Gravest Show on Earth

The AIDS circus is coming to town! POZ sneaks a peak as researchers and activists preview their death-defying acts.

June 1, 2002 By Angelo Ragaza , Mike Barr and Walter Armstrong

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The 14th International AIDS Conference hits Barcelona in July boasting a record number of participants (15,000) and papers (10,500) -- and, even better, a slew of good news from both the lab and the street. How do we know? POZ got the advance buzz on Barcelona from AIDS' best and brightest (19 world-class researchers, four awesome activists and one eagle-eyed reporter).

Brand-new classes of drugs are just around the corner, with a therapeutic vaccine not far behind. Meantime, a movement for equal access to HIV meds bestrides the globe. (For more, see below.)

But ever since the '96 Vancouver confab made "Is AIDS Over?" headlines, the media have been over AIDS. Let's face it: The epidemic needs a new hook.

So if POZ may be so presumptuous, we propose something a little more daring: the AIDS circus! Imagine: Scientists taming lions, activists eating fire, PWAs on the high wire! A whole global community working without a net!

And if daily death-defying feats don't make prime time, we'll try the hard sell and a catchier conference theme. How about "A cure or war in 2004!"?

THE BIG TOP

What has been the biggest breakthrough since the International AIDS Conference in Durban in 2000?

For an overwhelming majority of this opinionated crowd, the best news is on the vaccine front -- the therapeutic, not the preventive, kind. Veteran NIAID head Anthony Fauci makes it official: "Progress was made in demonstrating that monkeys can be protected from progression of HIV disease by vaccination with vectored vaccines." Science magazine's Jon Cohen adds color to this program: "Merck's vaccine program has exploded onto the scene in the past year, redefining the position of all the other players." The American firm's investment in long, slow, rational R&D has set a new standard in a field where quick-and-sloppy methods have prevailed in the name of urgency. Merck's novel "T cell-based" approach aims to kick-start cellular T-lymphocytes (CTLs) -- as opposed to the traditional vax view (think flu shot) that marshals an antibody attack.

Reality Check: The fact that the success is in monkeys, not humans, suggests how modest vaccine hopes remain.

Relevance for Research: But the finding "is in keeping with the hypothesis that one can achieve immune control," says Harvard's Bruce Walker, whose success in doing just that in the newly infected also got buzz.

Relevance for HIVers: Fully half of our soothsayers predict that such a "partial protection" vaccine will be a mainstay of treatment by the year 2007 and will allow for less time on drugs with fewer side effects.

Best Case: "If these results are confirmed in human trials, we will have gone a long way to identifying ways to control the epidemic worldwide," says NIAID's Mark Dybul. A therapeutic vaccine will be much cheaper and easier to use than daily HAART.

Minority View: Five experts gave the high-five to new classes of drugs, each of which targets HIV at a different point in its life-cycle. Robert Gallo, the PT Barnum of AIDS research, singles out entry inhibitors, which target the CCR5 co-receptor -- a discovery built on his own chemokine find. "[This] is likely to have a big impact," he says. "The immune system may kick in when you lower the virus very early, very fast. This receptor is disposable -- you can live well without it. So, why not blow it to pieces?" That's can-do spirit, even if he is tooting his own horn.

Last Word: "The days of big breakthroughs are behind us for the moment. Recent advances have come in baby steps. Fortunately, the same appears to be true of the setbacks," says UCSF's Donald Abrams.

TEARS OF A CLOWN

What has been the biggest disappointment since Durban?

Consensus: Fauci speaks for half of this elite: "The most progress and the biggest disappointment have been in the same area -- HIV vaccinology." Science finally invents a vaccine product that can stimulate the "right" immune responses, and while it succeeds mightily at slowing the virus, it fails miserably at preventing infection. Emilio Emini, the eminence grise (though he is far from gray) behind Merck's vaccine breakthrough, says, "Our efforts are based as much upon intuition as knowledge. It is not certain that a vaccine to prevent infection with the virus can actually be developed. Many more years of work will be required." Let's raise a toast to intuition, then.

Minority Views: Five doctors in the house specify the long-term toxicities of HAART as the major bummer. Brit doc Graeme Moyle fingers Pharma for foot-dragging on lipoatrophy: "The area of metabolic and morphological disturbance remains wallowed in agendas set by industry marketing that exaggerate possible minor differences between drugs rather than seeking to understand [lipo's] causes." One-third of our gang mourn the passing of HIV eradication. But in the view of renegade researchers Joseph Sonnabend and Franco Lori, science couldn't wipe that mess off its shoe fast enough. Lori explains: "Besides creating false expectations, the goal of eradication has driven us to an excessive, premature use of drugs."

Reality Check: Don't assume that AIDS researchers are locked up in their ivory labs. Many have not only beautiful minds but hearts that beat 'round the world. With prospects of a prophylactic vaccine at a new low, Britain's lord of AIDS Brian Gazzard adds, "the epidemic will continue to rage virtually uncontrolled in the developing world." In Bruce Walker's opinion, "the biggest disappointment is the lack of support for countering the enormous global inequities of access to drug therapy."

Mother's Helper: For eagle-eyed reporter Jon Cohen, the "social and technical hurdles" to implementing universal prevention of mother-to-child transmission is the most shameful setback. "One dose of nevirapine cuts transmission by 50 percent," he says. "And the company [Boehringer-Ingelheim] has offered to give it away for free. It's as though a working vaccine existed and wasn't being used."

Last Word: "AIDS is a problem of the highest priority and requires a global outlook," UCSF viral visionary Mike McCune says. "But after the events of 9/11, the focus of our government appears to be shifting away from [AIDS]. This trend must change."

TAMING THE LION

What is the next big thing we must learn about HIV?

Consensus: Three-quarters of this brain trust is obsessed with what lies beneath -- those "reservoirs," or "latent pools," of HIV that remain when HAART clears virus from the blood. "Why is there residual replication by drug-sensitive HIV when a patient is taking multiple antiretroviral agents?" asks Aaron Diamond's David Ho of these viral hideaways, the erstwhile eradicator's own Achilles' heel. "It seems that there is a form of 'resistance' not fully understood yet."

Relevance for HIVers: Italy's Franco Lori also frets over resistance, but for practical purposes: "We need to find drugs that suppress virus effectively without generating resistance, for example, ones that target the cell [as opposed to the virus]." OK, Lori, put your lira where your lips are.

Minority Views: Five researchers see the priority as decoding HIV transmission once and for all. "Does infection come about by free virus or by an infected cell?" asks immune-scene vet Jay Levy. "Without that knowledge," says John Moore, "it becomes much harder to rationally design a microbicide." And for Joseph Sonnabend and Brian Gazzard, the conundrum of exposed seronegatives (ESNs) -- which AIDS dogma says do not exist -- is a field begging to be plowed. Gazzard explains: "While the answer to a small subgroup [of ESNs] is a simple matter of genetics, in a much broader context, some people are clearly recurrently exposed to HIV but do not get infected. This gives very important clues as to how a vaccine might be developed." Another critical line of inquiry for two researchers is locating HIV's Achilles' heel -- "the conserved region (if it exists) that, if blocked, makes survival of the virus impossible," as Mark Dybul puts it. The MO for Ho is "how to eliminate the forces that shield the virion glycoprotein and render the virus resistant to antibodies." Yes, it's a mouthful, but it also spells a renewed interest in fiddling with the virus to enable antibodies to do their job.

Reality Check: John Moore, a favorite among activists because of his take-no-prisoners pronouncements, urges clinicians and drug companies to look beyond the scoreboard. “The present fad for measuring the rate of viral load decrease for a week or two and announcing that ’drug X is better than drug Y’ is ludicrous,” he says.

Prevention Priority: University of North Carolina’s Chris Pilcher’s must-do is to apply advances in our understanding of acute infection to a beefed-up prevention effort. This means faster identification -- and treatment -- of the newly infected as well as contact tracing and partner notification. Rapid PCR testing -- not slow-poke HIV-antibody -- should be de rigueur, too.

TRAMPOLINE TRICKS

What is the next big thing we must learn about immune restoration?

Consensus: Everyone’s top need-to-know is how -- or if -- the immune rebound triggered by HAART’s viral KO can ever be anything but partial. Beyond that, different experts focus on different pieces of this puzzle. Anthony Fauci, Mark Dybul and Jon Cohen, for example, ask if even the tiniest scraps of anti-HIV CD4s survive the assault of initial infection -- and if so, can these be fortified or mass-produced? Mike McCune, Jay Levy and Chris Pilcher argue that the thymus is primus. In the workshop of the immune system, if you’re looking for replacement parts, this gland is grand. But Bruce Walker advises looking at the big picture. “HIV vaccine development has been characterized by too much emphasis on single aspects of the immune action,” he says. “First it was all about neutralizing antibodies, and now it seems to be all about CTLs. My own suspicion is that T-helper cells play a far greater role than is currently accepted.”

Reality Check: Not so fast, warns Mike McCune, who calls for the development of tools that can measure how well these cells actually function (rather than just count ’em).

Minority View: While the majority fusses over recovering or protecting those critical HIV-specific CD4s, a few question the very premise of this line of research. As they see it, the immune system may be fully capable of restoring itself.

Last Word: “We need to learn to ’trust’ the immune system,” Franco Lori says.

JUGGLING & CYCLING

What is the most important question to answer about HIV treatment strategies?

When to Start: 11 votes. But no one wanted to be pinned down to only one question. “When is more important than what to start with because treatment-naïve individuals tend to respond very well to first-line therapy,” says Donald Abrams, who has long spearheaded clinical trials that throw light on these issues. “These are all essential questions that remain unanswered.” Interestingly, there was nary a peep about the recent revision of federal guidelines that recommend starting HAART when CD4s fall below 350 or viral load rises above 55,000. In fact, a handful would like to see the downward trend continue, to 200 CD4s.

Minority View: But not Graeme Moyle, who is un-Britishly bullish on early treatment. He says that "hit early, hit hard" got a bad rap because protease inhibitors were mistakenly used in most first combos. "When you are younger and have high CD4s, you have less serious adverse effects," he says. "Now that the majority of us advise initiating therapy with non-nucleoside-based therapy, many of these toxicity concerns may have been diminished."

When to Stop: 1 vote. "Whether and when to consider treatment stoppage in patients with good CD4 responses is the most burning issue," Chris Pilcher says, "[given] the problems of managing ongoing toxicity and multidrug resistance."

How to Sequence: 1 vote for this lottery. Unfortunately, Franco Lori didn't say why.

Custom Cabinet: Bruce Walker has one word for us: pharmacogenetics. "We will increasingly see regimens tailored to individuals based on comprehensive analysis of their own virus in the context of their own host genetics," he says.

Is "Undetectable" So Delectable?: Subversives Joseph Sonnabend and Jon Cohen question one of the basic assumptions of treatment failure: "How much benefit you get from a maximally suppressive regimen [undetectable] vs. a somewhat suppressive regimen [5,000 to 20,000]," Cohen says. "That knowledge would allow people to make much more rational choices." Sonnabend adds that many patients with stable detectable viral loads may have immune responses that are helping to control the virus. Are they in fact healthier than their undetectable peers?

Last Word: Four researchers cast a write-in vote, agreeing with UC/San Diego treatment-strategy whiz Diane Havlir, who snaps, "I am more concerned about having new and better drugs to sequence than about the details of sequencing."

INTERMISSION

Will structured treatment interruptions (STIs) become a safe, effective part of HIV treatment?

Consensus: Three-quarters gave STIs a clinical thumbs-up, but most had to hold their research noses while doing so.

Relevance for Research: STIs are a bust. Mark Dybul, who with boss Anthony Fauci pioneered successful pulsing studies, separates the wheat from the chaff: "If the purpose of [an STI] is intermittent therapy [toxicity breaks], there is a chance that it can become a safe, effective strategy. But if the purpose is auto-immunization, this will not be an effective part of treatment in patients who began therapy during chronic infection." Why? Graeme Moyle hypothesizes that it may be because "virus that emerges during each treatment interruption is different and therefore the immune system is not getting consistent stimulation."

Relevance for HIVers: STIs or bust.

Reality Check: NIAID's Dybul from on high: "If the strategy is for use during salvage therapy, I

think the jury is still out."

Best Case: Therapeutic vaccine to the rescue! "Hopefully, STIs will be replaced by immunization with effective viral antigens during HAART," Jay Levy says.

Minority View: For five researchers (you know who you are), the fact that going off drugs might constitute a significant treatment advance is too paradoxical or pathetic to admit. Gallo voiced a not-uncommon contempt for STIs' wimp factor. "What will people say about it 50 years from now?" he asks. "'Leaders in the field gave us STIs for a while.' Not exactly a breakthrough. It was pushed down the throats of clinicians by people on drugs who were anxious to get off of them."

Last Word: "It is increasingly the treatment -- not the disease -- that is the problem," establishment gadfly Joseph Sonnabend says.

DISAPPEARING ACT

Is HIV eradication still a useful investment of time and money?

Consensus: Eradication has become a bad word in the mouths of a majority, but most lab coats are diplomatic in their criticisms. Don Abrams says, "It's a noble goal, but it may never be possible. The virus becomes entwined in the genetic information of the cells it infects." But Franco Lori wins the prize for shooting from the hip: The E-word is a "waste of time and money because of the nature of retroviruses, as we have known since 1970."

Relevance for Research: No Nobels in the offing, but much more knowledge about HIV to build on. As surfer-dude dad Mike McCune says, "The line of inquiry is worthwhile to the extent that it teaches us about the ploys by which the virus persists."

Relevance for HIVers: You don't need a quick cure if you have a long, strong one. Harvard's Max Essex: "Eradication may not be necessary if viral load can be kept at negligible levels with long-term vaccine maintenance therapy in the absence of drug toxicity."

Minority View: Four diehards still believe a cure is theoretically possible. Martin Markowitz, who coined the word, gives an inch -- semantically. "Eradication is a bad word," Markowitz says. "Borrowing from oncology, we should have used remission."

Last Word: Ho, Dr. Eradication himself, stands firm. "The research must go on," he says. "Otherwise, if we throw up our hands, it will be certain that HIV infection will remain incurable."

THE FIRE EATERS

Do activists still have a role to play in setting the AIDS research agenda?

Consensus: Yes, unanimously. Fauci, who as the head of NIAID suffered both cries of "Murderer!" and kisses from Larry Kramer, toes the party line: "They should continue to be partners in setting the research agenda. Their role is to question the rationale and need for various directions of

research.” In practice, this means pushing to keep real-life issues, such as survival and quality of life, relevant in the abstract world of the lab. Mike McCune says, “I believe they have been incredibly effective in bringing ’bench’ researchers and clinicians together for collaboration that likely would not have otherwise occurred.” An example: STIs, which PWA advocates “pushed down the throats” of clinicians.

Constructive Criticism: One-third of the researchers -- most of whom are, interestingly, held in high esteem by activists -- took their “partners” to task on a number of issues. John Moore, an academic researcher not known for mincing words, says, “The established activists seem to be becoming over-conservative.” Franco Lori notes a similar slacking off. “The community should be more involved in challenging the large economical interests whenever they overcome the interests of patients and science,” he says, “as well as those scientists and clinicians who develop an unhealthy attraction toward these interests.” Others challenge activists’ exclusivity and elitism. “Activism could benefit from expanding its own demographic base,” Chris Pilcher says. “There remains a troubling under-representation of heterosexuals, people of color and people who are poor.” Michael Saag fears for the future: “My biggest concern is that I don’t readily see a ’new generation’ of activists coming along.”

Other Criticism: Martin Markowitz merits praise for expressing what researchers no doubt whisper behind closed doors: “It is hard to tolerate the current complaining about when to start, and lipodystrophy,” he says. “I know most of my friends who died fighting would trade life for HAART [with all its problems].” Maybe the air-conditioner is broken over at Aaron Diamond, because the typically sweet-tempered David Ho sounds all hot and bothered, too. “Activists who engage in constructive discussions with scientists and policymakers will continue to have a major role,” he says. “Those who only shout criticisms from the sidelines should follow their example.”

Last Word: “It is critical that the voices of the people living with HIV are heard,” says community-minded Donald Abrams. “Although perhaps not as loud, aggressive and dramatic as before, they are still here!”

DANCING BEARS

Are there any drawbacks to the FDA’s accelerated approval of AIDS drugs?

Consensus: Fast track -- which activists truly had to force down the throats of all but the most community-minded of doctors 15 years ago -- is cause for a love-in from this crowd. “It would be a huge mistake to change the process,” Michael Saag says flatly. “Talk to some of my patients who have run out of options.” While John Moore speaks for many when he says that “some tinkering with the system might be justified, but not its wholesale emasculation,” the message is less “Don’t mess with success” than “Don’t even go there.” Academic researchers are all too familiar with the coils and snares of government red tape that can strangle the best idea.

Italian Stallion: “I would accelerate the process even more,” Franco Lori sniffs.

Reality Check: All but a few docs are quick to acknowledge one glaring drawback. As Brian

Gazzard says, “The obvious disadvantage to accelerated approval is that unexpected side effects don’t emerge until after the drug is licensed. This could be dealt with by firmer rules about Phase 4 studies -- to which the drug companies are obligated.” But Big Pharma is notably negligent about follow-up -- why go looking for problems with your product? The trick, then, is to get drug companies to fulfill their commitment. A few researchers want to call in the activists, who, Jay Levy says, “can play a very important role by monitoring the clinical trials being undertaken by the companies.”

Last Word: NIAID’s Fauci, in an “if”-y jab at a fellow federal agency, says that the FDA requires a bigger stick to compel corporate compliance: “Accelerated approval works well if there is a commitment to post-marketing follow-up and the capability of reversal of approvals if it becomes clear the drugs really do not work as expected.”

THE GRAND FINALE

What will HIV treatment look like for the average patient in five years?

Consensus: Simpler, better, more. Unanimously, the future looks brighter -- simplified regimens, more time off drugs and a few more tricks. But it’s not a commercial for feel-good pills. Jon Cohen looks into his crystal ball and sees that “people will have more options and, paradoxically, more constraints. More resistant viruses will exist. More will be known about dodging side effects. An entry inhibitor [T-20?, T-1249?] and an integrase inhibitor [will Merck’s work?] will come to market. One pill that combines five drugs will be available. An immune-based therapy [IL-2?] will make it to market, but many clinicians will question it. No strategy will eradicate an infection.”

Reality Check: Fully half of our researchers are piling their chips on a viable therapeutic vaccine by the year 2007 -- carefully noting that an immune booster would be used only in conjunction with current virus-killing capsules and pills. But a mere five enthusiasts allow that this scenario will allow for more drug-free intervals. Franco Lori offers his vision for a radical regimen: “Every year a patient takes her drugs in January. At the end of the month, she is vaccinated. The cycle is repeated in March and May. The patient does not take drugs for the rest of the year.” Then he corrects himself, adding: “This is an ideal goal. However, we have a lot of work to do before we get there.”

Pet Peeve: Since the drug companies prefer not to test their products with the competition in real-world combos, let alone bundle them together for market, it is hard to believe in a five-in-one-pill. But Martin Markowitz conjures the spectre of a four-in-one Pharma: “One, two, at most three pills once a day, limited toxicity, produced by GSKMerckBMSRoche Ltd., the world’s only drug company.”

Planetary Peeve: “The scene in my crystal ball doesn’t look pretty,” Mike McCune says. “The vast majority of patients with HIV do not have access to care or treatment -- and I don’t see much happening today to effectively enhance access to underserved groups in the next five years.”

The Epilogue: “The next 10 years of our struggle against the HIV pandemic are more difficult and

more critical than the last 20," says Emilio Emini. "Our goals and expectations have been adjusted so that they are now much harder to achieve, but without achieving them, the virus will prevail." What else is there to say? Let's get to work.

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ON THE HIGH WIRE

Four world-spanning AIDS activists weigh in on the issues of the day.

What is the biggest breakthrough for HIVers since Durban in 2000?

Hands down, all agreed that expanded access to HAART in developing countries through the introduction of generic drugs was the great leap forward. "Treatment offers people hope and that hope is the basis for social mobilization against HIV," Health Gap pioneer Alan Berkman, MD, says. In Uganda and elsewhere, public education and pilot treatment programs -- good, old PWA empowerment -- have triggered demand for better health care and other resources. "The mindset of people is changing after seeing that even in Africa, people can have treatment," says PWA Milly Katana, who single handedly represents the entire southern hemisphere at the UN's global AIDS fund.

What is the biggest barrier you face as an activist?

Funding, stigma, denial and political cowardice still conspire to hinder headway. UNAIDS's pull-no-punches Peter Piot says that "the recurrent questioning of AIDS as one of the biggest tragedies of the century -- or that AIDS exists at all" -- is the real tragedy. The UN's global AIDS fund, which took 20 years to birth, goes begging for money."The most important barrier to our work is the failure of the Bush administration and of Congress to support the fund," Berkman says."It's the best opportunity we have to make serious progress in slowing the pandemic."

What is the next big thing we must learn as a movement?

"The next big thing is the same old thing: to respect and value each human life across [all] lines," Berkman says. Veteran Haitihand Paul Farmer toasts to that, adding, "Equality and social justice have their place in basic-science research. Also, it's possible to do complex health interventions in poverty. 'Everyone has the right to live,' to quote the patients here." A vaccine -- preventive or therapeutic -- and its viable distribution also topped the to-do lists.

Do activists still have a role to play in setting the AIDS research agenda?

A no-brainer for this crowd. Everything from coming out as positive to street demos created the critical mass that is getting HIV meds to the global poor. "Without activists, the epidemic would be even worse today," Piot says. "Access to treatment would still be largely academic." But breaking patents and generating generics are only the beginning -- communities must muster the political will to build an infrastructure that combats poverty and disease, let alone distributes HAART. "Activists have been more successful than we ever dreamed and yet not nearly successful enough," Berkman says.

What will HIV treatment look like for the average patient in five years?

For the wealthy: Kinder, gentler, once-daily-dosing meds.Fewer opportunistic infections (OIs). No pediatric AIDS deaths. More drug resistance. The crystal ball is much cloudier for the poor -- only a few will benefit from scientific advances. Berkman shines his crystal: "Globally, my dream is that 5 million people will be receiving appropriate treatment for OIs and HIV. If we get there, it will be a magnificent achievement." Then, only 20 million to go.

- Cindra Feuer

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