AIDS RESEARCH

# International AIDS Meeting Injects a Dose of Realism

**The upbeat mood of 2 years ago has given way to acknowledgment that even the best therapies have flaws—and they are not reaching millions who need them**

**GENEVA**—Every 2 years, researchers, policymakers, activists, clinicians, drug developers, and journalists gather at an international AIDS conference for what amounts to a giant group therapy session that, in the end, pronounces to the world the state of the field. At the politically charged 5-day meeting* held here last week, the mood was distinctly downbeat compared with the triumphalism at the last such gathering in Vancouver, British Columbia. Then, meeting goers rejoiced over the cocktails of anti-HIV drugs that were miraculously yanking people back from the brink of death, and speculations about curing the infection grabbed headlines. Last week, the nearly 14,000 participants heard that researchers are now scrambling to find new treatment strategies as the first-line drugs begin to fail in some patients, that drug side effects are mounting, and that new drug-resistant strains of HIV are emerging. "Remission," not cure, is the new buzzword.

To make matters worse, some untreated people who once appeared invulnerable to HIV are now seeing their immune systems begin to decline. And although the meeting's official theme was "Bridging the Gap" between wealthy and poor countries, participants heard of the formidable obstacles to making anti-HIV therapies available to people in poor countries. "The biggest AIDS gap of all is the gap between what we know we can do today and what we are actually doing," said Peter Piot, chief of UNAIDS, the United Nations AIDS program, at the opening session of the meeting—which, for the first time, was organized by both scientists and HIV-infected people.

The news was not all bad, however. New evidence that it might be possible to stimulate the immune system to fight off HIV provided some glimmers of hope. And, although much of the meeting rehashed findings that have surfaced at smaller meetings during the past year, the abundance of presentations, posters, and schmoozing between sessions offered many novel insights. Indeed, the session titled "Are World AIDS Conferences Worth It?" was canceled for lack of interest. Piot set the overall mood in the meeting's opening session: "Now is the time for us to embrace a new realism and a new urgency in our efforts," he told participants.

* 12th World AIDS Conference, Geneva, Switzerland, 28 June to 3 July.

### Losing control

Part of the new realism comes from accumulating evidence that while powerful combination therapies can chase HIV from the bloodstreams of infected patients, the virus continues to lurk in a dormant form in a small number of CD4 T lymphocytes, HIV's primary target (*Science*, 14 November 1997, p. 1227). Many AIDS researchers had hoped that this reservoir of latently infected cells would eventually die out, taking the virus with them into oblivion. But new work presented by David Ho, director of the Aaron Diamond AIDS Research Center in New York City, indicates that such hopes were premature. Ho reported that HIV continues to replicate at a low level even in patients with undetectable levels of virus in their blood. Moreover, the progeny viruses are wild-type rather than drug-resistant strains, meaning that even viruses sensitive to the drugs are not completely suppressed.


PIERS CAVENDISH

**Flash point.** Demonstrators protest Merck's decision not to cut the price of its AIDS drugs to developing countries.

While Ho's data present a more realistic view of treatment success, new studies by Diane Havlir and Douglas Richman from the University of California, San Diego, challenge the common wisdom about treatment failure, when HIV rebounds and becomes detectable. Havlir and Richman examined the virus in patients whose HIV rebounded while they were taking a cocktail of two drugs that attack HIV's reverse transcriptase enzyme and one that blocks its protease enzyme. They thought that it would have become resistant to all three compounds, but to their surprise, the virus was not resistant to the protease inhibitor, the most potent of the drugs. So, they conclude, the routine practice of switching rebound patients to an entirely new drug regimen may do more harm than good: They may be discarding an effective drug along with those that the virus has overcome.

That wasn't the only surprise in the Havlir-Richman study: The patients who had the biggest jumps in CD4 counts were the ones most likely to have viral rebounds. This seemed counterintuitive, because CD4s are the very cells that HIV selectively destroys, and boosting their numbers has become a central aim of AIDS treatments. But these data suggest that when CD4 levels increase after treatment, they set up many new targets for HIV, generating "fuel for the embers" of viral infection, said Richman. "Greater increases in CD4 are in general good, but they require greater vigilance in terms of lost control."

### Help on the way

While HIV continues to thwart efforts to defeat it directly with antiviral drugs, some immunologists have been making steady headway by trying to enlist the immune system in the battle. Bruce Walker at Massachusetts General Hospital in Boston presented the latest chapter in a compelling story he has told at a number of recent meetings. Walker has accumulated evidence that many so-called long-term nonprogressors—people who have controlled their HIV infections for more than a decade without taking drugs—have high levels of CD4s that specifically recognize the virus (*Science*, 8 May, p. 825). The CD4s, also called T helper cells, serve as battle commanders, orchestrating much of the immune system's assault on foreign invaders. Most infected people quickly lose HIV-specific T helpers, which led Walker to wonder what it would take to preserve these cells.

In collaboration with colleagues in the United States and Italy, Walker has aggressively treated people who had been recently infected with HIV but had yet to produce antibodies to the virus. Every one of the seven patients the team has followed over several months developed increasingly powerful anti-HIV T helper responses.

"This is beautiful," says virologist Andreas Meyerhans at the University of the Saarland in Homburg, Germany. Based on these new results, Walker argued that physicians should set up early warning networks to identify acutely infected people—some develop rashes and fevers—and offer them

potent drugs while there is still time to protect HIV-specific T helper responses. And in a late breaker session, Fred Valentine at the New York University Medical Center in New York City presented data suggesting that a "therapeutic" HIV vaccine can rev up the immune response against the virus in patients who are further along in their infections. Valentine and his colleagues gave 43 HIV-positive patients the standard cocktail of two reverse transcriptase inhibitors and a protease inhibitor. Four weeks later, when their virus was undetectable, the researchers immunized one group with an inactivated HIV that had been stripped of a protein called gp120, which studs the virus's outer coat. After 20 weeks, the group that received anti-HIV drugs alone scored very poorly in a key test of their T lymphocytes' ability to mount an immune response against HIV. But the immunized group demonstrated what Valentine called "huge" responses in the same test. These results are "quite striking," comments Walker, who adds that "the immune system can clearly contribute to controlling the virus."

**Live vaccines: a mortal blow?**

Despite these promising results, little progress was reported on one key immunological front: the development of preventive vaccines. Indeed, the controversial idea of developing a vaccine based on a weakened strain of live HIV received a setback with the latest news about a group of Australians who had been accidentally infected with a viral strain that had seemed benign. Everyone in the group, which now consists of a blood donor and five transfusion recipients infected by his blood, remains free of AIDS, despite having been infected for between 13 and 17 years. Their virus has a defective HIV gene called *nef*—the very gene deleted from a live, but weakened AIDS virus that has worked better in monkey experiments than any other vaccine strategy.

In Geneva, however, Jenny Learmont, a nurse with the Australian Red Cross Blood Service who first recognized the significance of the cohort, reported that the donor and two recipients have recently seen their CD4 counts drop. Their counts are still in the normal range, stressed Learmont, but the finding has given her pause. "It would have to change your thinking that it's not causing damage," said Learmont. "Obviously this now needs to be examined very hard."

A more encouraging development on the vaccine front came from an unlikely source: a study of babies in Nairobi, Kenya, born to HIV-infected mothers. Kelly MacDonald of the University of Toronto examined 141 mother-baby pairs to try to determine why some babies became infected and others did not. She reported that babies who had different genetic markers on their immune cells—so-called major histocompatibility complexes, or MHC—from their mothers were significantly less likely to become infected. MacDonald and others think this difference is protective because when HIV buds from a cell, it carries a piece of the host cell membrane—including MHC molecules—on its surface. So babies who build an immune response against their mothers' discordant MHC, explained MacDonald, are also building a response against HIV from their mother. Monkey and chimp experiments of AIDS vaccines have also shown that immune responses can develop against the MHC on the viral envelope. "The data on discordance are very intriguing," said pediatrician Arthur Ammann, head of the American Foundation for AIDS Research.

MacDonald and her colleagues also found that babies seemed to gain protection if they had a specific MHC known as a "supertype"—which is present in 40% of the world's population. When HIV infects a cell, MHC molecules present pieces of the virus to the immune system to indicate that the cell should be destroyed. Presumably, this supertype of MHC is better at presenting viral pieces than other MHCs. Putting the discordance and the supertype gene together, "this would suggest the protective effect is as strong as any intervention we've identified" to prevent maternal-infant transmission, said MacDonald, who is planning to develop vaccines that exploit these findings.

J. BALFOUR

"Now is the time for us to embrace a new realism and a new urgency."

—Peter Piot

**The gap not bridged**

Many speakers emphasized, however, that few such discoveries have benefited the developing world, where 90% of HIV-infected people live. "Why is it that despite our efforts the level of care is still so grossly inadequate for most people with HIV?" asked Piot. The short answer is the daunting cost of providing expensive therapies to the developing world. Robert Hogg of the BC Centre for Excellence in HIV/AIDS in Vancouver, British Columbia, presented an estimate of the cost of providing triple combination therapy to the more than 30 million HIV-infected people across the globe: $36.5 billion annually. Faced with those figures, UNAIDS has been trying to convince drug companies to lower their prices in developing countries. UNAIDS official Joseph Saba, who is coordinating this project, says five companies have officially joined the initiative, including Roche, Bristol-Myers Squibb, and Glaxo Wellcome, which has begun a pilot program to provide its anti-HIV drug AZT to 30,000 pregnant women in 11 countries at a 60% to 75% discount. Because nearly 600,000 infants worldwide acquired HIV from their mothers during 1997, Glaxo Wellcome will make at least a modest profit on AZT even at reduced prices. Says Glaxo Wellcome spokesperson Benedict Plumley, "it is important to be clear that we are not a charity." Eventually, the participating drug companies will negotiate separate prices in each country, based on what the market can bear.

Conspicuously absent from the agreement so far is Merck, which makes the best-selling protease inhibitor indinavir. Indeed, its absence prompted a demonstration, led by the AIDS activist group ACT UP, that spray-painted the company's exhibit at the meeting. Merck spokesperson Jeffrey Sturchio says Merck is reluctant to join the club because inadequate health care infrastructure in many developing countries makes it "impractical and potentially ineffective" to administer these drugs properly whatever their price. He adds that indinavir is already priced 25% to 30% lower than competing protease inhibitors. Rather than join the UNAIDS initiative, says Sturchio, Merck has concentrated on creating training programs for physicians in developing countries who might eventually prescribe combination therapies.

But even if drug companies cut their profits to a minimum, the price of therapy may still not be low enough to make a difference to millions of HIV-infected people. Says physician Elly Katabira of Mulago Hospital in Kampala, Uganda: "Even if the price [for combination therapy] was only $200 per month, which is peanuts in Western countries, this is more than many Africans earn in their lifetimes."

As if to underscore the magnitude of what remains to be done, a digital counter placed on the stage for the closing ceremony ticked off, in bright red numbers, the number of people around the world currently estimated to be infected with HIV. As the meeting ended and participants filed out of the conference hall, the counter reached 33,535,780 and kept on ticking.

—MICHAEL BALTER AND JON COHEN