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ADAP funding and Ryan White Act renewal is delayed by hurricane

HIV patients from disaster areas spread across U.S.

The AIDS Drug Assistance Program (ADAP) already was in trouble financially, particularly in Southeastern states, when Hurricane Katrina wreaked devastation in Louisiana, Mississippi, and Alabama, making matters worse.

"The current funding outlook is very, very bad," says **Bill Arnold**, director of the National ADAP Working Group and executive director of the Title II Community AIDS National Network, both of Washington, DC.

"It's going to be a rough month, two, three, four, five," Arnold adds.

HIV/AIDS funding is as bad as it can be, says **Gary Rose**, public policy director for the Title II Community AIDS Network.

"People think everything is going to be solved with the reauthorization of the Ryan White Care Act," Rose says. "But the way the care act is structured, the problem is with appropriations."

Congress has been slow to do any work on the Ryan White Care Act, so AIDS groups expect a much later reauthorization than is desirable, says **Murray C. Penner**, deputy executive director of domestic programs for the National Alliance of State and Territorial AIDS Directors (NASTAD) of Washington, DC.

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assistant professor in the department of community health at School of Medicine, Wright State University in Dayton, OH. Rapp also is with the Center for Interventions, Treatment and Addictions Research (CITAR) in Dayton. "Case management seemed to help keep people in treatment, and longer treatment led to better outcomes," Rapp says. "So that's our rallying cry for case management." With encouragement from the Centers for Disease Control and Prevention (CDC) of Atlanta, GA, Rapp and co-investigators developed a model of strength-based case management that was studied in the antiretroviral treatment and access study (ARTAS), which ran from 2003 to 2004. 113

Adherence strategies

Researchers study use of the 'MATI' for improving AIDS drug adherence

Investigators have found that an adherence tool that addresses multiple factors contributing to adherence difficulties can assist with better adherence. The Medication Adherence Training Intervention (MATI) is a newly-invented tool that prepares patients for adherence by incorporating medication adherence education, the patient's history and medication experiences, with motivation and empowerment interventions, says Shvawn McPherson Baker, PharmD, MPH, a research associate in the division of hepatology at the University of Miami School of Medicine in Miami, FL. "We developed the MATI along the context of clinical pharmacy, clinical medication, and clinical psychology, interfacing the three of them to come up with an approach to patient care," Baker says. "We looked at how to best incorporate the patient's abilities with our abilities." One aspect to the MATI that's important is how it is designed to be a nonjudgmental tool that doesn't admonish patients for their poor adherence habits, Baker notes. "The approach is ' Let's take off the white coat and work on this together,'" Baker says. "Let's see if there's a readiness for medication adherence and provide education on that.. 115

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Editorial Questions

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"What we need is a bill in the House or Senate to respond to, and we don't have anything yet," Penner notes as of mid-September. "We don't have a signal as to which direction things are going."

While some of the disproportionate problems experienced by Southeastern states could be alleviated with some changes to the act, but without additional funding the changes only will make things worse for other areas of the country, Rose says.

Among the states with major ADAP funding problems and ADAP waiting lists are North Carolina, Alabama, Kentucky, and Arkansas, Rose says.

"Also, Tennessee will be a mess because they're closing up TennCare, so a large number of those people will flood into ADAP," Rose adds.

In a revised Ryan White Care Act, the pie of funding will shift from Title I cities to the states that have no Title I cities, but have HIV problems, and this means San Francisco would be the hardest hit, unless funding is increased, Rose says.

"We've been forced into a position that in order to keep people alive with drugs we have to scavenge money from other programs that are doing people good," Rose says. "This is because we're not going to get enough money to do what needs to be done."

President George W. Bush had decided not to renew the $20 million presidential AIDS initiative, which was bringing antiretroviral drugs to hundreds of people who otherwise would lack access to help, Arnold says.

"Those people will have to be phased back into local ADAPs, which is problematic because they already have people on waiting lists," Arnold says.

North Carolina's ADAP has relied on the presidential initiative to support HIV medication for 792 people, says **Steve Sherman**, AIDS policy/ADAP coordinator for the North Carolina Department of Health & Human Services in Raleigh, NC.

"We've been advised that it's likely those dollars will run out sometime later this fall," Sherman says. "The hope is that most or all of those clients will be able to be transferred back into the state program."

However, the North Carolina ADAP already has 220 people on its HIV drugs waiting list, and the state's General Assembly has made available an additional $1 million, which won't go far enough in providing drugs to all who need them, Sherman says.

Meantime, North Carolina is one of the more than 25 states receiving the first wave of transplants from the areas devastated by Hurricane Katrina, and some of these people likely will be HIV infected and need someone to provide their medication.

Within 10 days of the hurricane's strike, the Texas ADAP had provided antiretroviral drugs to 25 HIV-infected people who had fled the Gulf Coast, says **Dwayne Haught**, ADAP manager at the Texas Department of Health in Austin, TX.

"From the first day of the evacuation, I worked out a deal with the drug companies to provide product reimbursement for eight weeks, and after that I'm hoping the Federal Emergency Management Association (FEMA) or the American Red Cross will have systems in place for HIV clients," Haught says.

The Texas state legislature committed $15.2 million in additional ADAP funding for the fiscal year 2006-2007, but the demand continues to exceed available funds, Haught says.

"The cost of medicines keep increasing, and the intensity of usage by clients is a big challenge," Haught says. "We have more people on medicines than ever before, and while it used to be three medications per person, now it's four or five."

Also, there's far less turnover among ADAP clients than there used to be, he says.

"We have a waiting list for the drug Fuzeon, which has a cap of 50 clients, and we have 50 on the drug and 50 on the waiting list," Haught says. "We're always a dog chasing its tail."

Most of the hurricane evacuees are from Louisiana, which has a more generous ADAP program than the one in Texas, Haught says.

"In Louisiana, they get eight drugs a month," he says.

Out of concern that disaster victims receive their antiretroviral drugs as quickly as possible, the Texas ADAP simplified the application process to make it a one-page qualifier. Among the first people to be given antiretroviral medication were those who were organized enough to bring with them their identification materials, including ADAP cards and drug bottles, Haught explains.

It takes a little longer to find qualify the HIV patients who arrived with nothing and whose knowledge of their treatment may be little more than reciting the color of their pills, he says.

"For those clients who don't have any information, we have them reassessed rather quickly by

an HIV-savvy physician, and then we get them on medicines," Haught says.

With 14,000 Texans already receiving assistance from ADAP and with the state's budget already contributing 40 percent of the ADAP budget, it would be very difficult for the state to handle any additional HIV clients without national assistance, Haught adds.

The National Association of People With AIDS (NAPWA) of Washington, DC, issued an alert two weeks after New Orleans, LA, was flooded, blasting the federal government for not making immediate provisions of emergency Ryan White funds to assist the estimated 32,000 HIV-infected people from the hurricane-devastated states.

"Valiant AIDS service organizations from the affected states are operating in exile in hotel rooms and makeshift offices," says **Terje Anderson**, executive director of NAPWA.

"Organizations in neighboring states are providing care and treatment for evacuees, even without identified financial resources," Anderson says.

But the problems faced by the states taking in disaster victims may be eclipsed by the troubles experienced in the states devastated by Hurricane Katrina.

In Louisiana, where the state's ADAP was based in New Orleans, the ADAP staff were scattered across the country, and no one was able to return to the building to salvage records within the first couple of weeks after the hurricane, Arnold says.

"The ADAP people are the poorest of the poor," Arnold says.

"ADAPs in affected states are starting to get HIV medications to evacuees, but even before this disaster, Alabama's ADAP had 500 people on a waiting list, and the rest of the affected and neighboring states were already filled to capacity," Anderson says.

No one can predict how many people will return to their home states and whether there will be records of their ADAP enrollment if and when they do, he adds.

"And what does it mean to have ADAP clients moving to other states?" Arnold says. "If the California ADAP has 18 more people, then that's not a problem, but what if Montana's ADAP has 18 more people? That's a problem."

The bigger issue regarding AIDS treatment funding is how Congress and the president will react to the reauthorization of the Ryan White Care Act, which was due at the end of September, 2005, and to pleas for additional funding when faced with unprecedented emergency fund needs after the hurricane and flooding at the end of August and beginning of September, experts say.

"We definitely think there should be more money [ADAP], and we definitely think the $10 million included in each of the Senate and House funding bills is completely inadequate," says **Christine Lubinski**, executive director of the HIV Medicine Association (HIVMA) in Alexandria, VA.

What's needed is emergency supplemental funding through hurricane relief, Penner notes.

"We are working in a coalition to get some set-aside in [Health and Human Services (HHS) funding] to trickle down to Ryan White programs," Penner says.

Although most of the emergency relief money will focus on the emergency itself, there's a good case to be made that state ADAPs, which are picking up the burden of hurricane victims who've relocated, should receive some emergency funding, as well, Penner adds.

Others agree.

"We've been told there are no additional resources available, but now we need to respond to the very urgent needs of people in those hurricane areas," Lubinski says. "And one part of the response should be an infusion of significant resources into the ADAP program generally and in ADAP specifically in affected states, including those directly affected by the hurricane and those states where people are now hanging out for who knows how long."

HIVMA and other AIDS organizations will explore the possibility of including additional HIV funding in disaster relief bills when they are able to meet again with their congressional champions, Lubinski says.

"As a practical matter, that may be the only potential vehicle for a funding increase for HIV services in the short term," she says.

Also, HIVMA and other AIDS groups will lobby Congress to stop the train that's pushing for a $10 billion cut in Medicaid funding over five years, Lubinski adds.

"The Republican leadership is moving forward, and those cuts were in large part based on tax cuts the administration and leadership have asked for," Lubinski explains. "We always thought that was a completely unacceptable trade-off, and in the context of this disaster, it's nothing short of outrageous."

AIDS groups are very concerned about Medicaid cuts because those will have a trickle down impact on Ryan White programs when individuals who had been receiving their HIV medications and health care through Medicaid are now forced to find for themselves or be added to ADAP waiting lists, she adds.

In addition to concern about ADAP funding, AIDS groups are looking closely at what happens with the Ryan White Act reauthorization because of the way changes to it could impact AIDS spending and programs.

So far the administration's principles regarding Ryan White provide no definitions for terms such as primary medical services or core medical services, and how these are defined would greatly impact what type of treatment HIV patients would receive, Lubinski says.

"One thing we're going to do is educate policymakers about our definition, which is a broad definition of core services," Lubinski says. "And also our recommendations speak to the continuing importance of services in the Ryan White Act that we don't want to see go away."

HIV substance abusers encouraged to use new case management program

Study shows program works

A strengths-based case management program for HIV-positive patients who are active substance abusers appears to have some success in directing such patients to HIV care and treatment, according to recent research.

For about 15 years, Ohio behavioral scientists have used a strengths-based case management model with substance abusers, having case managers meet with them over a nine month period with the purpose of improving their health care outcomes.

"What we found in summary is, indeed, case management did lead to better outcomes, including less involvement in criminal activity and lower levels of drug use," says **Richard C. Rapp**, MSW, assistant professor in the department of community health at School of Medicine, Wright State University in Dayton, OH. Rapp also is with the Center for Interventions, Treatment and Addictions Research (CITAR) in Dayton.

"Case management seemed to help keep people in treatment, and longer treatment led to better outcomes," Rapp says. "So that's our rallying cry for case management."

With encouragement from the Centers for Disease Control and Prevention (CDC) of Atlanta, GA, Rapp and co-investigators developed a model of strengths-based case management that was studied in the antiretroviral treatment and access study (ARTAS), which ran from 2003 to 2004.

What had been a nine-month case management program was condensed to five sessions with the case managers' entire focus and goal being to link HIV patients to care, Rapp explains.

"Originally, the program was a source of ongoing support to individuals with substance abuse problems," Rapp says. "We went into this one with a very specific intent, and we told clients up front that it was our hope they'd get involved with health care services."

The idea is that the case managers can help them deal with any barriers they encounter, including referring clients to mental health services or drug treatment programs if necessary, he says.

While most of the patients involved in case management care in Dayton were HIV negative, the pilot studies focused on HIV infected substance abusers, Rapp notes.

The ARTAS trial had promising results, so the CDC has decided to expand it to make a demonstration project in 10 cities, and it will conclude late next year, Rapp says.

"We're recruiting 50 people at each of 10 sites, and their primary characteristic is being newly diagnosed with HIV," Rapp says. "Some are substance users, some are homeless, and some are people with alternative lifestyles."

Ideally, the demonstration project will confirm the positive results already seen and convince the CDC to build case management into the HIV continuum of care, Rapp says.

"Forty percent of the people who are HIV positive don't access health care within six months," Rapp says. "And there are huge implications at all levels for this, including people passing the virus to others, declining health, and having a disease that's more expensive to treat at a later time."

The faster HIV patients can be brought into case management, the better, he says.

"It's always ironic that what seems like a simple task of linking someone to care can have an amazing set of barriers," Rapp says.

"For a lot of people we work with it's not a straightforward process," Rapp adds. "If they're homeless, have no transportation, if there are waiting lists, people become exasperated and give up."

So that's what the case management model is

about: having a skilled professional develop a relationship with the client and facilitate their linking to medical care, Rapp explains.

The demonstration project works this way: A person has been diagnosed with HIV in a health department clinic is told about this project, and if they're interested they are referred to one of the project case managers to see very quickly, Rapp says.

The case manager explains the program to the client and sees whether the person remains interested. If so, the client will schedule a first meeting and meet again up to five times, he adds.

Here is a breakdown of what happens at each session:

• **First session:** "The case manager gives clients a chance to talk about their feelings about being HIV positive in one-on-one sessions," Rapp says. "The case manager will focus very deliberately on the client's strengths and help clients identify times and situations where they've been successful."

Case managers focus on clients' assets and help them use these to take a first step in accessing care, Rapp says.

"Strength-based case management is used to engage people in talking about strengths and helps people move to that first step," he adds.

• **Second session:** "This is much more focused on strengths and helping clients identify what their most immediate barriers are," Rapp says.

The case manager helps clients develop a written plan to address barriers.

"We again make the assumption that many of the people we work with are living disorganized lifestyles, and we'll commit everything to writing when developing a plan about how the individual will deal with those barriers," Rapp says. "So if the barrier is 'I can't go to care because I haven't told my partner I'm positive,' then they develop a plan for how they can tell their partner or link to care without telling their partner."

Another barrier that the case manager could help the client overcome would be the lack of transportation. The case manager could arrange for the client to take public transportation or drive the client to the health care center, if necessary, Rapp says.

"Some case managers have taken pictures of the clinic and shown them to clients, saying, 'You'll walk down here and walk down this hall and talk with Nancy the intake nurse,'" Rapp explains. "They make it as easy as possible for the client to follow through."

• **Third, fourth, fifth sessions:** The case manager continues to look at barriers and helps the patient make a plan to deal with barriers and successfully link to care, Rapp says.

The written plans, called contact plans, are reviewed and updated with changes or additions, and these have turned out to be one of the most popular aspects of the case management sessions, Rapp notes.

"In follow-up interviews, we've heard how clients responded so positively to these written plans," he says. "That's always my bias to write it down and make sure the client has a copy of it."

Having a plan in writing gives clients a sense of order in what frequently is a disorganized life, Rapp explains.

"Many people in crisis don't think clearly or retain information very well, so this plan gives them the steps to follow," he says. "It will read: 'I talk with the case manager; here's what he does; here's what I'm supposed to do; here's my target date for handling that.'"

It serves as a gentle reminder, Rapp says.

Also, if the plan is revised because one strategy didn't work out, the case manager will explain that the change doesn't indicate a failure, but occurred simply because something was note anticipated, and now they must prepare for that, Rapp says.

"There's a cheerleading component to it," Rapp says. "We focus on strengths, and whatever goals the client sets are their own goals and not the case manager's."

At each meeting, the case manager is reminding the client that the meetings soon will come to an end, and that also might help motivate people to take the steps necessary to accomplish their goal, Rapp notes.

"At the last session, the goal is to have the patient walk out with a bundle of information so if the client decides to link with health care, the tools are there," Rapp says.

During the clinical trial, 78 percent of the people in case management visited an HIV clinician at least once in six months, while 60 percent of standard of care clients linked with an HIV clinician within six months.[1]

As a result of the program, some sites came up with system changes that helped to reduce barriers. For instance, one clinic would provide buffet food and child care for clients, taking care of the issue of finding a place to leave one's child while making an appointment, as well as acknowledging the reality that finding the next meal can be a financial issue for some clients, Rapp says.

"It's pretty minimal when compared with having someone who is untreated with HIV infection and then develops AIDS," Rapp adds.

Reference:
1. Rapp RC, et al. Strengths-Based Case Management: Implementation of an Effective Intervention for Encouraging Health Care Linkage Among Newly-Diagnosed HIV-Positive Persons. Presented at the 2005 National HIV Prevention Conference, June 12-15, 2005; Abstract: M3-F0404.

ADHERENCE STRATEGIES

Researchers study use of the 'MATI' for improving AIDS drug adherence

Early data confirm tool's usefulness

Investigators have found that an adherence tool that addresses multiple factors contributing to adherence difficulties can assist with better adherence.

The Medication Adherence Training Intervention (MATI) is a newly-invented tool that prepares patients for adherence by incorporating medication adherence education, the patient's history and medication experiences, with motivation and empowerment interventions, says **Shvawn McPherson-Baker**, PharmD, MPH, a research associate in the division of hepatology at the University of Miami School of Medicine in Miami, FL.

"We developed the MATI along the context of clinical pharmacy, clinical medication, and clinical psychology, interfacing the three of them to come up with an approach to patient care," Baker says. "We looked at how to best incorporate the patient's abilities with our abilities."

One aspect to the MATI that's important is how it is designed to be a nonjudgmental tool that doesn't admonish patients for their poor adherence habits, Baker notes.

"The approach is ' Let's take off the white coat and work on this together,'" Baker says. "Let's see if there's a readiness for medication adherence and provide education on that."

Often, clinicians see HIV patients who say they're taking their medication appropriately, but their lab work suggests otherwise, Baker says.

"I say to the patients, 'Don't tell me what you think I want to hear; tell me what you're doing, because you're saying one thing, but your numbers don't match,'" Baker says. "Then patients will say the medications make them sick or that they don't want to take them."

This is where the MATI comes in handy. It provides a checklist of items to cover when assessing a patient's adherence, and it helps the clinician find out what the patient's approach is to medication, Baker says.

"We go down a list of things we need to cover, like different parts of medication, medication history, experiences with medications, beliefs," Baker says. "We try to find out where patients are coming from in their approach to medication and what they believe about treatment."

For example, the MATI checklist, which is included in a March 2005 article published in Behavior Modification, includes the following:

o "Assess for basic knowledge about HIV; What is HIV? What do you know about HIV?"1

o "Understand drug 'cocktails' and how they affect the virus; What do you know or what have you heard about the drug cocktails?"1

o "Assess knowledge of medication strategies (compliance or adherence); If 100% is all the time, and 0% is not at all, during the past month, how much of the time have you taken all of your HIV and AIDS medicines?"[1]

o "Myths and rumors about HIV medications; What have you heard about antiviral medications? Protease inhibitors?"1

"We had a woman in the clinic who just recently came out of a treatment program for crack cocaine," Baker says, offering one case study example of how the tool is used.

"She's in her 40s, has two or three children, but most are grown," Baker notes. "She's functioning as her own entity and has a level of independence, but has never been treated for HIV."

"She found out she was HIV positive, and she has been clean from drugs for three months and is comfortable with being clean," Baker adds.

The woman's physician had discussed the possibility of her starting medications and had referred her to Baker for an assessment, but the prescription hadn't been written.

"The doctor wanted me to talk with her about the regimen they anticipate putting her on," Baker says. "They wanted me to discuss what it entails, what the side effects are, what she can expect from therapy, and when she can expect it from therapy."

Baker discussed these issues with the patient and asked whether she was comfortable with the information, and she said she was.

So Baker followed the MATI checklist and dis-

cussed other issues with the patient, including the stigma of being HIV positive, what her goals were, what her concerns were, and what her expectations were about treatment.

During this discussion, Baker was able to dispel some myths the woman believed, such as thinking that taking AZT might cause her skin to darken, which would let people know she was HIV positive, Baker says.

The woman recalled that a neighbor some years earlier had taken AZT, and then his skin got dark, and he looked like someone with AIDS, Baker adds.

"That patient was diagnosed with HIV infection at a time when we didn't have a lot of medications other than AZT, and that drug was reserved for people at the end-stage," Baker explains. "So this guy probably was very sick, and she believed that was the picture of HIV."

Baker also explained how much HIV infection has changed in recent years because of the multiple medications available for treatment.

"I let her know HIV infection is not a death sentence, and people can live relatively normal lives," Baker says.

While the woman's physician and other clinicians had already told her this, she needed the information repeated, Baker says.

"My role in the medication clinic is to do that with patients, because it's good to have another person who can reinforce the information," Baker says. "I was introduced as the pharmacist who was going to talk with her about medications."

The session worked.

"So she went home, thought about it, and came back, saying, 'I'm ready; I thought about what you said, and I want to live for my grandchildren.'"

The woman acknowledged that she knew she wouldn't feel good for a few weeks after initiating therapy, but she was ready to take charge of her life, Baker says.

"She's been successful, has gained weight, and is doing great," Baker adds.

Baker helped to develop the MATI as a way to give other clinicians a tool to use when discussing antiretroviral treatment with patients, so they might obtain optimal adherence.

"It's a way of finding an approach to patient counseling and bringing in the patient as part of the team," Baker says. "The goal is for patients to synthesize all of this information and to make sure they understand what their responsibilities and roles are and what they are to expect from their treatment."

Clinicians using the tool will need to have some medication knowledge base because they'll have to discuss how the medications work, what the side effects are, and answer questions in detail, Baker says.

"Inevitably these questions come up, and one of the things that helps to build that foundation of trust is patient knowing you know what you're talking about, and if they ask you a question that you can give them an honest answer," Baker adds.

So while it would help to have pharmacists use the tool with patients, other disciplines also could do the job, including social workers, nurse practitioners, physician assistants, and physicians, Baker says.

Reference:

1. McPherson-Baker S, et al. Development and Implementation of a Medication Adherence Training Instrument for Persons Living with HIV: The MATI. *Behav Modif*. 2005;29:286-317.

AIDS Alert Q&A

Italian researcher continues to focus on hydroxyurea treatment for HIV

[Editor's note: In this Q&A interview, Franco Lori, MD, scientific director of the Research Institute for Genetic and Human Therapy (RIGHT) of Washington, DC, and Pavia, Italy, discusses the recent positive outcomes of his research for an optimal hydroxyurea treatment for HIV and what he calls the "Virostatic" approach to HIV treatment.]

AIDS Alert: You've named the process "Virostatic therapy," which combines antiretroviral drugs that suppress HIV with hydroxyurea for the purpose of preventing cell activation. What is it in your latest research of this approach that you think will most interest HIV clinicians and other researchers?

Lori: Virostatics are drugs combining antiviral and cytostatic properties. The cytostatic (prevention of cell proliferation) activity of Virostatics represents a novel mechanism of action, in addition to the known antiviral activity of some Virostatic combinations, such as mycophenolate and abacavir, or hydroxyurea and didanosine. Preventing cell proliferation

breaks the pathogenic cycle of cell proliferation-HIV replication-cell proliferation. In fact, persistent HIV replication induces chronic immune stimulation, resulting in T cell activation and proliferation, and consequently, in the exhaustion of the immune system. Cell proliferation, in turn, sustains HIV replication, because proliferating cells produce a higher number of viral particles. At present, no antiretroviral drug addresses the issue of over-proliferation of immune competent cells. In this respect, Virostatic therapies are unique, as they attack HIV by "modulating" those cells that the virus needs to survive.

AIDS Alert: Hydroxyurea lost favor among HIV researchers and clinicians several years ago because of treatment failure and serious adverse events in clinical trials, including the deaths of some subjects. Why did you continue to pursue hydroxyurea as an HIV treatment, even in the face of these setbacks?

Lori: We are committed to developing the combination of hydroxyurea and didanosine (ddI) because hydroxyurea enhances the efficacy of ddI without increasing serious, life-threatening toxicity. A recent retrospective analysis of the AIDS Clinical Trials Group (ACTG) studies has shown that hydroxyurea does not increase the risk of pancreatic toxicity associated with ddI. The authors of the ACTG report suggest the possibility that factors other than hydroxyurea, such as lifestyle or predisposition, might have contributed to the death of those individuals.

Regarding antiviral activity, the four initial trials (>500 patients) in which hydroxyurea was added to a ddI or ddI-stavudine (d4T) backbone consistently showed that hydroxyurea increases the antiviral activity of ddI. Subsequently, hydroxyurea was used in addition to 3-4 other drugs that, by themselves, were fully suppressive. In this context, hydroxyurea could not demonstrate additional activity, and this has been interpreted as "treatment failure."

Our RIGHT 702 trial, published earlier this year, not only has confirmed the antiviral activity of the Virostatic combination of hydroxyurea and ddI, but also indicated that the optimal dosage of hydroxyurea (600 mg total daily dose) is half of the dosage used in previous trials. In the July manuscript published in AIDS, we explain the mechanism underlying this apparent paradox: by increasing hydroxyurea concentrations one does not increase the cytostatic activity of the drug, but one does increase its cytotoxic activity. In other words, lowering the hydroxyurea dosage decreases toxicity without loosing activity.

AIDS Alert: Since your most recent study was published in July, what kind of feedback have you received from other researchers regarding including the smaller dose of hydroxyurea in HIV treatment regimens? Also, have there been any pharmaceutical companies interested in pursuing your research into a single pill that contains an antiretroviral plus hydroxyurea?

Lori: Basic scientists continue to be intrigued by the concept. Among clinicians, in the United States there is a minority of strong believers, usually clinicians that had used, and continue to use, the drug. Most of the others are skeptical, and some of them clearly are against the idea. In Europe the climate is more favorable, and many colleagues believe that hydroxyurea suffered in the past from the lack of a clear, well-designed drug development plan. Several have expressed interest in revisiting the concept of a single pill that combines low-dose hydroxyurea with ddI. We are very committed to this concept. If no company is interested, we will develop the new pill ourselves.

AIDS Alert: Why do you feel it's important to continue investigating the virostatic approach? What will this add to the HIV drug arsenal that isn't already addressed?

Lori: Virostatics represent a novel class of drug combinations with a double mechanism of action. One component of the combination targets a cellular enzyme, and cellular enzymes are not prone to resistance. In addition, hydroxyurea compensates for didanosine resistance. Therefore, the resistance profile of Virostatics is unique. We expect that this unique resistance profile will endow Virostatics with the characteristics of durability; however, long-term studies are required to confirm this hypothesis. Preliminary results also suggest that Virostatics will be more "forgiving" of missed doses of drugs.

AIDS Alert: With the development of multidrug resistant HIV, particularly among HIV patients who have been in treatment for a decade or longer, do you believe the virostatic approach could prevent this trend or provide a successful salvage therapy?

Lori: A recent publication from a French group has shown that viruses that became resistant to HIV were more sensitive to hydroxyurea 14. For mutants carrying the M184V mutation or M41L+T215Y mutations, a defect could be detected by using target cells in which dATP pools had been reduced by pretreatment with hydroxyurea. The authors then found that many, but not all, viruses carrying RT resistance mutations display an increased sensitivity to hydroxyurea. Moreover, the 3D study has shown that hydroxyurea was more efficient in drug-experienced than in naïve patients. Therefore, we believe that Virostatics can be a useful component of salvage therapies in those patients that have developed drug resistance.

New streamlined risk assessment for HIV clinicians

It's based on CDC report on prevention for positives

The public health community noted improvements in sexual risk behaviors among HIV positive people in the 1990's, but the positive gains have been lost in the 21st century as unsafe sexual behaviors have increased among some HIV positive populations.

"We've had an alarming increase in sexually transmitted diseases (STDs) and unsafe sex behaviors among certain subsets of HIV infection," says **Jeanne Marrazzo**, MD, MPH, associate professor at the University of Washington in Seattle, WA.

"Unfortunately, HIV care providers and infectious disease physicians often are not in the forefront of taking sexual history from patients and talking about risk assessment and looking at ways to reduce risk in this population," Marrazzo says.

The Centers for Disease Control and Prevention (CDC) of Atlanta, GA, addressed this problem in July, 2003, in a consensus document of recommendations, titled, "Incorporating HIV Prevention into the Medical Care of Persons Living with HIV."[1]

The recommendations were made by the CDC, the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA).

Three main areas were addressed by the recommendations, including the following:

- STD-related risk assessment and drug use risk assessment in HIV infected people;
- delivering universal and tailored behavioral interventions;
- focusing on how best to approach and manage partners of HIV-infected people.

"What has happened since then is the CDC, amazingly, has allocated some funds from the HIV division to fund the group I'm involved in, which is the STD/HIV Prevention Training Centers," Marrazzo says. "We do clinical and behavioral and partner management for people with STDs."

The CDC funds were used to create a curriculum that delivers modules focusing on the recommendations from the earlier CDC report, Marrazzo says.

"A group of 12 of us met frequently over the last year and a half to create a pretty nice curriculum," Marrazzo says. "It includes speaker materials, speaker notes, participant guides, reference materials guide, an electronic finder package that helps HIV care providers learn about this issue, and tools to address the problems of HIV-infected people."

The program focuses on four priority strategies of the CDC's Advancing HIV Prevention campaign. The program's PowerPoint presentation cites these priorities as follows:

- Make voluntary testing a routine part of medical care;
- Implement new models for diagnosing HIV infections outside medical settings;
- Prevent new infections by working with persons diagnosed with HIV;
- Further decrease perinatal HIV transmission.

HIV and infectious disease clinicians need to be reminded as to the fundamentals of what's happening with HIV risk behaviors, and they need to know there are resources to help them with the behavioral pieces that might be outside their comfort zones, Marrazzo notes.

In the partner management module, for example, physicians are taught about legal issues involving HIV reporting and how to handle the delicate situation of a patient asking the doctor to help him or her tell a partner about the infection, Marrazzo says.

"It's important information that's not viewed as critical by the typical HIV continuing education courses, which are focused on antiretroviral therapy," she says. "But there's a lot more information that's needed."

The HIV prevention training curriculum has been taught in pilot sessions in six cities and was recently approved by the CDC, Marrazzo says.

"We're partnering with the Association of AIDS and HIV Medicine (AAHIVM) to deliver some of the modules," Marrazzo says.

So far the curriculum has been well-received, and a couple of hundred people have received training, Marrazzo says.

"We've delivered in our region to over 75 people," she adds. "We're training the leaders in the HIV field to get out there and go to their sites and take on this role."

AIDS Education and Training Centers are paid to assist with finding clinics and other sites where training can be delivered, Marrazzo says.

"It's an unprecedented effort by agencies that aren't often on the same page in a practical sense," Marrazzo says. "Most of the people doing the training are providers, so we're training doctors, as well as mid-level providers, including physician assistants and nurse practitioners."

Attendees are offered continuing medical education credits, and the training is marketed in the HIV

world. Eventually the course may be offered online, she adds.

Feedback shows that HIV clinicians are motivated to learn more about prevention, Marrazzo says.

"I think most physicians are frustrated right now with this upturn in the epidemic, and they're frustrated particularly with crystal meth—it makes everybody crazy," Marrazzo says. "They're very fatalistic about meth patients, which is too bad."

While the module doesn't address meth addiction directly, there is information about resources and behavioral counseling that is applicable to people using drugs, she notes.

"There's definitely a morale issue in HIV care, and we received a lot of feedback about that," Marrazzo says.

"And there are still people in the HIV world who don't realize that we're dealing with a syphilis epidemic among HIV-infected people."

Marrazzo says she's heard of secondary and primary syphilis cases being misdiagnosed, often in HIV care settings.

"So if this education does nothing but remind people that the STD epidemic is not over with HIV-infected people, and it's being driven in part by things like crystal meth, that will help people diagnose and treat this problem," Marrazzo says.

Reference:

1. CDC. Incorporating HIV Prevention Into the Medical Care of Persons Living with HIV. *MMWR Recomm Rep*. 2003;52:1-24. Erratum in: *MMWR Recomm Rep*. 2004;53:744.

FDA Notifications

The Food and Drug Administration (FDA), September 7, 2005, announced the tentative approval of zidovudine oral solution manufactured by Aurobindo Pharma LTD. Hyderabad, India. This product is the first tentatively approved generic version of Retrovir brand of the zidovudine oral solution (manufactured by GlaxoSmithKline). This oral dosage form of the drug is the first pediatric-friendly oral solution available for consideration for purchase under the President's Emergency Plan for AIDS Relief (PEPFAR).

Zidovudine is in the class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs), which

CE/CME *questions*

13. In a strengths-based case management approach to HIV prevention, which of the following approaches would be typical?
    A. The case manager gives clients a chance to talk about their feelings about being HIV positive in one-on-one sessions.
    B. The case manager focuses on the client's strengths and help clients identify times and situations where they've been successful.
    C. Case managers focus on clients' assets and help them use these to take a first step in accessing care.
    D. All of the above

14. The Medication Adherence Training Intervention (MATI) includes a checklist of topics for a pharmacist, physician, or another medical professional to discuss with patients who may be starting an antiretroviral drug regimen. Which of the following is not a topic on the checklist?
    A. Assess for basic knowledge about HIV.
    B. Learn whether someone lacks insurance coverage to afford HIV medications.
    C. Understand drug cocktails and how they affect the virus.
    D. Assess knowledge of medication strategies (compliance or adherence).

15. HIV prevention recommendations made by the Centers of Disease Control and Prevention (CDC) in Atlanta, GA, along with other agencies and organizations in July, 2003, included three main areas. Which of the following are the three?
    A. STD-related risk assessment and drug use risk assessment among HIV populations; formulating prevention for positives pro grams in local clinics; eliminating vertical transmission of HIV
    B. STD-related risk assessment and drug use risk assessment in HIV infected people; delivering universal and tailored behavioral interventions; focusing on how best to approach and manage partners of HIV-infected people
    C. Assessing sexual risk behaviors; making culturally sensitive behavioral interventions; encouraging early testing and linkages to care
    D. None of the above

help keep the AIDS virus from reproducing. It is intended to be used with other antiretroviral agents for the treatment of HIV-1 infection. This product contains 50 mg/5mL of zidovudine in an oral solution.

Tentative approval means that although existing patents and/or exclusivity prevent marketing of this product in the United States, it meets all of FDA's quality, safety and efficacy standards for U.S. marketing.

FDA issues guidance for product sponsors

The Food and Drug Administration (FDA) is issuing draft guidance to assist product sponsors in the development of antiviral drug products and to serve as a starting point for understanding the nonclinical and clinical virology data important to support clinical trials of antiviral agents. This guidance focuses on nonclinical and clinical virology reports, which are essential components in the review of investigational antiviral drugs.

Topics in the guidance include studies defining the mechanism of action, establishing specific antiviral activity of the investigative drug, submitting data on the development of viral resistance to the investigational drug, and providing data identifying cross-resistance to approved drugs having the same target.

The recommendations in the guidance are based on the review experience with antiviral drugs of the FDA Division of Antiviral Drug Products (DAVDP) and input from pharmaceutical sponsors and the scientific community. Because of the experience, history, and lessons learned with HIV-1 studies, the guidance focuses on studies commonly used to evaluate HIV-1 drugs and uses them as a model for future studies of drugs to treat other viruses. Since the field of virology is dynamic and continually evolving, this guidance will be revised as new information accumulates and as circumstances warrant.

The Federal Register document, including instructions for submitting comments to the agency, is available at: www.fda.gov/OHRMS/DOCKETS/98fr/05-10431.htm

CE/CME *directions*

To complete the post-test for *AIDS Alert*, study the questions and determine the appropriate answers. After you have completed the exam, check the answers **on p. 119**. If any of your answers are incorrect, re-read the article to verify the correct answer. At the end of each six-month semester, you will receive an evaluation form to complete and return to receive your credits.

CE/CME objectives

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

- **identify** the particular clinical, legal, or scientific issues related 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. ■

CE/CME *answers*

Here are the correct answers to this month's CME/CE questions.

Answers: 13. D; 14. B; 15. B

The draft guidance is available at http://www.fda.gov/cder/guidance/6568dft.htm.

FDA guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. ■