mantle versus upper mantle convection. There is whole-mantle convection, and [its form] seems to be rather simple."

Don L. Anderson of Caltech, a longtime proponent of a layered mantle, admits that the images are impressive. "The amazing thing to me," he says, "is that their models agree so well even though they use completely different data and [analysis] techniques." Van der Hilst and colleagues used only P waves—pressure waves akin to sound waves in the air—that pass directly through the mantle or the mantle and the core. Grand, on the other hand, used only shear waves—undulations that resemble ocean waves and that can follow many different contorted paths through the mantle, such as repeatedly bouncing off Earth's surface into deeper rock, then bending to the surface again.

Still, Anderson and other researchers who have advocated a layered mantle are holding out for more evidence. "I guess I'm not convinced," says mineral physicist Raymond Jeanloz of UC Berkeley. "To what degree is what is inferred from the patterns in the eye of the beholder? I appreciate that the guys who are doing the hands-on data analysis feel the results just leap out at them, that they really see evidence for slab penetration ... but how you link up these blobs of high velocity and whether you infer they represent slabs going straight through [the 660-kilometer barrier] is not quite so obvious to me as it is to them."

Jeanloz and Anderson would both like to know more about the chemistry and physics of the features behind the seismic images. The images could be compared more closely with computer models that simulate how past subduction should have shaped the mantle, Jeanloz suggests. And Anderson would like more comparisons of the seismic data with experimentally determined mineral properties, to prove that the seismically fast features are actually slabs: "Just because you found some [fast] regions, it doesn't mean anything until you know what that means in terms of temperature and chemistry."

To many seismologists, as Gurnis puts it, these are "details" that "remain to be worked out," not fatal flaws. And before such studies are finished, even more persuasive images may appear. Grand notes that there are plenty of seismic data in hand that can be analyzed to sharpen the still-fuzzy spots in the images, which reflect gaps in the distribution of earthquakes and seismic stations. Of course, many mysteries remain, such as whether slabs now imaged only into the midmantle can be seen to extend to the bottom and the ultimate fate of slabs that have come to rest at the core-mantle boundary. Slabs may be buried deep, but that doesn't mean that their rest is undisturbed.

–Richard A. Kerr

AIDS

Advances Painted in Shades Of Gray at a D.C. Conference

Success often comes at a price. Researchers who gathered here last week for the most influential AIDS meeting in the United States heard one speaker after another praise the dramatic advances in drug treatments that recently have captured the media spotlight. But the 2300 attendees also heard scores of reports about the less glamorous task of filling out and qualifying last year's bold claims. "We're not hearing the headline stuff we heard last year. The data at this meeting were much broader and deeper," said the conference's chair, virologist Douglas Richman of the University of California, San Diego (UCSD). Organizers of the 4th Conference on Retroviruses and Opportunistic Infections* also had to contend with their own success: The gathering has become so popular that they had to set strict attendance limits, angering many AIDS activists and scientists who were locked out.

"We must dutifully avoid unwarranted triumphalism [as well as] the undue pessimism that prevails in some circles."
—David Ho

David Ho, head of the Aaron Diamond AIDS Research Center in New York City, set the tone for the meeting in the opening session, when he cautioned his colleagues to put the recent progress in AIDS treatment in its proper perspective. "We must dutifully avoid unwarranted triumphalism [as well as] the undue pessimism that prevails in some circles," he said. "The state of HIV treatment is neither black nor white. We must paint the situation in the proper shade of gray." Indeed, many fundamental questions about the new anti-HIV drugs are still unresolved, including how best to use them and how to assess their limitations. And the treatment picture will take on even subtler shading as drug companies attempt to bring a flood of new drugs to market.

One aspect of AIDS research in 1997 can be rendered in black and white: For the first time since the start of the epidemic, HIV-infected patients and clinicians have at their disposal an arsenal of potent, virus-crippling drugs. A new class of drugs that inhibit HIV's protease enzyme, which the virus uses to assemble new copies of itself, is the arsenal's mainstay. When combined with older drugs like AZT and 3TC that disable the enzyme that copies the virus into the host cell, the protease inhibitors can pound the virus so hard that, in many patients, even the most sensitive tests cannot find it in the blood cells.

Several studies presented at the meeting attempted to assess the impact of the new drug regimens on patients by looking at how frequently they were becoming ill. As AIDS researchers constantly point out these days, reducing the viral load (the total amount of HIV) in a patient's blood does not necessarily mean he or she will suffer fewer AIDS-related diseases. The hope, of course, is that the drugs will help HIV-infected people to live longer. But at present, most drugs win regulatory approval based primarily on viral-load data, and few of the trials measure clinical outcomes.

The largest analysis of links between new drugs and illness was presented by Yves Mouton of Dron Hospital in Tourcoing, France. Mouton and colleagues looked at 7757 patients from 10 AIDS centers in France. In the study period, between the fall of 1995 and 1996, the use of anti-HIV drugs in these patients jumped by 49%. At the same time, AIDS-defining diseases dropped 36%, said Mouton. The number of days patients were hospitalized also plummeted by more than one-third. Mouton attributed these improvements largely to the drugs.

Mary Ann Chiasson, assistant commissioner of the New York City Department of Health, reported similarly upbeat statistics. In New York City, which accounts for 16% of U.S. AIDS cases, AIDS deaths last year dropped by 30%. But health officials did not attribute the drop to increased use of protease inhibitors. According to Chiasson, the AIDS death rate began to fall before the two most powerful drugs reached the market last spring. She suggested that the decline in deaths may instead be linked more closely to an increase in federal funding in 1994 for AIDS patients, which led to better prevention and treatment of opportunistic infections.

* 4th Conference on Retroviruses and Opportunistic Infections, 22–26 January, Washington, D.C.

Other researchers reported efforts to unravel how much virus remains in the bodies of people who have "undetectable" HIV in their blood. As Northwestern University molecular biologist Steven Wolinsky stressed, "Even though we don't have evidence of virus in blood by currently available tests, it doesn't mean it's not there."

One provocative study of twins infected by HIV at birth underscored this point. Katherine Luzuriaga from the University of Massachusetts, Worcester, described how she and her coworkers treated a baby boy and girl with three anti-HIV drugs after they showed signs of infection at 10 weeks of age. The drug combination soon drove viral RNA in the blood down to undetectable levels. Their levels of antibodies against the virus also steadily declined, another signal that the drugs had knocked back the virus. "You can initiate therapy early in children and achieve a spectacular effect," says Wolinsky.

But after 16 months of treatment, one child's blood suddenly tested positive for HIV RNA. Since then, the researchers have pushed the viral load back down with a different drug combination. But the case highlights the fact that the new drugs have yet to cure anyone of HIV infection—and it's still unclear whether they ever will, says Wolinsky. "The study lends credence to modeling studies that say the duration of therapy has to be measured in years," Wolinsky says, referring to a mathematical model presented at the meeting by mathematician/immunologist Alan Perelson of Los Alamos National Laboratory and Ho that estimates it will take 2.3 to 3.1 years of viral suppression to rid the body of HIV.

And as Winston Cavert of the University of Minnesota, Minneapolis, noted at the meeting, 99% of the HIV in the body ordinarily resides in the lymph nodes. In collaboration with Sven Danner at the Academic Medical Center in Amsterdam, the Netherlands, Cavert, Ashley Haase, and co-workers compared HIV levels in blood and samples of tonsils (a type of lymph node) biopsied from 10 patients who had taken the protease inhibitor ritonavir along with AZT and 3TC for 24 weeks. The researchers saw "a dramatic decline" in HIV in both blood and tonsils, said Cavert. But this good news was tempered by the bad news that the one tonsil they examined that had no apparent HIV RNA still harbored its DNA—the form of the virus that infiltrates a cell's nucleus and can lie dormant for months or even years.

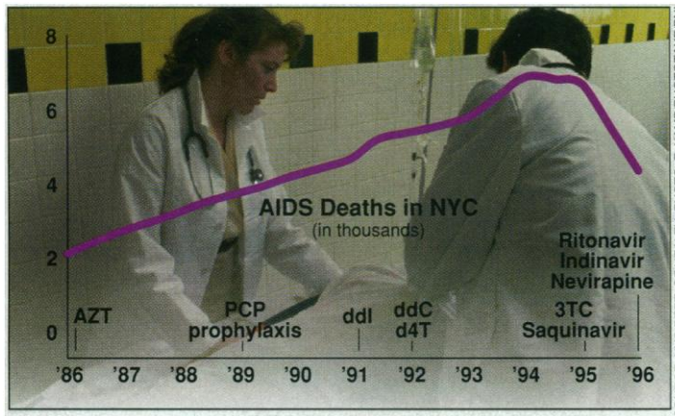
While such studies help answer fundamental questions about how well the drugs work now, a question on everyone's mind is how long the new combinations of anti-HIV drugs will work before resistant strains of the virus crop up, as they quickly did with first-generation treatments such as AZT. One encouraging study suggests that if patients consistently adhere to a regimen of more than a dozen pills a day, resistance can be kept at bay. UCSD's Joe Wong and colleagues reported data from a study sponsored by Merck & Co. in which 18 of 21 patients who have taken the company's protease inhibitor, indinavir, plus AZT and 3TC, have undetectable or extremely low levels of HIV RNA after 68 weeks of treatment.

Several reports at the conference, however, indicated that in the real world, many patients don't follow drug regimens strictly, and it may only take a few days off treatment for resistant strains to appear. Moreover, as many presenters pointed out, physicians who aren't current with the latest research and prescribe single drugs or weak combinations that do not fully suppress HIV often inadvertently encourage resistant strains. "Great mistakes are being made by people who think they know what they're doing," said Joep Lange of Amsterdam's Academic Medical Center.

Lange was particularly critical of clinical trials that included as part of their designs "suboptimal therapy," which he blamed on "regulatory requirements, stupidity, and greed." He singled out drug companies for testing what he called "incestuous combinations" of compounds that they own, rather than working with other companies to optimize treatments.

Part of the problem, says meeting vice chair Constance Benson of Rush Medical College in Chicago, is simply that changing a clinical trial to reflect new findings requires input from many people. Benson acknowledges that right now, for instance, the AIDS Clinical Trials Group (ACTG), sponsored by the U.S. National Institutes of Health, has "three or four" trials under way that include potentially suboptimal treatments. In each case, the researchers had designed the studies before the potent drug combinations now considered "optimal" were available. Benson, a member of ACTG's executive committee, says the group will meet soon to discuss changing the studies.

But according to several presenters, even people who develop resistance to today's drugs still have reason for hope because of the many new drugs in the pipeline. The hands-on favorite to make it to market next is a protease inhibitor, nelfinavir, which William Powderly of Washington University in St. Louis noted could give patients a big leg up in the resistance battle. HIV strains that are resistant to one protease inhibitor often are resistant to others. But an HIV strain that develops resistance to nelfinavir still is susceptible to other protease inhibitors, says Powderly.



Death-defying. Health officials attribute this recent drop in deaths largely to better prevention and treatment of opportunistic infections.

Made by Agouron in La Jolla, California, the drug has been tested in nearly 700 patients. Powderly reported that when the drug was combined with AZT and 3TC, investigators could not detect HIV in the blood of fully 60% of the patients after 6 months. The triple therapy also boosted CD4 cells, the immune-system actors HIV destroys, by an average of 155 to 160 cells per cubic milliliter of blood. This is comparable to the current triple therapies now being used. Agouron has asked the Food and Drug Administration to license the drug and is hoping to receive approval in the next few months.

Further down the pipeline is a new protease inhibitor described at the meeting by scientists from Abbott Laboratories, the makers of ritonavir. Called ABT-378, the drug is 10 times more potent at knocking back HIV than are other protease inhibitors, said company scientist Hing Sham: "Importantly, ABT-378 shows potent inhibition of even highly resistant HIVs." The drug is currently in small safety trials in uninfected humans.

Still very much up in the air is the fate of the conference itself. The gathering turned away many would-be attendees, including some AIDS activists who threatened to disrupt the conference and even harm organizers. Indeed, safety concerns led the organizers to hire a team of security guards, who shadowed every move the organizers made. Conference chair Richman says the organizers haven't yet decided whether they will allow more people into the meeting next year. "We hear strong opinions in both directions," he says. They plan to make their decision after reviewing comments from this year's attendees.

–Jon Cohen