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Special Series: Drug Resistance

Clinicians and researchers continue to work at staying a step ahead of HIV by developing new drugs and treatments that will be effective against drug-resistant virus. We continue our two-part series on drug resistance, which begins on p. 8, with a story on what some of those new drugs are and how they will give physicians more options in selecting treatment regimens.

Special Report: Medicaid and HIV

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Special Report: Medicaid and HIV

More states are expanding Medicaid reimbursement for poor HIV patients

HIV/AIDS advocates press for more coverage

Now that new technology and medications are making HIV a treatable, chronic disease, clinicians and AIDS service organizations are frustrated that many of the newly infected people have no insurance to cover such treatment.

Federal Medicaid legislation, recently sponsored by Sen. Robert Torricelli (D-NJ) and Rep. Nancy Pelosi (D-CA), would have allowed states to expand their Medicaid coverage to all low-income people who have HIV. However, the legislation died an early death in 1999.

The good news is that some states are beginning to pass their own legislation to expand Medicaid coverage and to request waivers from the federal law governing Medicaid access.

"There is no question we could do a better job of preventing the progression of HIV disease by providing treatment to uninsured people who don't have access to Medicaid," says **Robert Greenwald**, director of public policy and legal affairs for the AIDS Action Committee of Massachusetts in Boston.

The oldest and largest AIDS service organization in New England, the AIDS Action Committee of Massachusetts has successfully lobbied the state legislature to expand Medicaid access to people with HIV. Massachusetts, which passed the bill last

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New drugs on the way to combat mutating HIV

Research clearly shows that HIV mutates so rapidly that its drug-resistant strains have taken mere years to grow in strength. Although this may cause some clinicians and HIV patients to despair of ever finding a cure for the disease, it has served as a hearty challenge to pharmaceutical companies that are racing to bring the newest, most potent HIV drugs to market. 8

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While HIV clinicians increasingly are confronted with failing combination drug therapies, some existing drugs are effective against drug-resistant HIV. 10

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COMING IN FUTURE ISSUES

■ **Simpler doses:** Drug companies are working hard to make combination drugs in one pill and once-a-day dosing HIV medications

■ **Teaching adherence:** Massachusetts has an array of strategies designed to keep patients on their HIV medications

■ **CMV prophylaxis:** Research shows a decline in CMV viremia when HIV is suppressed, so prophylaxis may not be necessary

■ **Resistance cause:** One cause of HIV drug resistance appears to be a gene known as MRP4, research shows

■ **Rising drug costs:** A recent Veterans Affairs study documents the rising health care cost of treating HIV patients with antiretroviral drugs

Special Report: Medicaid and HIV

fall, is one of the first states to pass legislation aimed solely at expanding Medicaid coverage for HIV patients.

"The program will expand Medicaid coverage for people who have HIV but are not sick enough to be labeled 'disabled,'" says **Joe Carleo**, associate director for public policy with AIDS Action Committee of Massachusetts. "These are people in the early stages of HIV infection who have not become sick yet and are in need of access to treatment that will prevent them from getting sick."

Under the state's old program, Medicaid would cover people with HIV who had incomes of up to 133% of the federal poverty level, but only when they became ill enough to be diagnosed as having AIDS.

HIV patients stay sick without Medicaid

"It's a Catch-22 in the way the system works traditionally," Carleo says. "You didn't have access to health care until you became sick, while with the success of new HIV treatments, it makes more sense to keep people healthy."

Massachusetts will fund the program with \$10 million in tobacco settlement money during its first year, Carleo says. About 2,000 people are expected to be enrolled once it is under way.

The program eventually should become budget-neutral because by funding early treatment, the state may prevent many of the costs associated with AIDS, such as hospitalization, skilled nursing care, hospice care, and other treatment, Greenwald says.

Maine and other neighboring states have watched Massachusetts' new bill with interest and could soon be following in its footsteps, Greenwald says.

"I think they'll look at our model because the bottom line is that people are increasingly recognizing that we have a stated standard of care for HIV disease, published by the federal government, and their own Medicaid programs don't address giving people access to that standard," he explains.

Some states are seeking federal waivers or expansions of their current Medicaid waivers so they can provide coverage to people with HIV, says **Arnold Doyle**, MSW, director of HIV

treatment programs for The National Alliance of State and Territorial AIDS Directors, based in Washington, DC.

Some states, including Tennessee, Oregon, Florida, and New York, already have Medicaid programs that entitle low-income, HIV-positive people to receive health coverage for clinical care. (**See story on what some state Medicaid programs offer, p. 4.**)

The way the Medicaid law currently works, only people whose HIV has progressed to AIDS, defined by two opportunistic infections and a low CD4 cell count, may receive Medicaid coverage. Some states have expanded this coverage to any uninsured and low-income person who has HIV by relying on Medicaid waivers under section 1115a. (**See story on Medicaid waiver program, p. 5.**)

ADAP funds drugs, but more help needed

The federal AIDS Drug Assistance Program (ADAP) has been successful in providing antiretroviral treatments to many low-income people with HIV, but access varies from state to state. Also, ADAP money primarily covers drugs, and any clinical care for the uninsured is left to Medicaid or charitable institutions. (**See story on ADAP funding in AIDS Alert, September 1999, p. 97.**)

Medicaid's general requirement of covering only HIV-infected people who have a disability has left a void in medical coverage that some health care providers have been trying to fill by scraping together federal and private funding sources.

For example, the AIDS Healthcare Foundation of Los Angeles provides comprehensive health care to uninsured HIV-infected people in California through the use of government grants and private funding, says **Ged Kenslea**, the foundation's community relations director. The nonprofit, community-based provider has six clinics and a hospice program and provides skilled nursing care.

"We provide medical care to about 5,000 people in Southern California, regardless of their insurance status," Kenslea says.

The AIDS Healthcare Foundation has spent several years lobbying California legislators to pass a bill that would expand the state's Medicaid

program, called Medi-Cal, to cover asymptomatic HIV-positive people. The bill died in committee in September, but may be resurrected this year, Kenslea says.

"By way of comparison, back in the mid-to-late 1980s, President Reagan cut back on funding to inner-city health clinics, and it inadvertently led to the development of antiviral medicine-resistant tuberculosis."

Although ADAP funding covers most of the medically indigent individuals who need HIV antiretroviral drugs, these people still need adequate clinical care to help them adhere to their medication regimens and to prevent opportunistic infections, Kenslea says.

Kenslea points to the AIDS Healthcare Foundation's START program (Success Through Antiretroviral Treatment) as an example. The program provides training for people who have just started HIV antiretroviral therapy. Targeting people who are at risk for not complying with their drug regimen, the program provides them with beepers, pill boxes, psychosocial support, and other interventions that encourage them to stay on track. The \$2 million program, funded with a federal grant, is necessary to prevent the spread of drug-resistant virus, Kenslea says.

"By way of comparison, back in the mid-to-late 1980s, President Reagan cut back on funding to inner-city health clinics, and it inadvertently led to the development of antiviral medicine-resistant tuberculosis," he says. "What happened is that when clinics saw their budgets slashed, they cut back on compliance programs, such as directly observed therapy, and patients would stop taking the entire regimen of antibacterial TB drugs.

"So with a \$6 per month per patient cutback, you ended up with a superstrain of TB," he concludes, adding that this is one public health reason why Medicaid should provide clinical care and services to HIV-infected individuals. ■

Medicaid already covers some poor HIV patients

Here's how the programs work

While Medicaid typically does not cover care for all low-income people who have HIV, it does offer coverage in certain states, including Oregon, Florida, New York, and Tennessee. Also, Massachusetts soon will join them with expanded Medicaid coverage for HIV-infected people.

Here's a look at what those programs cover and how they work:

- **Florida.** Florida has a Medicaid demonstration project that pays for comprehensive health services for an estimated 12,500 Medicaid AIDS and HIV patients. The state's project also includes a new disease management program that will track continuity of care among about 7,500 Medicaid HIV/AIDS patients.

The state originally had proposed including only AIDS patients in the project, but ultimately decided to cover eligible people who have symptomatic HIV disease, says **Fred Goldstein**, president of Specialty Disease Management Services of Jacksonville, FL. Goldstein is in charge of implementing the disease management program. (**See story about Florida's new HIV disease management program, p. 6.**)

- **Massachusetts.** Massachusetts' Medicaid expansion, which was passed by the state legislature in November 1999, will provide complete health care coverage for all HIV-positive people who have incomes at or below 200% of the federal poverty level. This amounts to \$16,000 per year for a single individual and \$32,000 per year for a family of four. The coverage will include primary care services, diagnostic services, prescription drug coverage, mental health care, and substance abuse treatment.

An estimated 2,000 people will have immediate access to the new expanded program, says **Joe Carleo**, associate director for public policy with AIDS Action Committee of Massachusetts in Boston.

- **New York.** New York's Medicaid program is expansive, and people infected with HIV who qualify for the medically needy program have been receiving AIDS services since 1986, says **Ira Feldman**, MPS, deputy director for health care

for the AIDS Institute of the New York State Department of Health in Albany.

New York's program covers HIV-infected patients with incomes of up to 185% of poverty level, which is equal to \$15,448 annual income for a single person or \$20,802 per year for a household of two. An estimated 50,000 to 70,000 HIV-infected people receive Medicaid coverage, Feldman says.

"We have a full litany of services," he adds. "We have an extremely generous Medicaid package in the state."

The package includes an infrastructure of providers, outpatient services, and adherence programs funded through the state's Medicaid program.

- **Oregon.** Oregon was one of the first states to start a Medicaid waiver program that expands health coverage to all low income residents. Called the Oregon Health Plan (OHP), the program, implemented in 1994, expands Medicaid coverage to all Oregonians living in households below 100% of the federal poverty level, including people who are infected with HIV.

"Oregon Health Plan is a truly innovative approach, one that has accomplished its goal of increasing access to health care," says **Mark Loveless**, MD, director of the HIV/STD/TB programs of the Oregon Health Division in Portland.

Unfortunately, the program also has been threatened by financial problems, Loveless says. "Because it's been so successful and because people have accessed it and benefited from its services, it currently is struggling financially."

Data show expanded Medicaid access works

However, state elected officials know how well the program has worked in keeping people healthy, and HIV statistics are the most telling data offering proof, he adds.

"The outcomes that we've seen in Oregon have been a dramatic decrease in death rates and a dramatic decrease in AIDS cases since the program began," Loveless says.

One interesting feature of OHP is its focus on prioritizing various diseases and medical conditions. When funding is cut, the plan doesn't cut potential enrollees through a change in admission criteria. Instead, the plan cuts services according to the prioritized list.

"This plan says, if we can't afford to take care of all the people who are eligible for all the conditions

What you need to know about Medicaid waivers

Medicaid health coverage typically is for families eligible for government assistance through the former Aid for Families with Dependent Children (AFDC) program; pregnant women; or permanently disabled people.

The Personal Responsibility and Work Opportunities Act of 1996 replaced AFDC with a block grant program called Temporary Assistance for Needy Families (TANF). Families eligible for TANF are eligible for Medicaid.

About 20 states either have or are in the process of implementing section 1115a Medicaid waivers that provide more flexible Medicaid eligibility requirements. Some states permit people who meet income requirements but are not

listed, then we will move the line up so we're reducing the number of conditions and diagnoses that are covered," Loveless explains. "Explicit rationing of care is based on the prioritized list of medical conditions rather than rationing care by access barriers."

This has enabled HIV patients to continue to receive the best available treatment and care throughout funding crises. This is because HIV treatment is a relatively high priority on the list.

"Originally, HIV was placed on the list very low because it was viewed as an incurable disease with only palliative care," Loveless says. "And we advocated strongly that antiretroviral therapy, which was in its infancy at the time, was likely to improve and change the natural history of the disease."

HIV disease is listed at 172 on the priority list, which currently is funded partway through the 500s. The first priority list, for example, has conditions such as severe/moderate head injury and insulin-dependent diabetes mellitus as numbers one and two on the priority list. At the other end of the spectrum, dental services for basic prosthetics is listed at 537 and allergic rhinitis and conjunctivitis is listed at 630.

- **Tennessee.** Tennessee was one of the first states to implement a Medicaid waiver program. The state's program, called TennCare, provides Medicaid coverage to anyone who is uninsured

considered disabled by AIDS or other diseases to receive Medicaid coverage. Massachusetts is the first state to request a waiver solely for the inclusion of people with HIV.

These waivers basically permit states to be more flexible in providing Medicaid benefits through the implementation of a research and demonstration project. Most of these projects involve providing Medicaid through managed care plans.

The Baltimore-based Health Care Financing Administration adopted rules in 1994 that made it easier for states to obtain 1115a Medicaid waivers. Arizona has had a waiver since 1982, but all the others were implemented in the mid-to-late 1990s.

Some states, like Tennessee, have expanded Medicaid coverage to all people who are uninsured through the 1115a waiver. ■

and has an income of 300% or less of the federal poverty level. The service is entirely free to people who have 100% or less of the federal poverty level, and for those who have between 100% and 300% there is a small premium charge, says **Drema Mace**, director of AIDS Support Services of the Tennessee Department of Health in Nashville.

The state has medical care managers in each of 18 "centers for excellence" across the state. Medical care managers are the point of entry for TennCare enrollees. The managers help HIV patients receive medical services, antiretroviral drugs, and any other health services they might need.

"The medical care manager enters that client into the system, and on the same day they can walk to the pharmacy within that building and pick up their drugs," Mace says. "In the state of Tennessee, if someone needs something related to their HIV care, there's nothing they can't get."

About 2,400 HIV-infected people have been enrolled under TennCare.

State officials give the TennCare program some of the credit for the state's sharp decline in AIDS-related deaths. Those deaths dropped by 23% from 1995 to 1996, by 30% from 1996 to 1997, and by 21% from 1997 to 1998, Mace says.

There have been funding problems, however. "The legislature has appropriated extra dollars to carry it through this year, and they're working on a plan for how to continue the services," she says. ■

Florida program offers new method of HIV care

Nurses will track HIV patients and their health care

The state of Florida has launched a novel statewide disease management program in order to provide patients with a better continuum of care and make the state's Medicaid funding for HIV/AIDS more cost-effective.

The program, funded with about \$9 million from the state, will track health care services for about 7,500 Floridians who have HIV and who qualify for the state's Medicaid program. Called Positive Healthcare/Florida, the program was created by the AIDS Healthcare Foundation of Los Angeles, which has a contract with the state's Agency for Health Care Administration.

AIDS Healthcare Foundation is a nonprofit, community-based provider of AIDS care in California. The organization has the first and largest Medicaid capitation demonstration project for AIDS. The foundation has established a managed care type of health services model for Florida.

HIV-infected enrollees receive health care coverage from the state's Medicaid program. The program's goal is to keep HIV patients healthier with fewer hospital admissions or emergency room visits.

"We're applying a level of scrutiny and different interventions to HIV care under Medicaid, and we're infusing them into the model to make them more streamlined for people with AIDS," says **Peter Reis**, director of business development at AIDS Healthcare Foundation.

Florida program provides doctor education

The program also entails holding educational forums for providers to bring them up to date on the latest medical advances in HIV treatment.

The educational component is especially important because 40% of the HIV patients in Florida are receiving their primary care from providers who have fewer than 20 HIV patients, Reis says. "Those providers really need our help."

"We have our own HIV protocols that are indexed, and we make those available to providers," Reis adds. "A lot of physicians don't have

the time or experience to navigate dense treatment guidelines."

After several years, the program will provide Florida officials with outcomes data, showing how well patients have done with maintaining their disease and how much money it has cost the state to pay for their health care services, says **Fred Goldstein**, president of Specialty Disease Management Services in Jacksonville, FL. Goldstein is in charge of implementing the program.

Here's how the program works:

- **Enrolling clients.** All Florida Medicaid-eligible HIV-infected patients are enrolled unless they choose not to be involved. The program has an opt-out model in which people receive a letter from the state telling them they're eligible for Positive Healthcare/Florida, Goldstein says.

To protect clients' privacy, the letters do not specifically refer to HIV or AIDS. Instead, the letters mention all the disease management programs the state has. People have 30 days in which to choose not to be in the program. They can disenroll by calling a state district office.

Locating clients is sometimes a challenge

One of the program's earliest challenges was locating the clients. In the first month, they sent out 850 letters and enrolled 723 clients. Few people opted out of the program, but some could not be enrolled because the letters were returned with no forwarding addresses, Goldstein explains.

- **Initial assessments.** The program, when fully implemented later this year, will have about 70 registered nurses and 10 support employees.

Nurses meet with each client to introduce the program and cover a detailed, six-page clinical assessment tool that helps them determine the status of the client and how well the client understands HIV disease, and helps them identify specific client needs. They also ask patients for the names of their treating physicians, which they later match with state information on patients' listed primary care physicians. And they identify the client's case manager and AIDS service organization.

"They get clients to sign medical information releases, and they determine which drugs they're on, when they were infected, what their T-cell count is, what's their viral load, and whether they

use drugs or alcohol," Goldstein adds. "There is no actual hands-on clinical care."

One of the biggest obstacles the program has faced so far involves setting up that initial consultation with clients, says **Judy White**, RN, director of health operations for Specialty Disease Management Services. Patients sometimes didn't have telephones and were difficult to reach.

- **Assigning risk.** Using the patient's CD4 cell count data, nurses assign patients to a risk category of low (CD4 cell count of 500 or above); medium (cell count between 200 and 500), and high (cell count of below 200). Those in the low-risk category are contacted once a month; clients in the medium-risk category are contacted at least twice a month; and people in the high-risk category are contacted at least weekly, White says.

- **Medical record review.** Staff use the patient releases to obtain clients' medical records to see what type of care has been provided. They pull out information on patients' CD4 cell counts, types of antiretroviral medications prescribed, and whether patients were receiving prophylaxis drugs for certain opportunistic infections.

Then staff chart this information to identify trends among the entire group of clinicians serving the Medicaid HIV patients and to give individual physicians a look at how they are doing when compared to national and state data, Goldstein says.

Medical records prove difficult to obtain

The program initially had some difficulty in obtaining medical record information from clinicians and AIDS service organizations, White says.

"With any insurance coverage, when you ask for payment for a service, you give permission to that insurer to share information within a network, and we're considered an agent of the state in providing this service," she explains. "We've even gone a step further and said, 'We'll get a second permission form from the patient to submit to providers.'"

But even with all of these precautions, some organizations and clinicians were unwilling to release medical records until the program had the medical release forms rewritten in a way that met their own guidelines, she adds.

- **Meeting with physicians.** Nurses meet with physicians or their staff to explain how the

program works and what educational services are available. They also show doctors how their HIV treatment compares with state and national treatment guidelines and statistics.

Disease management officials have discovered that Florida's health care services for HIV patients vary dramatically.

"You have sophisticated urban centers and state-of-the-art medical centers, and then you have rural backwater counties that may have physicians with one or two HIV patients in their practice," says **Ged Kenslea**, community relations director for AIDS Healthcare Foundation.

So physician education is a top priority of the program.

Experts educate physicians at seminars

For example, the program held a seminar in the fall at a private foundation's Florida retreat called White Oaks Plantation, which is where President Clinton vacationed last year. The retreat, which is on an endangered species preserve, is not open to the public, and it is a very desirable place to visit, Goldstein says.

Physicians involved with the disease management program were invited to the seminar to hear HIV experts talk about the latest drugs and treatment.

The program also will soon have a variety of HIV educational materials, including a treatment magazine that has an upscale look and design. The magazine's editorial board will include 50 to 60 HIV scientists, and the magazine's focus will be on minorities with HIV. Called *Thrive*, the magazine is set to be launched in March, Reis says.

- **Cutting costs.** Nurses will stay in close contact with clinicians to discuss outcomes and more efficient ways to provide care, Reis says.

For example, some physicians may be unaware of how often their HIV patients are admitted to the hospital. If they aren't contacted while the patient is admitted, then they can't supervise the inpatient stay to make sure the hospital is motivated to discharge the patient in a reasonable amount of time, Reis explains.

"We're interested from a patient care perspective in taking a look at some of these issues and communicating information to physicians in an ongoing dialogue," he adds. ■

New weapons on the way in battle against mutating HIV

Expect more powerful meds in the next five years

Research clearly shows that HIV is a resilient and crafty virus that can rapidly adapt to its surroundings and begin to rebound against some of the most potent antiretroviral medications on the market.

While it has taken decades for some viruses to develop drug-resistant strains, HIV mutates so rapidly that its drug-resistant strains have taken mere years to grow in strength. Although this may cause some clinicians and HIV patients

to despair of ever finding a cure for the disease, it has served as a hearty challenge to pharmaceutical companies that are racing to

bring the newest, most potent HIV drugs to market.

The next generation of drugs will have been tested for the ability to defeat drug-resistant viral strains, including viruses that have found ways to get around the major protease inhibitors.

"There definitely are several promising drugs in development that have been targeted against resistant viruses," says **Richard D'Aquila**, MD, associate professor of medicine at the Harvard Medical School and Massachusetts General Hospital in Charlestown, MA.

"Until now, HIV drug resistance has been seen as a more limited problem, and therefore there's a more limited market for new drugs," D'Aquila notes. "Now we're beginning to realize these viruses are increasingly going to be a problem, and many companies are focusing more attention on developing drugs specifically against resistant viruses."

Pharmaceutical companies are taking note. For instance, companies like Glaxo Wellcome Inc. of Research Triangle Park, NC, are devoting a great deal of research and resources toward developing drugs that are effective against drug-resistant HIV strains.

"We were studying resistance to AZT from practically the time when it went out on the market, and maybe even before that," says **Eric Furfine**, PhD, senior research investigator of Glaxo Wellcome.

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"If you look at HIV drugs' failure rate over two years' time, roughly 50% of patients taking a triple-drug regimen, even naive patients, fail therapy for whatever reason," Furfine says. "Usually, it's just one of the three drugs that fails, but it's enough to permit the virus to rebound."

Besides the fact that new drugs will be needed to keep HIV patients healthy and living longer, new technologies also are pushing drug resistance research forward. Now there are better methods for detecting resistant virus strains. Both genotyping and phenotyping may soon become standard tests for clinicians who want to make sure they select the most effective drug combination for HIV patients. AIDS researchers have discovered that nearly 28% of people who are newly infected with HIV may have become infected with a virus that is resistant to one or more antiretroviral drugs. (See **AIDS Alert**, December 1999, p. 133.)

These are among the most exciting times with regards to HIV research, partly because of the success of protease inhibitors and the current wide array of drugs available for treating HIV, says **Daniel Kuritzkes**, MD, associate professor of medicine and microbiology at the Division of Infectious Disease at the University of Colorado Health Sciences Center in Denver.

"When we saw the first wave of patients failing on HIV drugs, there was a lot of concern because we had nothing else available," Kuritzkes says. "But now there are 20 drugs currently in development from different classes, including several novel classes of antivirals."

New drugs target resistant strains

And most of these new drugs show potential for having activity against some of the drug-resistant HIV strains, he adds.

In fact, most drugs under development now are being designed to work against drug-resistant virus. These include new nucleoside reverse transcriptase inhibitors, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors.

"In addition, there are a whole series of virus entry or virus fusion inhibitors that are in earlier stages of development but are showing promise," Kuritzkes says. "Then there are the integrase inhibitors that are finally making their way to early clinical trials. So there's a lot of reason to be optimistic that we're seeing considerable effort at stopping resistant mutations."

While researchers stage a stealth battle to undermine drug-resistant virus and HIV's mutation rate, clinicians can help from the war's front lines. Their challenge is to use new and existing drugs correctly by combining them for greater potency, rather than simply adding them on top of failing regimens, Kuritzkes says.

"We'll always be in a race with the virus, much as we are with standard antibiotics," he notes. "But this is a much faster-paced race because of the speed with which HIV replicates and generates mutation."

HIV is probably the most complex chemotherapeutic challenge in medicine, says **Bruce McCreedy**, PhD, vice president for clinical virology and diagnostics at Triangle Pharmaceuticals in Durham, NC.

"We learned very early on, in the late 1950s, that the way to treat TB is you hit it early with good potent combinations up front, and then you can get rid of the organism," McCreedy says. "Whereas with HIV, even a solid good potent combination is not able to eradicate the virus."

Medications can suppress, not cure

Medications will only suppress the virus because it hides in places in the body that the drugs have trouble reaching.

This means the best treatment solution is to suppress the virus for as long as possible through use of very potent medications. These drugs' potency will fade with time in any particular patient, but pharmaceutical companies are trying hard to stay ahead of resistant strains by creating new and different medications. (**See story on new and existing drugs, p. 10.**)

"I think we all would agree in the field that we need some drugs that work against resistant viruses, as opposed to some drugs that look great in naive patients," McCreedy says.

Clinicians can stay ahead of this problem through careful monitoring of the patient's viral load and altering drug combinations when a particular medication begins to fail.

With increasing numbers of HIV antiretrovirals to choose from and more than 1,800 combination possibilities, clinicians may find it difficult to select the most effective combination that can be tolerated by patients, McCreedy says.

"The second challenge is: How do you plan therapies for patients who begin to fail on a first regimen or don't tolerate it?" he adds. "So

the challenge is not only to find molecules that are active against resistant viruses; the challenge is how to put a combination of drugs together that may allow options after the first failure."

When HIV drugs are used correctly, they are potent and will suppress the virus. This means patients need to be closely monitored and then switched to a new fully active set of drugs as soon as the first combination begins to fail, D'Aquila says.

Physicians who follow this pattern will have patients who do much better on antiretrovirals, and they'll avoid major problems with resistance, he adds.

Soon, clinicians routinely will use resistance tests to determine which drugs are failing in a combination therapy.

Previously, if a patient was on a three-drug regimen and the clinician saw viral replication return, then he or she would assume that none of the drugs had any activity against HIV, says **Robert Schooley**, MD, head of the infectious disease division of the University of Colorado in Denver.

"We now know that if you follow a patient's viral load closely, the drugs fail sequentially, and that it might well be the case that in a three-drug regimen you have resistance only to one of the drugs," Schooley says. "And that means the other two drugs can still be used in the future in treating that patient."

Being able to salvage drugs will be very important as patients live longer with the disease, he adds.

Clinicians also play an important role in educating patients about HIV prevention and medication adherence.

Researchers say most drug failures occur because patients did not adhere to their combination therapies. When the virus has even short-term breaks from antiretroviral drugs, it can begin to replicate and mutate into strains that are no longer affected by those drugs.

"When you have previously HIV drug-naive patients come into treatment and receive a drug regimen they can tolerate, then I would say 80% to 90% of these people are able to have their virus suppressed," Kuritzkes says. "The failures are in general caused by problems with medications where people have difficulty adhering to their medication regimen." ■

Special Series: Drug Resistance

Some existing drugs work on resistant HIV

Not all protease inhibitors are equal

HIV clinicians increasingly are confronted with failing combination drug therapies. Patients do well for weeks with the virus remaining suppressed, and then suddenly their viral load begins to rise. So physicians search through the current arsenal of medications to find combinations that will again fully suppress HIV.

Pharmaceutical companies are on the brink of offering clinicians a slew of new pharmacological weapons that are designed specifically to defeat drug-resistant HIV.

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shown to be effective against drug-resistant virus:

- **Amprenavir:** Currently available, amprenavir has shown a smaller degree of susceptibility to protease inhibitor (PI)-resistant virus than four other PIs.

In vitro data presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in September in San Francisco, showed that 22 (24%) of 92 virus samples isolated and cultured from patients had eightfold resistance to amprenavir. Nearly all of the patients had been previously treated with at least one PI, and the median number of PIs they had taken was three.

By comparison, the study found that 43% of the isolates showed a similar level of resistance to indinavir; 63% were resistant to ritonavir; 61% were resistant to nelfinavir; and 53% had resistance to saquinavir.

"We like to think [amprenavir] will have benefit in a second-line therapy, and maybe even more benefit if you boost its levels by adding ritonavir as well," says **Eric Furfine**, PhD, senior research investigator with Glaxo Wellcome in Research Triangle Park, NC.

Amprenavir, which was developed by Vertex Pharmaceuticals in Cambridge, MA, is manufactured by Glaxo Wellcome. The drug was approved by the Food and Drug Administration (FDA) in mid-1999.

Its most common side effects are an early onset of nausea, diarrhea, vomiting, rash, and perioral paresthesia. On rare occasions, the drug also has been associated with severe and life-threatening drug interactions, including Stevens-Johnson syndrome, spontaneous bleeding in patients with hemophilia A and B.

- **DAPD:** This is a dioxolane purine nucleoside reverse transcriptase inhibitor (NRTI) that has shown in vitro activity against drug-resistant strains of HIV, according to research presented at ICAAC.

A new drug, DAPD is a different-looking molecule chemically and structurally from other NRTIs, says **Bruce McCreedy**, PhD, vice president for clinical virology and diagnostics for Triangle Pharmaceuticals in Durham, NC.

Triangle Pharmaceuticals is developing DAPD, which currently is in the preclinical phase of development and probably is a couple of years away from FDA approval.

"DAPD has shown very good activity against a variety of HIV-resistant isolates," McCreedy says. "Because of its different structure, it does have in vitro activity in the lab against resistant HIV, especially against HIV that has resistance to AZT and 3TC."

This means DAPD could be a potent drug for patients who have failed combination therapies of AZT and 3TC. However, the drug will need to undergo extensive clinical research before this can be proven, McCreedy says.

"We've done extensive preclinical work to characterize its in vitro resistance profile," he explains. "We've been doing the dose range-finding trials to determine what the optimum dose of DAPD might be in HIV-infected patients, including patients who harbor resistant forms of HIV," he adds.

DAPD is a guanine derivative, as is abacavir.

- **Lamivudine:** A commonly prescribed NRTI, lamivudine shows promise of having antiviral activity in patients who have a mutated HIV strain that is resistant to other NRTIs.

Five clinical trials, involving patients receiving initial treatment with an NRTI combination of either lamivudine plus zidovudine or lamivudine plus stavudine, showed that 92% of patients exhibited the M184V mutation, which is associated with a reduction in susceptibility to lamivudine. However, although the mutation emerged, patients continued to maintain low HIV RNA levels after a third NRTI or a PI was added to the lamivudine-containing combination, according to research presented at the Third International

Workshop on HIV Drug Resistance and Treatment Strategies held in June in San Diego.

Lamivudine, developed by BioChem Pharma of Laval, Quebec, and manufactured by Glaxo Wellcome, is generally well tolerated. Its most commonly reported side effects include headache, nausea, malaise, fatigue, nasal congestion, runny nose, and diarrhea. In some cases there have been lactic acidosis and severe hepatomegaly with steatosis with the use of nucleoside analogues alone or in combinations that include lamivudine.

- **Tipranavir:** The first of a new class of non-peptidic protease inhibitors, tipranavir is active against HIV strains that are highly resistant to four commonly used protease inhibitors: indinavir, ritonavir, nelfinavir, and saquinavir.

Developed by Pharmacia & Upjohn of Peapack, NJ, tipranavir was effective against 90% or 96 out of 107 strains of HIV that were resistant to PIs, according to research presented at the Third International Workshop on HIV Drug Resistance and Treatment Strategies.

Researchers speculate that tipranavir is immune to these PI-resistant strains because it is not a peptidic PI, as are the other protease inhibitors. Tipranavir binds in a flexible manner to the protease-active site.¹ Tipranavir studies also have shown that the drug is well tolerated, with the main side effects related to gastrointestinal problems, including diarrhea. The drug is in Phase II clinical studies.

In addition, Glaxo Wellcome is working on a second-generation protease inhibitor program that is focused on treating resistance, Furfine says.

The program's basic strategy is to make molecules that are so potent against HIV that even if there is some resistance, they still will have enough potency to be effective, he explains. PIs already are the most potent class of HIV drugs.

Although the company is years away from clinical trials, the laboratory work so far shows that researchers can synthesize molecules that have significantly improved activity against wild-type virus and retain significant activity against viruses that are highly cross-resistant to the currently available PIs. Wild-type virus is a strain of virus most similar to what an HIV patient would have before taking any antiretroviral drugs.

The company's also developing new non-nucleoside reverse transcriptase inhibitors and

Special Series: Drug Resistance

CE objectives

After reading this issue of *AIDS Alert*, CE participants should be able to:

- identify the particular clinical, legal, or scientific issues relates to AIDS patient care;
- describe how those issues affect nurses, physicians, hospitals, clinics, or the health care industry in general;
- cite practical solutions to the problems associated with those issues, based on overall expert guidelines from the Centers for Disease Control and Prevention or other authorities and/or based on independent recommendations from specific clinicians at individual institutions. ■

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Special offer for alternative medicine nursing newsletter

American Health Consultants, publisher of *AIDS Alert* and *Alternative Medicine Alert*, is pleased to announce a new monthly publication for nurses on alternative medicine and holistic nursing. Beginning in January 2000, each issue will contain review articles of specific alternative therapies and modalities; abstract and commentary from current medical and nursing journal articles; and columns on controversies in holistic nursing, applying therapies to clinical nursing practice, and legal and ethical issues surrounding holistic nursing and alternative medicine.

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NRTIs, again with the focus on improving potency, Furfine says.

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AIDS GUIDE

For

Health Care Workers®

NIOSH releases guidelines on preventing needlesticks

HIV transmission rate via needlestick injuries is 0.3%, so risk to health care workers is low

More than 8 million health care workers in the United States run the risk of being infected with HIV or hepatitis through needlestick injuries. Each year, an estimated 600,000 to 800,000 such injuries occur annually. Federal statistics estimate that workers experience needlestick injuries at the rate of about 30 per 100 hospital beds per year.

However, the risk of actually becoming infected with HIV is low. Health care workers who are exposed to HIV-infected blood through a needlestick injury rarely become infected with the virus, according to studies and government statistics.

A recent analysis of 20 studies, involving 6,498 exposures to HIV-infected blood, showed that a total of 21 infections occurred, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. This made an average transmission rate of 0.3% per injury.

Other research has shown that health care workers increase their risk of contracting HIV when they're exposed to a larger quantity of blood from the patient, caused by a bloody device, a procedure of placing a needle in a patient's vein or artery, or a deep injury.

The CDC reports that between 1985 and June 1999, there were a total of 55 documented cases and 136 possible cases of occupational HIV transmission to U.S. health care workers. The documented cases were of health care workers who had documented HIV after occupational exposure. The possible cases were of health care workers who had no identifiable behavioral or transfusion risks, who reported having percutaneous or mucocutaneous occupational exposures to blood or body fluids or laboratory solutions, and who had no documented HIV seroconversion resulting from a specific occupational exposure.

Most of the workers involved in the documented cases were nurses or laboratory technicians, and 89% of the transmissions were caused by percutaneous injuries. Furthermore, of the 49 needlestick injuries, 44 involved hollow-bore needles used to collect blood or insert an IV catheter.

The CDC statistics also show that about 38% of percutaneous injuries occur during the use of a needle, and 42% occur after use and before disposal. Other risk factors are caused by certain work practices, such as recapping, transferring body fluid between containers, and failing to dispose properly of used needles in puncture-resistant sharps containers.

The National Institute for Occupational Safety and Health (NIOSH) recently released needlestick prevention guidelines for health care workers. According to NIOSH, needlestick injuries, including injuries caused by hypodermic needles,

blood collection needles, intravenous stylets, and needles used as part of IV delivery systems can cause a number of serious and potentially fatal infections with HIV, hepatitis B, and hepatitis C.

Here are some of the new NIOSH prevention guidelines:

- **Use safer devices.** Health care employers should eliminate the use of needles when it's possible to use safe and effective alternatives. Also, they should implement the use of devices with safety features.

- **Establish needlestick program.** Employers also should implement a needlestick safety program that incorporates these features:

- Analyzes needlestick and other sharps-related injuries within the workplace to identify hazards and injury trends.

- Sets strategies for prevention by examining local and national information about risk factors for needlestick injuries.

- Ensures that health care workers are properly trained in the safe use and disposal of needles.

- Modifies work practices that pose a needlestick injury hazard to make them safer.

- Promotes safety awareness among workers.

- Establishes procedures that encourage the reporting and timely follow-up of all needlestick and sharps-related injuries.

- Evaluates the effectiveness of prevention efforts and provides feedback on performance.

- **Promote safety among workers.** Health care workers also should take certain steps to protect themselves and their coworkers from injury. These include:

- Avoid the use of needles where safe alternatives are available.

- Help employers select devices with safety features.

- Use devices with safety features.

- Avoid recapping needles.

- Plan for safe handling and disposal before beginning a procedure involving needles.

- Dispose of used needles promptly in appropriate sharps disposal containers.

- Report all needlestick and other sharps-related injuries promptly to ensure they will receive follow-up care.

- Tell their employers about any hazards from needles in the workplace.

- Participate in bloodborne pathogen training and follow recommended infection prevention practices, including hepatitis B vaccination.

- **Distribute the NIOSH Alert.** NIOSH's new guidelines, called "Preventing Needlestick Injuries in Health Care Settings," provides detailed information about prevention techniques and statistics regarding health care worker needlestick injuries.

The document is available from: NIOSH — Publications Dissemination, 4676 Columbia Parkway, Cincinnati, OH 45226-1998. Telephone: (800) 35-NIOSH. Fax: (513) 533-8573. E-mail: pubstaft@cdc.gov. Web site: www.cdc.gov/niosh. Request document: DHHS (NIOSH) Publication 2000-108.

- **Follow OSHA standards.** The U.S. Occupational Safety and Health Administration (OSHA) has standards regarding bloodborne pathogens that require the following:

- A written exposure control plan designed to eliminate or minimize worker exposure to bloodborne pathogens.

- Compliance with universal precautions (an infection control principle that treats all human blood and other potentially infectious materials as infectious).

- Engineering controls and work practices to eliminate or minimize worker exposure.

- Personal protective equipment (if engineering controls and work practices do not eliminate occupational exposures).

- Prohibition of bending, recapping, or removing contaminated needles and other sharps unless such an act is required by a specific procedure or has no feasible alternative.

- Prohibition of shearing or breaking contaminated needles (OSHA defines contaminated as the presence or the reasonably anticipated presence of blood or other potentially infectious materials on an item or surface).

- Free hepatitis B vaccinations offered to workers with occupational exposure to bloodborne pathogens.

- Worker training in appropriate engineering controls and work practices.

- Postexposure evaluation and follow-up, including post-exposure prophylaxis when appropriate. ■

AIDS Guide for Health Care Workers is written especially for the person working in the health care setting. It explains important issues concerning AIDS in a thorough, yet easy-to-understand style.

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