the HIV pandemic will come from research that brings a better understanding of viral pathogenesis leading to the discovery of better interventions to prevent and treat HIV infection. Currently the nation's health research system, led by the National Institutes of Health, is bearing the brunt of five years of budget stagnation, leading to what is effectively a shrinking biomedical research and AIDS research budget. The solution for medical research as a whole—and for AIDS research more specifically—depends on reinvigorating the NIH by providing it with a guaranteed multiyear sequence of budget increases that overreach biomedical inflation and allow a new generation of researchers to have careers in biomedicine and AIDS research. We are therefore proposing a 15% increase in NIH funding overall, and a concurrent 15% increase in AIDS research funding for at least five years, and thereafter for funding to outpace inflation.
• Antiretroviral treatment will probably need to be initiated earlier, at both the individual and population levels, to have a greater impact on HIV transmission as well as length and quality of life. However, the evidence base for this needs to be strengthened.
• A national AIDS strategy needs to foster greater inclusion of women and people of color at all levels of the biomedical research and care system so that leaders and participants in AIDS research efforts reflect the diversity of the populations most affected by the epidemic.
• A national AIDS strategy will not succeed unless the people it is intended to benefit can receive integrated services for their health—including, when necessary, HIV care, prevention and treatment for coinfections such as viral hepatitis, tuberculosis, STIs, or other opportunistic infections; drug substitution therapy, if necessary; mental health services; and psychosocial support. Currently the infrastructure to provide these services is fragmented.

It is not clear that the United States is capable of rising to the challenge of reversing and ultimately ending the AIDS epidemic.

What Are Our Greatest Hopes for and Concerns about a National AIDS Strategy?

The United States has been a leader in some aspects of responding to the pandemic, such as research, while failing to serve many or most of the communities worst hit by the epidemic. A much stronger focus is needed to respond to the epidemic in the African American and Latino communities as well as among men who have sex with men, among women, and among younger people.

The lack of trust among the people, the government, and the health system is probably the biggest obstacle to change.

Institutional obstacles include the fragmented health system, lack of transparency by industry with respect to pricing, and the ongoing ineffective and punitive "war on drugs."

Local and regional U.S. support for effective HIV programming is weak, especially in the South and in rural areas.

Racism and homophobia continue to drive the inequities that persist.

Overcoming these obstacles will be an enormous challenge, and will require a new kind of solidarity, new leadership, and a massive infusion of resources.

It is not clear that the United States is capable of rising, after 27 years of incomplete and sometimes contradictory responses, to the challenge of reversing and ultimately ending the epidemic.

However, a national AIDS strategy with measurable goals, a budget, and regular progress reports and improvements based on results is greatly needed. To be effective, however, it must set ambitious goals and deploy sufficient leadership, money, and people from affected communities to enable them to intervene. ●

CROI 2008:
Webcast Review

Online webcasts make CROI (the Conference on Retroviruses and Opportunistic Infections) the most accessible major scientific meeting on AIDS. See them at www.retroconference.org/2008.

BY BOB HUFF

The annual Conference on Retroviruses and Opportunistic Infections—known as CROI—is the most important AIDS research meeting of the year. Thousands of the best scientists and doctors from around the world—and the world recognized by CROI increasingly includes Africa and Asia—meet for three days to look at the latest data and discoveries about HIV and the diseases that accompany it.

CROI is dominated by technical topics. Unlike the biannual International AIDS Conference there is little discussion of the economic, social, and psychological reasons why this virus is so pervasive and so destructive. For a nonscientist, much of this conference is incomprehensible. But with a little orientation, insights into the newest and most exciting ideas about understanding and defeating HIV can be grasped. At CROI one can get a glimpse of how HIV infection might one day be prevented, disabled, and even cured.

CROI is a uniquely accessible conference because all of the main science sessions are made available on the Web for free viewing as soon as the meeting is over. Webcasts offer video and audio of the presenter, while his or her slide presentation displays in a separate window. Those with slower Internet connections can skip the video and simply listen to the presenter, along with a slide presentation.

Here are a few highlights from this year's CROI webcasts.

Log On

CROI webcasts are accessed through the main website at www.retroconference.org/2008.

Click on View the Webcasts and Podcasts. The webcast sessions are accessed by clicking tabs corresponding to the Conference Day, Sunday through Wednesday.

Click on the Speaker Name tab at the top of the page and you will see an alphabetical list of speakers for each of the conference days. Select one of the viewing options on the buttons to the right and wait for the slides to download onto your computer. The program will automatically begin to play the program you have selected.

The viewing console allows you to enlarge the slide display or to skip back or forward through the presentation. If you click Index you will be able to view other presentations by speakers who participated in that session.

SUNDAY, FEBRUARY 3, 2008

A special orientation program for young investigators was presented on Sunday before the conference officially began. This session offers a preview of important news emerging at the conference, accompanied by basic background lectures intended to introduce newcomers to the field. This is an excellent place to plunge into learning about what's new in AIDS research.

The Early AIDS Epidemic in the US: Views from Atlanta and Hollywood
Harold Jaffe

Do you know the story of how AIDS appeared 27 years ago? In this moving presentation, illustrated by clips from the Hollywood film *And the Band Played On* (based on Randy Shilts's book of real-life reportage), Harold Jaffe recalls how the horrifying disease was first recognized and how he and his medical-detective colleagues slowly came to understand that a sexually transmitted, deadly new virus was spreading throughout the country. This presentation is aimed at young doctors, some of whom had not yet been born in 1981. For those who were young in those days, it's difficult to recall a time before AIDS. It's also painful to remember that nearly 15 torturous years ticked by until effective treatments finally stemmed the tide of death in 1995. Jaffe's presentation is easily one of the most engaging and educational of the CROI webcasts. Must viewing.

HIV/AIDS: Where Is It Going and What Does It Mean?
Kevin De Cock

Do you know that 40,000 to 60,000 people in the United States become infected with HIV every year? Did you know that over one million people in the United States have been infected with HIV since the epidemic began—and that half of them have died? Kevin DeCock provides a simple and clear orientation to the epidemiology of HIV in this country and around the world. Because many years can pass following HIV infection before serious disease appears, the virus can spread widely in a population before it is recognized. In most places in the world the peak rate of new infections has now passed. But this early peak is accompanied by a rising number of deaths that may follow many years later. This second deadly peak still lies in the future for many countries. However, as an increasing number of people around the globe gain access to HIV treatment, the peak in deaths may be blunted, as fewer will die of AIDS and the total number of people living with HIV grows.

Cellular and Viral Factors in HIV-Host Cell Interplay
Mario Stevenson

The science is tough going, but Stevenson looks at some of the hottest topics in HIV research and gives us a glimpse of possible future treatments.

Because HIV has a very limited set of its own genes with which to work, it

depends heavily on resources found in its host's cellular environment (and several hundred new host proteins that enable HIV have recently been uncovered). Some host proteins act as anti-HIV factors, however, and HIV carries three small "accessory" genes that can defeat these natural defenses. When these viral proteins are switched off, HIV is unable to replicate, which makes the accessory proteins potentially exciting targets for a new type of drug therapy that would unleash the body's natural HIV blockers.

It is commonly imagined that infected cells shed virus particles into the bloodstream, where they travel until they meet and infect new target cells. Stevenson now thinks it "highly unlikely" that this is the main way infection spreads. New evidence (and there are amazing pictures that show this in action) finds that infected cells actually send out long, skinny tendrils that contact fresh cells directly and pass viruses—including HIV—like beads along a string. Video footage of how this happens can be found in Walter Mothes's symposium on Monday, February 4 (see box).

Action Movies

MONDAY, FEBRUARY 4, 2008

Symposium: *Voyages through the Cell: Imaging Viral Traffic; Live Imaging of Cell-to-Cell Transmission of Retroviruses*
Walther Mothes

Microwave some popcorn and watch these cool, time-lapse videos of immune cells communicating with each other and of viruses surfing along strands of filopedia to infect fresh cells. Advances in imaging are shaking up some old ideas about how the virus replicates. Simply amazing.

TUESDAY, FEBRUARY 5, 2008

Symposium: *Aging and AIDS*
Amy Justice

Justice relates that it is not only HIV and the drugs used to suppress the virus that determine the health outcome of an infected individual, but also drug side effects and interactions between drugs; the non-AIDS-related effects of HIV; other infections, illnesses, and addictions; and, increasingly, the effects of aging. For example, lifestyle issues such as obesity and inactivity are now playing a greater role in the health status of people with HIV.

Justice outlines challenges that face researchers concerned with studying an aging HIV population: How does one select comparison groups when looking at cardiovascular event rates in people with HIV to see if there is an increased risk? As she points out, comparisons with well-established cohorts of mostly white men are unlikely to be of much value.

Bruno Ledergerber describes the epidemiology of aging in the Swiss HIV population. The proportion of persons over the age of 40 has been growing steadily, with longer life due to treatment being a primary factor. Trends in new infections show an increasing proportion of injection drug users (IDUs) and, looking ahead, Ledergerber predicts a significant number of former or current IDUs over the age of 40 burdened with other risk factors, including drug and alcohol dependencies, tobacco use, and hepatitis C.

In the United States, the proportion of women with HIV over the age of 50 is increasing faster than that of their male counterparts. But this may not only be a story about people living longer with HIV; one study has shown that the median age at the time of seroconversion has been increasing. And an increasing number of older people are being diagnosed with HIV, often with more advanced disease symptoms and lower CD4 counts when they first come into care.

Older people may be overlooked by medical providers who don't perceive them as being at risk, while at the same time certain HIV symptoms may be attributed to aging. Yet older people may be at a higher risk for HIV than they think. This population is rarely targeted for safer-sex messages and HIV education, and since such messages are targeted at youth, older people may not believe HIV is something that can affect them. Condom use may not be thought necessary by postmenopausal women, and men with erectile dysfunction may not like condoms. But older people may have active sex lives. Enabled by Viagra, and with free time after retirement or divorce, an increasing number of older people are exploring their sexuality.

Some studies have shown that when older people are infected with HIV they may progress faster to disease. Also, liver and kidney illnesses, which naturally increase with age, do so faster in people with HIV. Furthermore, rates of non-AIDS types of cancer increase rapidly in people with HIV over the age of 50 compared to their non-AIDS counterparts.

In a bit of good news, when older people go on antiretroviral therapy, HIV tends to become suppressed faster than in younger people, though Ledergerber thinks this may be due to poor medication adherence among younger people rather than to a biological factor. Better virologic control results in improved CD4 response, but these gains are partially outweighed by the greater burden of other disease factors that affect older people with HIV.

And there is much more . . .

These are just a few of the more accessible presentations available at www.retroconference.org/2008. Other sessions on mother-to-child HIV transmission, breast feeding, and the threat of drug-resistant tuberculosis are equally interesting and important topics to explore. CROI's free webcasts are invaluable for delivering this wide range of lectures by the world's top experts to all who want to understand the state of AIDS in 2008. ●

World CAB 4: The Future of Indian Generic Antiretrovirals

The Indian generic pharmaceutical industry, operating under Indian patent laws that permitted liberal copying of medicines, made possible the revolution in antiretroviral treatment access that has occurred in Africa since 2001.

BY BOB HUFF

In April, 25 treatment activists from 16 countries met in New Delhi, India, with representatives of three Indian manufacturers of generic antiretroviral (ARV) drugs. The Indian generic drug industry is a major supplier of affordable ARVs to HIV treatment programs in Africa, and its impact has facilitated placing nearly two million people on lifesaving treatment.

Aurobindo and Matrix are each producers of bulk quantities of ARVs and are relatively new to the production of finished formulations. Ranbaxy does not manufacture bulk drugs, but purchases bulk supply from Matrix. It has been producing individual and combination ARV formulations since 2001.

The Next Generation of Drugs

Despite success with the common initial drug regimen, international treatment guidelines now call for switching to newer, safer drugs. But these drugs, such as tenofovir and efavirenz, are more costly to make and deliver. The activists of the International Treatment Preparedness Coalition's World Community Advisory Board (ITPC's 2008 World CAB) were keen to understand how the generic drug makers were planning to respond to the need for tenofovir and more affordable second-line drugs.

Q: How are you planning to handle the transition to tenofovir?

Aurobindo: There are 1.89 million people currently on treatment. The target is 10 million by 2010. It will take three or four years for the shift to happen. You can't shift them all at once, especially when the current drugs are working for them.

There are not many generic manufacturers of tenofovir currently; it is a costly product. But we don't do this on a small scale; we don't just buy the bulk drug from China and make pills.

Ranbaxy: We have several formulations of tenofovir under development. We are filing for everything you can think of—multiple, creative combinations. They should all be filed by later this year.

"We don't do this on a small scale; we don't just buy the bulk drug from China and make pills."

Q: Do you have licenses with major pharmaceutical companies?

Matrix: We have a license with Gilead and use that license to make all of the tenofovir combinations. We are negotiating to get a license with BMS to make atazanavir. We have developed atazanavir-based products and should soon have a fixed-dose combination, boosted atazanavir tablet.

Developing the drug is one thing, but developing in volume is another. All of our bulk drug manufacture is done in-house. Volumes have grown enormously. We are looking to scale up tenofovir in a big way, going to ten tons a month.

Second-Line Regimens

Although protease inhibitors are used as first-line therapy in the United States and Europe, they are strictly reserved for second-line treatment in the developing world. One problem with drugs that require "boosting" with ritonavir is that Abbott Laboratories, the original producer of ritonavir, only makes a soft gel capsule, which tends to melt in tropical heat. However, the Indian generics have leapfrogged this problem and are the first to offer heat-stable ritonavir.

Q: Are you planning to produce other second-line drugs?

Aurobindo: FDA approval of lopinavir/ritonavir is expected by June. We have also filed for a pediatric formulation. We have ddI in a chewable tablet and in an enteric coated tablet.

Q: What process is used to make the lopinavir/ritonavir tablets heat stable?

Aurobindo: We use the melt-extrusion process (Meltrex) to make heat-stable lopinavir/ritonavir. It is the same process as in Abbott's Aluvia/Kaletra. We buy the equipment from the same supplier.

Q: How about atazanavir and darunavir?

Aurobindo: We will do atazanavir alone first, but copackage it with ritonavir. We will be the first with heat-stable ritonavir. A fixed-dose combination of atazanavir/ritonavir will come later. The shift to second line is not creating a big market yet. We will finish this wave of second-line products before making newer drugs like darunavir.

Matrix: The pressure to make heat-stable ritonavir is that you cannot give atazanavir without ritonavir. And everybody knows why Abbott is not selling heat-stable ritonavir. [*According to recently unsealed documents in a court case, Abbott planned to restrict access to ritonavir in order to protect Kaletra in the market.—ed.*]

Q: Have you talked with Merck about integrase inhibitors?

Matrix: Not yet. We are taking the stand that we are going to develop them. It will take a year or two.

Q: What about drugs for OIs and TB?

Aurobindo: We do TMP/SMX for HIV; however, there are restrictions

in manufacturing it because a lot of pollution occurs as a by-product of production. We manufacturer it for Health Canada and they give it to Zambia. We have nothing for hepatitis C. We are not doing TB drugs because they require a separate facility for manufacture.

Ranbaxy: We might consider something for TB in the future when we move in this direction. We would be interested in a good lead compound in this market. We would work with a public/private-funded project and we might be a good partner for a global company. Our research people are looking for leads, too.

Prices

The low prices on drugs offered by the Indian generic makers are the enabling factor that has allowed the drive to universal access to ARVs. However, in order for the planned expansion of ARV access to take place, prices must fall even farther.

Q: How do you set prices and how do they vary from region to region?

Aurobindo: The Clinton Foundation comes and negotiates with us. PEPFAR negotiates with us. The market drives the price. If there is a choice between two suppliers of the same product, and they are both prequalified by the WHO or by the FDA, the buyer will go with the lower price.

Ranbaxy: Everything these days is tender-based. It is more like a commodity. Whatever the price of the last sale was determines the price of the next sale. The key determinants for setting prices are initially cost recovery and making a little margin to keep the project going. But then the prices come down and we can no longer do that. These days prices have come way down and there is very little margin.

It is all economy of scale. The bulk drug cost is the prime driver of price, and that does not come down until you have large demand and economy of scale. Up the supply chain there are people who make chemicals that go into many products, and they won't lower their price unless you buy in quantity.

Q: If you find an acceptable partner in Africa will you sell them bulk drug?

Aurobindo: We would, or we would sell tablets and let them package it, but we have not found anyone yet. We will help in planning the plant if we can count on having a long-term relationship. But prices will not come down if you produce locally; the volume is too limited and it is too costly to hire the right people.

Patents

The Indian patent system has been the key that allows the generic drug industry there to copy and distribute affordable but high quality versions of drugs that are patented in the United States. Until recently, Indian patents could only cover the process by which a drug is made, not the final product.

The bulk drug cost is the prime driver of price, and that does not come down until you have large demand and economy of scale.

This allowed the generic makers to copy drugs as long as a different manufacturing process was used. But recent changes in the law may grant patent protection to drugs invented after 1995, which could limit the availability of affordable, newer drugs. Activists in India are fighting the changes.

Q: What is your intellectual property (IP) policy?

Matrix: We don't have a standard IP policy. We would advocate—especially for HIV—that it should be more lenient. We think there should be protections where necessary and freedom where it is possible. It is necessary for research to be done; you need money to do research, and you need protections to make money.

Q: Do you think about challenging patents to get around evergreening [*extension of market protection beyond the life of the original patent*]?

Aurobindo: No, it is a waste of money.

Q: But a lot of patents are weak.

Aurobindo: That is a different department. We have an IP division. The penalties for violations are huge. Under Indian law, we have to make the drug using a different process. If we can do that, we will go for it. If we are not confident we can, we will not. If not we have to wait for patents to expire.

Ranbaxy: We opposed the tenofovir patent but then we got the license. We will file oppositions—sometimes the business group files and we don't even know. It helped in negotiations for the tenofovir license that we had an opposition filed.

The Future

Finally, the companies were asked to speculate about the future of their business in ARVs and to describe some of the challenges they face.

Q: What expectations do you have for the ARV market in the future?

Aurobindo: Funding will double in a few years. PEPFAR was $15 billion but will go to $30 billion.

Matrix: The challenges we saw three to four years ago were in enrollment and infrastructure. Now critical mass has been achieved and things have improved a lot. We are now ready to scale-up much faster than we were a year or two ago. Second-line drug prices will be coming down significantly and will come down further in the coming years—the shift will begin happening seriously then.

Ranbaxy: We are investing significant time and effort in developing ARVs within the Indian patent situation. We are early in some areas and late in others, but we are not abandoning ARVs.

Q: What are some of the problems facing your business?

Aurobindo: Having to manufacturer so many regimens is confusing. We make regimens that no one wants. We went with emtricitabine (FTC) because people

said they wanted it, so we produced it. Now they say lamivudine will be just as good. I wish they would settle on fewer regimens and not change them every year. It would be easier for us.

Ranbaxy: In the past there has been a lot of focus on access. Most of the focus was on prices, which was good at that time. But we can see a shake-up coming. If prices and margins continue to fall, we could be headed in the direction of TB, where there were once a lot of good companies manufacturing products, but after the margins fell, the big ones left and now there are only small companies, and one big one left in TB.

We have been thinking about the TB market because it is synergistic with our HIV business—but we cannot compete with the prices offered. In HIV you may see a few big players getting out and once they go it would be too difficult to get them back.

Intellectual property protection is another risk. Newer products coming along would be patent protected, and as they replaced the older ones the big generic companies would be under pressure. The market would shrink and that would push up costs. ●

What's in the HIV Drug Pipeline? Not Nearly Enough

In the midst of a "golden age" of abundant antiretroviral treatments some worry that our "embarrasment of riches" will leave us wanting unless we continue the search for better drugs.

BY BOB HUFF

TAG's Antiretroviral (ARV) Pipeline Report is usually a story about what's new and what's coming in the world of experimental HIV drugs—and the story typically ends with FDA approval. In 2008, with only a few new drug candidates in the pipeline, the bigger story may be what's happening (or not happening) with three drugs that were approved during the past 12 months.

Merck's raltegravir, approved in October 2007, seems to be a star that shines brighter day by day. Prior to approval it was an object of giddy speculation by the medical elite, some of whom called it a "wonder drug." And it enjoyed a glittering debut among people with multidrug-resistant HIV who, for the first time in many years, found a regimen able to durably suppress their virus. (Many of them apparently even felt comfortable enough to drop the inconvenient injectable Fuzeon—a potentially catastrophic development for Trimeris and Roche, makers of Fuzeon; this development has also led some to speculate that future Pipeline Reports may become obituaries.) Some observers warn, however, that this "golden age" of viral pansuppression may not last as a growing number of individuals on the newer drugs experience loss of viral control due to resistance and require even newer options. Unless the pipeline is refilled, their options may be few.

Yet for now, at least, some clinical investigators seem content with taking a breather and enjoying the lighter burden in their clinics. One editorial even termed current options "an embarrassment of riches" (Hirschel 2008).* There is a worrisome aspect to this, however, if the complacency expressed by some clinicians and investigators regarding the need for improved first-line regimens manifests as reluctance to participate in clinical trials for better drugs.

The other important new drug of 2007, Pfizer's maraviroc, approved in August, has not fared as well as raltegravir, and while not a candidate for the obituary column it may one day find itself adrift if Pfizer decides to cast off its involvement with HIV. Sales of maraviroc have been far below expectation, mainly because the drug faces formidable barriers to acceptance in clinical practice. Currently, using maraviroc requires an expensive and slow-to-report blood test that indicates baseline viral susceptibility to the drug—and susceptibility rates fall to about 50 percent in people with long time infections and lower CD4 counts. Because such an assay does not catch everyone who lacks susceptibility, there is a risk of loss of viral control—and possible loss of the rest of the regimen due to resistance. Then there are worries about the safety unknowns of maraviroc's novel mechanism that targets the host rather than the virus. Finally, a high state of nervousness at the FDA over the Vioxx drug safety scandal likely contributed to a black box warning about liver damage based on one episode with maraviroc and multiple cases with a different, subsequently discontinued drug in the same class.

Still, an intriguing result of early clinical trials provides optimism for the use of maraviroc and other treatments in the CCR5 inhibitor class. It's been

* Bernard Hirschel, M.D., and Alexandra Calmy, M.D. Editorial: Initial Treatment for HIV Infection—An Embarrassment of Riches. *New England Journal of Medicine* 358, no. 20 (2008): 2170-2172.

observed that some patients who lacked susceptibility to the drug and obtained no virologic benefit from it still had paradoxical increases in CD4 counts. Because the CCR5 inhibitors attach to signaling proteins on CD4 immune cells, there is some speculation that they may have immune modulation activity independent of their antiviral effect. Another explanation may be that the specific suppression of HIV that uses CCR5—even if it is not the dominant strain as measured by viral load—helps protect against CD4 cell loss. If this turns out to be the case, then the need for a susceptibility assay may be jettisoned, as CCR5 antagonists are prescribed to quell a particularly toxic form of HIV, whether it shows up in the viral load or not. Until recently there were five CCR5 inhibitors under development, though this number was reduced by one when Incyte discontinued its candidate, INCB9741, in 2008. We may expect that this number will shrink further in the future.

Another less heralded drug approval, in January 2008, was that of the NNRTI etravirine, from Tibotec. This drug is active against many—but not all—NNRTI-resistance mutations that arise with efavirenz and nevirapine, and it was approved for treatment-experienced patients with resistance problems. Etravirine followed an unusual development path since it was most always paired in clinical trials with Tibotec's protease inhibitor darunavir. While offering two experimental agents was a step forward in clinical trial practice and provided people with few treatment options extra protections while in the study, it also meant that there was little data produced on using etravirine in any other context than with darunavir. It turns out that there are a complicated set of interactions when etravirine is combined with several other drugs. Nevertheless, it works well with darunavir, tenofovir, and raltegravir, and these combinations may be all anyone really needs. Unfortunately for Tibotec, neither etravirine nor darunavir have been as widely embraced by clinicians as had been hoped. Rilpivirine, another NNRTI from Tibotec being developed as a first-line drug, has finally initiated phase III studies at 25mg/day after a long delay.

With the success of raltegravir (and the disappointment of maraviroc) the gold rush in ARV development has shifted to the integrase inhibitor class. Next in the pipeline is elvitegravir, a candidate from Gilead Sciences with once-daily dosing potential when combined with the pharmacologic booster ritonavir. At first glance, the need for ritonavir seems like a drawback (Abbott Laboratories only offers an inferior and expensive form of the drug—part of a market-protection scheme for its Kaletra product), but new thinking about ARV development looks to the regimen, not just the drug. Due to favorable drug interactions between elvitegravir and the Bristol-Myers Squibb (BMS) protease inhibitor atazanavir, Gilead may be well-positioned to offer the first all-in-one NRTI-sparing regimen. A successful cooperative venture between Gilead and BMS resulted in the wildly successful single-pill version of efavirenz, tenofovir, and emtricitabine called Atripla. Since BMS also makes atazanavir, the precedent is in place for a next-generation powerhouse with access to a boosting agent being the main sticking point. Gilead and Pfizer are both said to be working on boosting agents to replace ritonavir.

The United States may fall behind the rest of the world in the variety of ARV formulations available to its citizens.

This brings us to another trend in ARV manufacturing. Due largely to Abbott's monopoly on ritonavir, the United States may soon fall behind the rest of the world in the variety of ARV formulations available to its citizens. The Indian generic pharmaceutical industry operates under a set of patent laws that protect the process for manufacturing drugs but not the final drug product itself. This means the industry has become skilled at inventing new processes, and as a result has been able to supply ARVs to mass treatment programs in Africa at a cost of under $200 per year per person. Millions of people are alive today because of low-cost, high-quality Indian-made ARVs made possible by this patent system. However, this system is changing, and Indian generic drug makers may be prevented from manufacturing certain newer drugs such as atazanavir and raltegravir without permission. Yet because the need for ARVs is so great and continues to grow (some plans call for treating ten million additional people within the next few years), patent holders such as Gilead have issued licenses that allow the Indian companies to produce and sell tenofovir in Africa with few restrictions. Looking ahead, these Indian drug companies are already planning to produce novel all-in-one regimens of generic ritonavir-boosted atazanavir/tenofovir/lamivudine, and even raltegravir/atazanavir/ritonavir. The generics are ready to release a heat-stable version of ritonavir (which Abbott has not yet done) and will be able to combine it with a drug like atazanavir in smart, convenient combinations that may never become available in the United States.

The Current Pipeline

Of ARVs in phase II or beyond, only one drug currently appears to have the staying power needed to make it to the finish line—and not before 2010. Gilead has the money and experience to move its integrase inhibitor elvitegravir forward, and it has a strategy and a market waiting for it when it emerges. What it doesn't have is heat-stable ritonavir available in 25mg doses (a quarter of the Abbott dose and all that is required by elvitegravir) or a substitute pharmacologic booster.

After many years of setbacks and missteps, Schering's CCR5 blocker vicriviroc may continue to limp forward, but the rationale for investing in large phase III trials seems slim given the dismal performance of maraviroc during its first year on the market.

Tibotec's rilpivirine could be a very important drug for the developing world due to its compact 25mg dosing, which would make it cheap and easy to put into single-pill regimens. But potency may be an issue, since rilpivirine suppressed HIV

HIV Drug Pipeline in 2008

Phase II or III

Rilpivirine (TMC278), NNRTI; Tibotec, phase III
Vicriviroc, CCR5 antagonist; Schering, phase III
Elvitegravir, integrase inhibitor; Gilead, phase II
Bevirimat, maturation inhibitor; Panacos, phase II
KP-1451, viral decay accelerator; Koronis, phase II
TNX-355, CD4 blocker, Biogen Idec, phase II
Apricitabine, NRTI; Avexa, phase IIb
Amdoxovir, NRTI; RFS Pharma, phase II

TAG's complete 2008 Pipeline Report, *including vaccines and drugs for TB and hepatitis, will be avialable in July.*

at a slower rate than did efavirenz in a head-to-head trial (although by 48 and 96 weeks its performance was equivalent to efavirenz, with fewer side effects). Still, after seeing the unprecedented rapidity with which raltegravir suppresses HIV, there may be a perception that the bar for antiviral activity has been set higher.

Beviramat, a novel maturation inhibitor, once had its day as a bright and promising newcomer. That luster is now long gone, however, as the drug has suffered problems with formulation, unconvincing trial results, and missteps by an underresourced small pharmaceutical company trying to go it alone. Tiny companies like Panacos must inevitably partner with a larger company if they hope to get a drug through expensive phase III trials. That no big pharmaceutical partner has appeared to take beviramat forward means that most of them had a look at the drug and decided to pass.

KP-1451 is a (very) novel compound from Koronis, another small-pharmaceutical start-up. The idea is that the molecule incorporates into the growing HIV DNA chain during reverse transcription, but instead of terminating the chain, as do NRTIs, it flips its identity to an alternate base, thereby introducing a point mutation that is integrated and propagated as the virus replicates. Eventually these randomly inserted mutations accumulate and lead the virus to extinction. This has worked in the test tube, but the drug has yet to decisively impact HIV levels in actual persons. Until that happens, this drug survives only on hope. Larger phase II trials are being enrolled now.

TNX-355 is a promising idea from a small company that may have been lost in a corporate shuffle. The drug is a monoclonal antibody that prevents HIV from attaching to the CD4 receptor on target cells. Its developer, Tanox, was acquired by Genentech, which then shipped the drug off to Biogen, where it awaits a development plan. A drawback is the need for infusion, although one dose might last for a full month. The drug would occupy a niche market at best.

With only one or two drugs in the pipeline that have a strong chance of emerging by 2010, the outlook for new HIV agents looks bleak. If we seek hope in compounds still in phase I trials we may not be reassured. Merck undoubtedly has a follow-on integrase inhibitor with once-daily dosing properties; GlaxoSmithKline also has an integrase candidate on tap, as may others, since this is where the action is.

A surfeit of CCR5 blockers (where the action used to be) is already starting to become apparent. Incyte canceled its CCR5 program, though newcomer Tobira has entered the scene with two candidates. Pfizer has a follow-on to maraviroc, but it is hard to imagine the company giving it much attention after maraviroc's poor showing. A couple of monoclonal antibody CCR5 blockers are on the books at Progenics and Human Genome Sciences, but they are not causing much buzz. Development of a CXCR4 blocker, which might make a nice companion to its CCR5 cousin, has at present been suspended by Genzyme.

New and improved versions of well-established classes, such as NNRTIs and protease inhibitors, may be a safer bet. Pfizer and Boehringer-Ingelheim each have an NNRTI in the early pipeline, though whether either of these companies—which have each suffered significant disappointments in the marketplace recently—will stick with them, or even with HIV treatment, remains to be seen. Smaller companies, such as Ardea, are also working on NNRTIs.

The protease inhibitor class may still have some life in it if compounds from Merck and promising newcomer Sequoia gain traction.

Finally, there are a gaggle of NRTI molecules from small companies that have been languishing for several years at early development stages; none seem poised for greatness. Still, despite great enthusiasm for NRTI-sparing regimens, a good, clean NRTI active against current NRTI mutations might find a happy home in a fixed-dose combination pill from Merck or Gilead. ●

HIV Vaccine Research Summit
Hindsight versus Foresight

While still analyzing data from the third ever AIDS vaccine efficacy trial, the field is serenaded by a chorus of opinions.

BY RICHARD JEFFERYS

On March 25, the National Institutes of Allergy and Infectious Diseases (NIAID) convened a special one-day summit in Bethesda, Maryland to solicit input on three major issues in AIDS vaccine research:

- vaccine-related basic research, discovery, and development
- animal model development and utilization
- clinical research and trials

On the first topic, there was widespread agreement that the generation of effective antibodies remains a key goal, and a better understanding of whether nonneutralizing antibodies can aid in protection is urgently needed. (Some scientists have suggested that just binding to HIV can be a useful property for antibodies, as it may facilitate elimination via a mechanism called antibody-dependent cellular cytotoxicity.)

Unfortunately, however, some panelists could not resist resorting to hyperbole. Cellular immunologist Rafi Ahmed from Emory University claimed that he "cringed" when hearing that Merck was developing a T cell–based vaccine, even though he is on the immunology advisory committee of the HIV Vaccine Trials Network and does not appear to have voiced this feeling at any time during the trials development. Ahmed has also previously expressed optimism that T cells could mediate control of viral replication in the absence of antibody, because he has documented this in his own studies of the murine virus LCMV. In arguing at the summit that antibodies—even nonneutralizing antibodies—are likely to be critical, Ahmed may have been alluding to the DNA/MVA vaccine developed by his colleague Harriet Robinson at Emory; Robinson reports that her vaccine candidate induces binding antibodies, and claims (based on evidence from SHIV89.6P challenge studies) that these antibodies will increase the likelihood of efficacy.

Discussion of T-cell responses revolved around the likely inadequacies of current assays, which may not measure the most important functions (e.g., for CD8 T cells, the ability to recognize and kill HIV-infected cells). Lab assays typically test responses to small protein slices from HIV called peptides, and in the lab dish the high concentrations of these peptides may be far easier for T cells to recognize than they are when they're being presented (by infected cells or antigen-presenting cells) in the body. The ability of a T cell to proliferate was frequently cited as critical. Notably to date, there has been just one poster presentation regarding the proliferative capacity of the HIV-specific T cells induced by the Merck vaccine (the results were not impressive). Several participants raised the issue of breadth; the researcher David Watkins pointed out that macaque monkeys typically respond to multiple epitopes in the Gag protein while recipients of the Merck vaccine displayed an average response to just one epitope from each of the three proteins included in the vaccine (Gag, Pol and Nef). Responses to multiple epitopes in Gag were also mentioned as a correlate of lower viral load infected people.

The section on animal models and utilization lamented the lack of resources and also reviewed the shortcomings of the SHIV89.6P challenge virus. SHIV89.6P is a lab-created hybrid comprised of the internal components of SIV, HIV's simian relative, and HIV's outer envelope. It was originally created to facilitate studies of antibody-based vaccines. However, because it was shown to consistently cause a very rapid and immediate crash in macaque CD4 T cell counts (unlike SIV, which typically has a variable and inconsistent impact on CD4 T-cell counts), it was also used in tests of T-cell vaccines, including Merck's. The reason was that the consistency of CD4 T cell loss meant that, if a vaccine preserved CD4 T-cell counts in immunized animals, statistically significant differences between vaccine and placebo groups could be captured in studies involving only small groups of animals. With macaques in short supply for research, this was not a trivial issue. But it eventually became clear that SHIV89.6P was not useful for evaluating T cell–based vaccines: a number of vaccines known to offer no protection against other viruses showed some efficacy against SHIV89.6P, and long-term control—a key goal for T cell approaches—was shown to also be associated with the presence neutralizing antibody responses. Merck conducted a follow-up study using an SIV challenge of macaques, and in this case adenovirus alone had no effect while a DNA vaccine followed by adenovirus immunization had a significant effect, but only in macaques with particular immune response genes known to be beneficial in controlling SIV.

The general view among the summit panelists was that the stringent SIV/macaque model remains the best method for preclinical evaluation of HIV vaccine candidates, as there is no doubt that it predicted the STEP trial outcome better than any other animal study. Some participants noted that SHIV viruses

PAVE's Predicament

Also hanging in the balance as a result of the STEP trial is another phase IIB efficacy trial, dubbed PAVE100.

This trial also involves an adenovirus vector, given once after a series of three DNA vaccine shots. Originally designed as an 8,500-person study involving multiple populations internationally, there is now a proposal for a smaller trial (PAVE100A) enrolling 2,400 men who have sex with men.

This trial will be discussed at a meeting of NIAID's AIDS Vaccine Research Subcommittee. TAG has serious concerns about whether this trial should be conducted and will release a detailed position statement prior to the meeting.

utilizing HIV envelopes that target the CCR5 coreceptor appear to more closely mimic HIV's impact on the immune system than the X4-using SHIV89.P, and suggested that these viruses may deserve additional evaluation. Other issues raised included the importance of analyzing the ability of vaccine candidates to protect against SIV containing proteins that are different from those used in the vaccine (this has rarely been done to date) and also refining models that attempt to mimic the acquisition of HIV infection (e.g., by using repeated, low-dose mucosal challenges with SIV instead of a single high-dose challenge).

In the last section on clinical research, there was general agreement that human trials remain important but should be viewed as part of the "discovery" process. A number of participants argued for small, preliminary screening trials that might provide information as to whether a candidate had the potential for efficacy. The International AIDS Vaccine Initiative describes this idea as "screening test of concept," or STOC. These trials would be conducted in very high-risk populations. One potential downside to this approach is that in such studies there is a much greater likelihood of participants being exposed to HIV while still receiving immunizations; in lower-risk settings, exposure would be more likely to occur after a vaccine-induced immune response has had time to develop and mature, and this difference could conceivably be important.

South African researcher Glenda Gray made an eloquent plea for continued clinical research, stressing that the incremental progress that results from analyzing data on unsuccessful candidates is critical for moving the field forward. Gray also argued that in the high-incidence area in which she works, research participation is not so much based on expecting instant success but on the hope of contributing information that will ultimately lead to success. Gray's comments in this regard were echoed from the floor by summit attendees from Uganda.

One of the other members of the final panel, immunologist Mark Connors from NIAID, offered some intriguing comments regarding ongoing analyses of the STEP data. Connors has studied HIV-specific T-cell responses and authored many skeptical articles questioning some of the correlations with control of HIV replication that have been reported in the literature. In 2002, however, he identified HIV-specific CD8 T-cell proliferation as a potentially important correlate, a finding several other research groups have now confirmed. In his comments at the summit, he cited additional assays his lab is working on, and expressed confidence that robust and broadly applicable correlates of immunological control are within striking distance. Furthermore, he cited the fact that several Merck vaccine recipients who became infected in the STEP trial and carry the favorable immune response gene HLA B*57 are controlling their viral loads at undetectable levels. The implication is that while the Merck vaccine was far from optimal, it may have been able to enhance the HLA B*57 effect.

The buzzword of the day was *innovation*.

Connors's comments, like several made from the floor by STEP investigators such as Juliana McElrath, highlighted the slightly bizarre nature of listening to a day's worth of opinions on the future of HIV vaccine research when—for only the second time in the history of the epidemic—there is a trove of actual data from an HIV vaccine efficacy trial that may shed more substantive light on the issues at hand. The HIV vaccine field has long been beleaguered by an excess of opinions and a dearth of data, and it is unfortunate that the summit—while clearly well-intentioned—ended up continuing this trend.

The specter that stalked the entire event was diminishing NIH funding for investigator-initiated grants. This severe problem is the result of the flat funding of NIH by the Bush administration and Congress over the past several years, leading to a net decrease because of inflation. It was clear that many people at the summit were hoping that more money would be shifted into the investigator-initiated grant pool, either from clinical vaccine research or somewhere else (such as the federally funded AIDS Clinical Trials Group). At least one person questioned the wisdom of the multimillion-dollar, multiyear NIAID grant to the Center for HIV/AIDS Vaccine Immunology (CHAVI), posing the question, "Would four CHAVIs be better than one?" The implication being that a large mechanism under a single investigator (in this case, Barton Haynes from Duke University) may not be the best way to foster innovation in AIDS vaccine research. This issue of where additional funding might come from—certainly the biggest concern for many summit attendees—was rarely commented on directly (Martin Delaney from Project Inform was one of the few who mentioned it explicitly) and certainly wasn't resolved by the end of the event.

In terms of buzzwords of the day, *innovation* was certainly one of them, although how exactly to define or encourage it was not resolved. The importance of enticing young investigators into the field was also emphasized, although no one seemed to contemplate what a young investigator might make of the summit itself, and what it said about the HIV vaccine field's ability to react rationally to the failure of a single AIDS vaccine candidate. Finally, the most repeated quotation was surely "We're all in this together," a friendly platitude but perhaps inadequate in terms of balancing the worries of some scientists about basic research grant funding with those of participants focused more on HIV decimating their immediate communities.

The immediate results of the summit are two requests for advice from NIAID on the creation of a new grant funding pool aimed to foster innovation in biomedical prevention science, including vaccine research, and "to solicit input and ideas on priorities in basic vaccine discovery research." Responses to these announcements will undoubtedly shape the direction HIV vaccine research takes from here.

There was much more discussion at the summit than any one article can capture, and the entire day can be viewed via webcast online: www.macrovolt.com/live/dgi_032508/. ●

Complacency Will Inhibit Search for Better HIV Drugs

Better drugs are urgently needed for most of the people in the world who still lack treatment for HIV. Yet physician contentment with current treatment options in Europe and the United States may hold back research to develop new drugs.

BY BOB HUFF

"We've never had it so good."

So say some AIDS doctors who are enjoying a respite of unprecedented clinical calm due to a wave of recently approved medications that have allowed longtime problem patients to finally achieve viral suppression, and a dependable set of drugs that can keep HIV in first-timers reliably suppressed with minimal maintenance. Apparently they think that if treatment fails due to patients' inability to stick to their drug-taking schedules, then those patients have no one to blame but themselves.

So when clinical trials of new drugs for first-line therapy are proposed to prominent clinician/investigators in the United States, the answer is, "No thanks; we're happy with what we have."

This complacency is shortsighted.

While current first-line options are relatively trouble-free in the States and in Europe (and that is debatable), they are far from optimal for the developing world where—due to cost, side effects, and drug interactions—a better first-line regimen is one of the critical unmet medical needs. And it is crucial that new drugs are supported by substantial evidence from U.S.- and European-based trials if they are to become viable options.

The best of current treatment regimens are still not optimal for the developing world.

Martin Delaney has noted that U.S. patients have always been motivated to enter clinical trials as much or more by altruism as self-interest. But if patients do not hear from their doctors that there is important research going on that could help people all around the world, then they will not have an opportunity to choose to participate. ●

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Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

Program areas include antiretroviral treatments, basic science, vaccines, prevention, hepatitis, and tuberculosis.

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