Six years ago, new cocktails of anti-HIV drugs transformed prospects for infected people in industrialized countries. Now, serious limitations have become apparent

Confronting the Limits Of Success

HIV/AIDS

Researchers will gather in Barcelona, Spain, next week for the XIV International AIDS Conference. This special package looks at two pressing issues on the agenda: problems limiting the effectiveness of current treatments and puzzles over what kinds of immune responses might lead to vaccines.

▶ THERAPIES
VACCINES

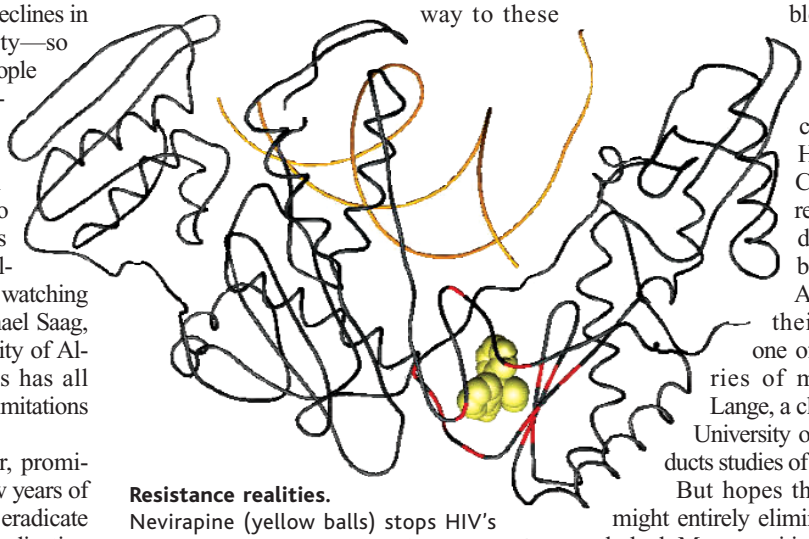
To veteran AIDS researchers, "Berlin" is shorthand for "gloom and doom, 1993." "Vancouver" translates to "elation, 1996." "Durban" means "waking up to the global crisis, 2000." The tags refer to the field's Zeitgeist in the years these cities hosted the international AIDS conference. Next week, Barcelona, Spain, will welcome more than 10,000 participants to the XIV International AIDS Conference, and the tag line this year could well be "the limits of success."

In 1996, researchers first proved that new cocktails of drugs could thoroughly stymie HIV. There was even talk of cures. The 16 different anti-HIV drugs now approved by the U.S. Food and Drug Administration have indeed led to dramatic declines in AIDS-related disease and mortality—so much so that in countries where people have access to the drugs, HIV infection has changed, for many, from a death sentence to a chronic, manageable disease. But the honeymoon is over. "If we look back 6 years ago to the euphoria of Vancouver, it was appropriate, because we'd been dealing with 16 years of depression and watching people die right and left," says Michael Saag, a clinical investigator at the University of Alabama, Birmingham. "But as this has all played out over the last 6 years, the limitations have become quite apparent."

In the heady days of Vancouver, prominent researchers suggested that a few years of treatment with potent drugs might eradicate HIV from a person's body. Now eradication is the E-word, something that makes researchers cringe. After Vancouver, many clinicians advocated a treatment philosophy dubbed "hit early, hit hard," based on the assumption that infected people would fare better the earlier they started taking anti-HIV cocktails. Now, so many serious long-term side effects have surfaced with these drugs that consensus panels of experts have recommended delaying treatment until infected people are in imminent danger of symptomatic disease. And, in a vicious cycle, these side effects, combined with the psychological burden of taking a dozen or more medicines each day for months on end, have led many infected people to abandon their treatment plans because of "pill fatigue." The result: As time passes, HIV has become increasingly resistant to existing drugs, and transmission of these resistant strains is on the rise.

These issues, sadly, remain of little concern for developing countries because they have yet to encounter the limits of success. Despite campaigns launched after Durban that have slashed drug prices and raised billions of dollars for AIDS treatment and prevention in developing countries—where 90% of the estimated 40 million HIV-infected people live—only a tiny fraction of the world's poor currently receive medication to protect them from the ravages of HIV (see p. 2324).

As the euphoria of Vancouver gives way to these realities, AIDS researchers will be bringing to Barcelona some hard-headed views of the new challenges and complexities they face. "We've made tremendous strides, but we've kind of reached that plateau," says Anthony Fauci, head of the U.S. National Institute of Allergy and Infectious Diseases (NIAID). "When I put people on therapy and they do extremely well, I don't have any illusions that it's necessarily going to last 25 years."



Resistance realities. Nevirapine (yellow balls) stops HIV's reverse transcriptase enzyme from transcribing viral RNA (gold strand) into DNA—but mutations (red) thwart the drug.

CREDIT: (BOTTOM) ROBERT SHAFER/STANFORD UNIVERSITY/LANL

Unnatural history

The 1993 Berlin conference marks the low point in the search for anti-HIV drugs. Nearly a decade after HIV had been unmasked as the cause of AIDS, only three anti-HIV drugs had made it to market: AZT, ddI, and ddC, all of which attempt to cripple HIV's reverse transcriptase (RT) enzyme. None of them, either alone or in combination, packed much wallop, and huge debates roiled the field about how much benefit they truly offered. At best, they added a few years of life to people who had developed AIDS.

By 1996, a combination of RT inhibitors and new drugs that target HIV's protease enzyme had radically changed the prospects for infected people. Various regimens of "highly active antiretroviral therapy" (HAART) could routinely drive the amount of HIV in the blood—the viral load—down below what the most sensitive tests could detect. The critical immune cells that HIV targets and destroys, CD4s, made spectacular rebounds. Hospital wards devoted to AIDS patients began to empty, and AIDS hospices closed their doors. "HAART is one of the great success stories of medicine," says Joep Lange, a clinical investigator at the University of Amsterdam who conducts studies of anti-HIV drugs.

But hopes that these potent drugs might entirely eliminate HIV were quickly dashed. More sensitive tests revealed that the virus hides out in various reservoirs in the body that would take decades of treatment to

empty. The implication: An HIV-infected person must take medications for life. And, as with any long-term treatment, side effects and resistance are major concerns. "If people start with the right combination and they tolerate the drugs, I don't think there's any indication that there's going to be viral escape," says Lange. "They can lead normal lives. But the big problem is that toxicities are in the way."

Physicians knew that the new drugs would cause nausea and anemia, but 2 years after the introduction of HAART, they began to see a new side effect in their patients: odd distributions of fat known as lipodystrophy. Other metabolic abnormalities have since surfaced that lead to diabetes-like problems, brittle bones, and heart disease. Because of these toxicities, many people switch medications or stop taking them altogether. As a result, clinicians no longer can answer one of the most common questions from patients: How much benefit do the drugs offer? "When you have multiple drugs, and each one has toxicities, it's really impossible to give people a meaningful answer," explains leading AIDS clinician Robert Schooley of the University of Colorado Health Sciences Center in Denver.

But some indication of long-term effects is emerging, dubbed "the unnatural history" of HIV by epidemiologist Scott Holmberg of the U.S. Centers for Disease Control and Prevention. On the positive end, Holmberg, Frank Palella of Northwestern University in Evanston, Illiois, and co-workers have shown that with the introduction of HAART, the numbers of AIDS-related diseases and deaths dramatically plummeted in a cohort of more than 1200 HIV-infected people they routinely monitor (see graphs, p. 2323).

Evidence exists, too, that—at least for some—HAART does not lose its power over time. Virologist Douglas Richman of the University of California, San Diego (UCSD), says that about half of the 33 people who participated in a landmark HAART study he helped run have tolerated the drugs and continue to fully suppress HIV. The patients began with an average of 144 CD4s per milliliter of blood (healthy people have 600 to 1200; 200 or less is considered AIDS), and after 7 years of treatment with AZT, the RT inhibitor 3TC, and the protease inhibitor indinavir, "they're doing amazingly well," says Richman.

But a recent analysis of a much larger study of the same three drugs in a slightly sicker population—the patients started with only 87 CD4s on average—gives a less rosy picture. Kenneth Freedberg of Massachusetts General Hospital in Boston and colleagues reported in the 15 March 2001 *New England Journal of Medicine* that although the treatment clearly was cost-effective, these patients' average life expectancy was only three and a half years.

Neither of these studies is likely to reflect what happens outside clinical trials, however. In the real world, patients start HAART with every imaginable treatment history and a wide range of CD4 counts and virus levels. They might have a lot of drug-resistant virus or none at all. And, because they are less motivated to take several pills each day on a schedule, treatments often fail sooner than they do for people in trials.

Studies that attempt to gauge the impact of HAART in real-world settings have arrived at troubling conclusions about durability. When people fail on HAART because of toxicities or side effects, they typically switch to a different cocktail of pills. But with each successive switch, says the University of Alabama's Saag, HAART works for shorter periods before another switch is required. In a study of some 400 people on various HAART regimens, Saag and colleagues found that few people could stay with a treatment plan for long. "Only about 25% of the people are on their original regimen 4 years out," says Saag.

Researchers stress, however, that these limits should not overshadow the obvious benefits that the new treatments provide. "Those of us taking care of patients in the early to mid-1980s" remember how people "were dying miserable deaths all around us," says UCSD's Richman. Visit his clinic now, and "it's a no-brainer" that HAART has dramatically improved the ability to prevent AIDS and death. "The real issue," says Richman, "is when to initiate treatment."

Hit when?

In the wake of Vancouver, "hit early, hit hard" quickly became the conventional wisdom. Motivated by the dream of eradication and lessons from other branches of medicine, many physicians began giving the new drugs to all patients who had a detectable viral load. "When this started, we were still quite influenced by other fields, like oncology: The idea was if you wait to treat a cancer, you don't have any chance of a good result," explains AIDS researcher Bernard Hirschel of the University of Geneva in Switzerland. In particular, researchers worried that if they waited too long to treat, the virus would be more difficult to control, and the immune system would have less chance to recover. Now, however, the consensus on early treatment has given way to debate.

The shift is reflected in changing guidelines issued by the U.S. Department of Health and Human Services (HHS). In 1998, HHS recommended that HAART be offered to all patients who had 500 or fewer CD4 cells or viral loads that rose above 20,000 copies per

ANTIRETROVIRAL DRUGS APPROVED BY U.S. FDA FOR HIV

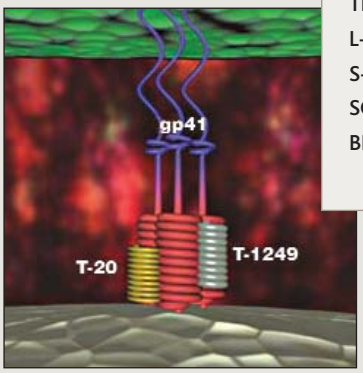
Generic Name	Adult dose (pills/day)	Target	Manufacturer	Approval date
AZT (zidovudine)	2	RT	GlaxoSmithKline	March '87
ddI (didanosine)	1–4	RT	Bristol-Myers Squibb	October '91
ddC (zalcitabine)	3	RT	Hoffmann–La Roche	June '92
d4T (stavudine)	2	RT	Bristol-Myers Squibb	June '94
3TC (lamivudine)	2	RT	GlaxoSmithKline	November '95
saquinavir	16–18	Protease	Hoffmann–La Roche	December '95
ritonavir	12	Protease	Abbott Laboratories	March '96
indinavir	6	Protease	Merck & Co. Inc.	March '96
nevirapine	2	RT	Boehringer Ingelheim	June '96
nelfinavir	9–10	Protease	Agouron Pharmaceuticals	March '97
delavirdine	6	RT	Pharmacia & Upjohn	April '97
AZT and 3TC	2	RT	GlaxoSmithKline	September '97
efavirenz	1	RT	DuPont Pharmaceuticals	September '98
abacavir	2	RT	GlaxoSmithKline	December '98
amprenavir	16	Protease	GlaxoSmithKline	April '99
lopinavir and ritonavir	6	Protease	Abbott Laboratories	September '00
abacavir, AZT, 3TC	2	RT	GlaxoSmithKline	November '00
tenofovir	1	RT	Gilead Sciences Inc.	October '01

SOURCES: FDA, AIDSMEDS.COM, GSK

Raising the Limits

Physicians treating HIV-infected people now have a massive armamentarium at their disposal: 16 anti-HIV drugs are on the market in the United States, and more are in the pipeline. The impressive flow of new drugs—10 have been approved in the past 6 years—is giving researchers hope that they can alleviate some of the problems with current therapies (see main text).

All 16 approved drugs target either HIV's reverse transcriptase (RT) or protease enzymes, proteins critical to the virus's ability to replicate. Different drugs home in on different regions of the target enzyme, which makes them effective in combination, and they often produce different side effects. This means that physicians can vary the mix of drugs in a cocktail to attack HIV strains that have become resistant to some drugs or to make therapy more tolerable. Some of the new drugs also combine several compounds into a single pill or reduce multiple doses to one tablet, which can simplify drug regimens. "We're seeing gradual progress on a whole series of fronts," says Robert Schooley, who conducts clinical trials of anti-HIV drugs at the University of Colorado Health Sciences Center in Denver. But, Schooley notes, the array of choices can be bewildering for physicians: "This is as complicated as oncology."



No entry. The drugs T-20 and T-1249 interfere with HIV's gp41 as it attempts to gaff a CD4 cell and then infect it.

And it is only going to get more complicated. Next week, at the XIV International AIDS Conference in Barcelona, Spain, researchers will learn about several promising drugs now in clinical trials. Some attack the familiar RT and protease enzymes, but others go after new targets such as receptors that allow HIV to slip into cells or a critical viral enzyme called integrase (see table).

Researchers are awaiting news, for example, about efficacy studies of T-20, a drug that attempts to stop the virus from entering cells by gumming up a viral protein, gp41, that's critical to the process. Although T-20 must be injected, preliminary evidence suggests that because it inhibits a novel target, the drug will work in people who have developed resistance to other antiviral compounds. Researchers hold out similar hopes for other novel compounds further back in the pipeline.

These advances should raise some of the limits of current therapies. But they are unlikely to have the dramatic impact that protease inhibitors had when they were added to the mix 6 years ago. "We need something else in addition to antiretrovirals; otherwise we are not going to move forward in this field," says José Gatell, a clinical investigator at the University of Barcelona, who is co-chair of the international conference. Gatell is heartened by increasing interest in immune-based treatments, such as vaccines that aim to help infected people. "We need to treat the immune system," he says. "With antiretroviral therapy, we have reached the roof."

–J.C.

ANTI-HIV DRUGS IN CLINICAL TRIALS

Drug	Manufacturer	Target	Stage	Attributes
T-20	Trimeris/Hoffmann–La Roche	Entry (gp41)	Phase III	Novel target
atazanavir	Bristol-Myers Squibb	Protease	Phase III	Low lipid tox., 1 pill/day
FTC (emtricitabine)	Triangle Pharmaceuticals	RT	Phase III	1 pill/day
tipranavir	Boehringer Ingelheim	Protease	Phase II/III	Resistance
DPC-083	Bristol-Myers Squibb	RT	Phase II	Resistance
DAPD	Triangle Pharmaceuticals	RT	Phase I/II	Resistance
T-1249	Trimeris	Entry (gp41)	Phase I/II	Novel target
TMC 125	Tibotec-Virco	RT	Phase I	Ultrapotent
L-870,810	Merck & Co. Inc.	Integrase	Phase I	Novel target
S-1360	Shionogi/GlaxoSmithKline	Integrase	Phase I	Novel target
SCH-C	Schering-Plough	Entry (CCR5)	Phase I	Novel target
BMS-806	Bristol-Myers Squibb	Entry (gp120/CD4)	Phase I	Earliest entry stage

milliliter of blood. But last year HHS took a more conservative approach, recommending that treatment be offered at 350 CD4s or a viral load higher than 55,000. Several other countries have similar guidelines. (Experts widely agree that everyone with 200 or fewer CD4s should receive treatment, as well as the minority of people who seek care within 6 months of becoming infected, as this might preserve vital immune functions that otherwise will suffer permanent damage.)

Some support for delaying treatment has come from studies indicating that people treated later in the course of disease fare just as well in the long run. European researchers headed by Andrew Phillips of the Royal Free and University College Medical School in London, U.K., for example, saw little difference in long-term outcome in their studies of 3400 patients on HAART. They reported in the 28 November 2001 *Journal of the American Medical Association* that the treatment could fully and durably suppress HIV irrespective of whether a person had an initial CD4 count below 200 or above 500.

A second study by Canadian researchers Robert Hogg, Julio Montaner, and colleagues reached similar conclusions. They found that for the 1200 patients they treated at the British Columbia Centre for Excellence in HIV/AIDS, viral load offered a poor guide for starting treatment. Only people who started HAART at less than 200 CD4s progressed to disease and death more quickly.

These results are not persuasive to many in the field, however. "It's clear in the short term that you don't have benefit from starting treatment early, but we won't see the negative effects from delaying treatment for 10 years," says Stefano Vella, chair of the HIV/AIDS Clinical Research program run by Italy's Istituto Superiore di Sanità in Rome. And Steven Deeks, a clinical investigator at the University of California, San Francisco (UCSF), predicts that "as we begin to under-

CREDITS: (LEFT TO RIGHT) TRIMERIS INC. AND F. HOFFMANN–LA ROCHE LTD.; SOURCES: COMPANIES, AMFAR, *TREATMENT NEWS*

stand the cause of toxicities and the ways to prevent them by using drugs more rationally, there's going to be a swing back toward treating earlier."

David Ho, director of the Aaron Diamond AIDS Research Center in New York City, says the pendulum has already swung too far toward deferring treatment. "I don't know where to draw the line, but I'm personally uncomfortable with 350," says Ho. "This is a deadly virus, and unless you control it, it will take its toll on the immune system in ways that are not so apparent in routine laboratory testing."

"We will never have the right answer" about when to start treatment, says Vella, because "it will be too difficult" to learn it from a controlled trial. But that has not stopped NIAID from trying. In January, NIAID launched a massive study to compare the benefits of "hit early, hit hard" versus "go slow." The controversial study, called Strategies for Management of Anti-Retroviral Therapies (SMART), plans to monitor up to 6000 people over the next 9 years. Researchers will assign participants randomly either to start HAART immediately or defer treatment until their CD4 count drops to 250. People in the go-slow group will stop taking medications whenever their CD4 count rises above 350.

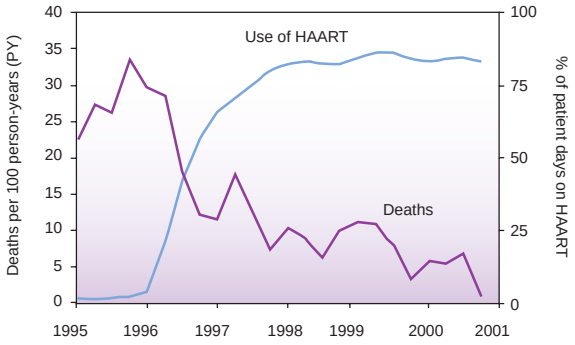
UCSD's Richman and others have strongly criticized the study, which NIAID estimates will cost up to $121 million to complete. The "design, statistics, and scientific rationale provide no hope of providing useful information," charges Richman. But AIDS activist Mark Harrington of the New York City–based Treatment Action Group sees SMART as precisely the type of study the federal government should support, because drugmakers have little incentive to do such a complicated comparison.

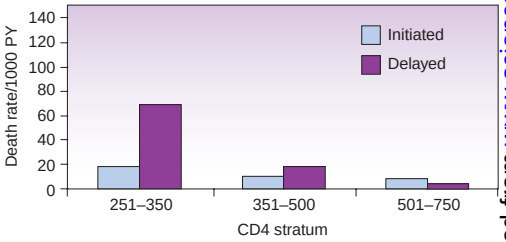
While researchers debate when best to start treatment, "the reality for many practitioners is that it's a moot point," says Richman. The sobering reason: HIV-infected people often seek care for the first time when they end up in an emergency room with an opportunistic infection of AIDS. Saag has reported that his patients have an average of 100 CD4s at their initial visit. "I'd love to get a patient with 400 CD4s and have to make that decision about whether to recommend treatment," says Saag.

HAART stopping

As the limits of HAART have become evident, AIDS researchers have begun to look into a novel strategy for making the treatment less onerous: carefully monitored drug holidays, known as structured treatment interruptions (STIs). If they work, STIs would not only provide some relief, but they would also cut the cost of treatment, which could have a major impact in developing countries. But the idea is controversial.

Bruce Walker, Eric Rosenberg, and their co-workers at Massachusetts General Hospital have shown that STIs have promise—at least for people recently infected with HIV (*Science*, 19 November 1999, p. 1470). The group followed 14 patients who went on HAART within weeks of learning they were infected. After an average of 18 months of treatment, they went off the drugs and restarted them whenever their viral loads spiked. The researchers found that over the 3 years they have been tracking these patients, the periods between halting treatment and viral spikes have lengthened. Moreover, they have found that the immune system seems to gain strength: When the virus returns, it boosts the production of killer cells that target cells infected by HIV.





Big bang. With the introduction of HAART, deaths have plummeted (*above*), but deciding when best to introduce HAART remains controversial. The study at right shows that those with 251 to 350 CD4s who started treatment clearly did better than those who deferred.

Because these results are from a small, uncontrolled study, Walker is careful not to claim that STI has worked. "These people are clearly getting boosted immunity, and they're clearly controlling better with subsequent interruptions," he says. "But there are no data that say STIs are clinically beneficial."

Although Walker has convinced many AIDS researchers that STI has promise for patients treated early in their infections, there's no such agreement on its use for chronically infected people. Outside the newly infected population, STIs are "sheer nonsense, absolute crap," scoffs the University of Amsterdam's Lange. In the 2 May issue of *Nature*, Lange notes, a study by Daniel Douek and Richard Koup of NIAID and their co-workers suggests that STI might actually be dangerous. The researchers show that HIV prefers to infect CD4 cells that have been trained to recognize HIV. When HIV returns during an STI, they reported, this increases production of HIV-specific CD4s, thus providing HIV with more potential targets.

The University of Geneva's Hirschel recently presented data from the largest study yet done of STIs in chronically infected people. At a gathering known as the Retrovirus Conference held in Seattle, Washington, in February, Hirschel reported on the Swiss-Spanish Intermittent Treatment Trial, which recruited 133 people on HAART to stop their drugs every 8 weeks for 2 weeks. At 1 year, only 67 people remained in the trial, because, for safety reasons, people could continue only if they suppressed virus each time they went back on treatment. Of those 67, only 23 suppressed their virus after completely stopping treatment. There was no evidence that the people who did better had boosted immunity from intermittent exposure to their HIV. "I wouldn't argue with those who say the results are not encouraging," says Hirschel.

One approach that might avoid some of the problems with STI in chronically infected people is to keep the drug withdrawal period short, so that HIV doesn't have a chance to spike. NIAID's Mark Dybul, working with Fauci, has studied a 7 day on/7 day off cycle in 10 people for 2 years, and, says Fauci, "they're doing very well." Clinical trials of the concept are now enrolling patients in the United States. A trial called Stacato is recruiting 600 patients in Switzerland, Thailand, and Australia to compare the week on/week off approach to continuous therapy and, separately, an STI strategy of stopping treatment each time CD4s rise above 350.

Disorganized resistance

The combination of new toxicities, "pill fatigue," and frequent changes in drug regimens is setting up conditions for the mother of all limitations: drug resistance.

If any of the existing anti-HIV drugs is used in a solo attempt to thwart HIV, the virus quickly gains the upper hand by creating a mutant strain that can dodge the attack. The success of HAART rests on a concerted multipoint attack that shuts down HIV replication so effectively that it reduces the likelihood that drug-resistant viral mutants will emerge. But if a patient doesn't follow the demanding regimen and concentrations of anti-HIV drugs in the blood taper off gradually, pressure on the virus is reduced, giving resistant strains a chance to

CREDITS: FRANK PALELLA/NORTHWESTERN UNIVERSITY/CDC

The High Cost of Poverty

A great awakening occurred 2 years ago in Durban, South Africa. Researchers, activists, caregivers, economists, and politicians at the XIII International AIDS Conference finally focused attention on an unfolding catastrophe: Tens of millions of HIV-infected people in poor countries would soon die because they had no hope of treatment. The response was swift. Drug companies slashed prices, the United Nations (U.N.) helped launch the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and an array of public and private groups began their own initiatives to shrink the treatment gap between rich and poor.

These efforts helped, no question about it; but formidable obstacles remain. Many governments have been slow to pony up money, and disputes have broken out over how to allocate the funds that do exist. Experts are concerned that improper use of medications will spawn widespread drug resistance. And some leaders worry that poor coordination and overblown expectations might undermine progress.

Global attention. Protesters at the international AIDS meeting in Durban 2 years ago helped raise awareness of the disaster looming over many poor countries.

Even people at the front of the battle acknowledge that few pills have made it to the people who need them most. "It's been nearly a total failure," says Peter Piot, director of the Joint United Nations Programme on HIV/AIDS (UNAIDS). The World Health Organization estimates that the drugs have reached only 230,000 of the 6 million residents of low- and middle-income countries who most desperately need them—and half of those who have benefited live in Brazil, where the government dispenses the medicine for free. In sub-Saharan Africa, where 70% of the world's 40 million HIV-infected people live, a mere 36,000 now receive the drugs, according to the latest estimates from Accelerating Access, an initiative spearheaded by UNAIDS that links pharmaceutical companies to the World Bank and other U.N. branches.

Still, there have been remarkable changes. Before the Durban meeting, the notion of offering the latest cocktails of drugs to people in developing countries was a nonstarter because treating one person costs $10,000 or more annually. Over the past 2 years, however, generic drugmakers and large pharmaceutical companies have offered deep discounts for developing countries, reducing the annual cost of treatment to as little as $300 to $400 per person. But even that's too expensive for most developing countries, Piot notes.

The Global Fund promises to help. "The hopes of many people ride on our success," says epidemiologist Richard Feachem, the fund's executive director designate. But the fund has money issues, too. When U.N. Secretary-General Kofi Annan first pushed to organize the fund in an April 2001 speech, he said it would need a "war chest" of $7 billion to $10 billion each year just to fight HIV/AIDS. The fund, which is supported mainly by donor nations and philanthropists, to date has raised only $2 billion.

Feachem, founder of the Institute for Global Health at the University of California, San Francisco (UCSF), says $2 billion is "more than enough to get started." He predicts that donors will provide more money in due time. "Large amounts of additional resources will become available when the Global Fund demonstrates results and impact on the ground," he predicts.

AIDS workers are joined in a fierce debate over how best to use those limited funds. In the 25 May issue of *The Lancet*, Elliot Marseille and colleagues at UCSF made a case for a simple, low-tech approach. They argue that prevention efforts such as promoting condom use and treating other sexually transmitted diseases are—based on a model they constructed—more than 28 times as cost-effective as even the steeply discounted drug therapies. "Over the short term, while we're way short of the $10 billion that's really needed, we should be putting the bulk of the funds in prevention," says Marseille, a public health specialist. "The basic reality is there's not enough to do both very well."

Piot groans when this study is mentioned: "I find the analysis extremely simplistic," he says. "We've got to do far more prevention, but we've got the emergency today. If we don't offer treatment to health staff, to the teachers, the whole of society is going to break down more rapidly."

Kevin De Cock, who directs the U.S. Centers for Disease Control and Prevention program in Kenya, cautions against setting unrealistic expectations for what AIDS therapies can accomplish in many poorer locales. "There's a real need to temper the discussion about all of the major diseases with the cold reality of technical and financial limitations," says De Cock, who focuses largely on HIV/AIDS, malaria, and TB. "For each of those three diseases there are real unknowns about long-term impact of interventions."

–J.C.

emerge and crowd out the "wild-type" virus.

At the Interscience Conference on Antimicrobial Agents and Chemotherapy held in Chicago, Illinois, last December, Richman and Sam Bozzette of UCSD and their co-workers presented data suggesting that variants have escaped to an alarming extent. The researchers found HIV strains resistant to one or more drugs in a staggering 78% of more than 1000 blood samples from people treated during the HAART era.

Equally disturbing, UCSD's Susan Little, a clinical investigator who collaborates with Richman, has found that resistant strains are being transmitted to new patients with increasing frequency. Little found that only 5.5% of newly infected people between 1995 and 1998 carried HIV with well-described drug-resistant mutations. But in samples taken from newly infected people in 1999 and 2000, the number had skyrocketed to 18.5%. UCSF's Robert Grant, James Kahn, and colleagues have found a similar trend. At the February retrovirus meeting, they reported that between 1996 and 2001, the proportion of newly infected people with resistant virus jumped from 16.7% to 27.6%. "San Francisco has always been the canary in the coal mine, and what happens here will happen everywhere else," cautions Kahn.

Frightening as these data are, many AIDS researchers hope that new and improved drugs—and a better understanding of how to use them—can cut the links between toxicities, adherence problems, and, ultimately, resistance (see sidebar on p. 2322). Yet no miracles are on the horizon. "We have made significant advances in HIV therapeutics, but we haven't cured anybody yet," says Saag. "This is still a disease that nobody wants to have." Success clearly has its limits.

–JON COHEN

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